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CLINICAL AND THERAPEUTIC DECISION MAKING IN PAEDIATRIC AUTOIMMUNE AND INFLAMMATORY NEUROLOGICAL DISEASE

"DECISION MAKING" CLINICO E TERAPEUTICO NELLE MALATTIE NEUROLOGICHE AUTOIMMUNI E INFIAMMATORIE IN ETÀ PEDIATRICA

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ABSTRACT

1. Background. Paediatric neuroimmunology is a rapidly evolving field both as regards clinical-radiological phenotyping, biomarker development, and therapeutic possibilities. In this latter aspect, while a growing armamentarium of treating agents is becoming available, this is not mirrored by quality evidence and definite recommendations on treatment strategies, drugs' efficacy and tolerability. This is especially true in paediatric age, where most data is derived from adult studies.

Objective. To investigate clinical and therapeutic aspects of decision making in paediatric autoimmune and immune-mediated inflammatory conditions. In particular, the aims of this work include: exploring the available immune therapeutic agents and their mechanisms of action; investigating the use of immune therapy in autoimmune encephalitis; investigating the use, efficacy and tolerability of individual immune therapeutic agents in different clinical situations in paediatric neurology (intravenous immunoglobulin in Sydenham's chorea; intravenous immunoglobulin in paediatric neurology; therapeutic plasma exchange in anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis; rituximab in neuromyelitis optica spectrum disorders; mycophenolate mofetil, azathioprine and methotrexate in anti-NMDAR encephalitis; mycophenolate mofetil in paediatric autoimmune and immune-mediated central nervous system (CNS) conditions).

2. Methods. The present PhD thesis is articulated into sub-projects carried out at the Department of Women's and Children's Health in Padua, Italy, and at the Children's Hospital at Westmead, Sydney, Australia. Study designs include six literature reviews (available immune therapeutic agents and their mechanisms of action; immune therapy in autoimmune encephalitis; immune therapy in herpes simplex virus-induced anti-NMDAR encephalitis; intravenous immunoglobulin in Sydenham's chorea; therapeutic plasma exchange in paediatric anti-NMDAR encephalitis; mycophenolate mofetil, azathioprine and methotrexate in paediatric anti-NMDAR encephalitis) and four original studies with observational retrospective design (immune therapy in paediatric anti-NMDAR encephalitis; intravenous immunoglobulin in paediatric neurology; rituximab in neuromyelitis optica spectrum disorders; mycophenolate mofetil in paediatric autoimmune and immune-mediated CNS conditions). Of these latter original studies, one includes an Italian population (immune therapy in paediatric anti-

NMDAR encephalitis), one a single-center Australian population (intravenous immunoglobulin in paediatric neurology), and two include an international cohort of paediatric patients (rituximab in neuromyelitis optica spectrum disorders; mycophenolate mofetil in paediatric autoimmune and immune-mediated CNS conditions). Most of the projects have been concluded, whereas two are in their final phases (mycophenolate mofetil, azathioprine and methotrexate in paediatric anti-NMDAR encephalitis; mycophenolate mofetil in paediatric autoimmune and immune-mediated CNS conditions).

3. Results. Key findings are presented for the main study objectives.

3.1 Immune therapeutic agents and their mechanisms of action.

3.1.1 Immune therapeutic agents and their mechanisms of action (literature review). First-line treatments typically include corticosteroids, intravenous immunoglobulin, and plasmapheresis, while for severe disease second-line 'induction' agents such as rituximab or cyclophosphamide are used. Steroid-sparing agents such as mycophenolate mofetil, azathioprine or methotrexate are often used in potentially relapsing or corticosteroid-dependent diseases. Lessons from adult neuroimmunology and rheumatology could be translated into pediatric autoimmune CNS disease in the future, including the potential utility of monoclonal antibodies targeting lymphocytes, adhesion molecules for lymphocytic migration, cytokines or their receptors, or complement. Finally, many agents used in other fields have multiple mechanisms of action, including immunomodulation, with potential utility in neuroimmunology, such as antibiotics, psychotropic drugs, probiotics, gut health, and ketogenic diet.

3.2 Immune therapy in autoimmune encephalitis.

3.2.1 Autoimmune encephalitis with antibodies targeting neuronal surface antigens (systematic literature review). Most studies on immune therapy in autoimmune encephalitis associated with antibodies to cell surface antigens are retrospective cohorts, and there are no randomised controlled trials. Most clinicians use first-line therapy (steroids, intravenous immunoglobulin, plasma exchange), and if severe or refractory, second-line therapy (rituximab, cyclophosphamide). When present, tumours should be removed. There are common therapeutic themes emerging. Firstly, patients given immune therapy do better and relapse less than patients given no treatment. Secondly, patients given early treatment do better. And thirdly, when patients fail first-line therapy, second-line

therapy improves outcomes and reduces relapses. Given the retrospective uncontrolled data, the literature has inherent bias, including severity and reporting bias.

3.2.2 Clinical and therapeutic aspects of the Italian cohort of paediatric anti-NMDAR encephalitis (national retrospective observational study). We described a new case series of 20 children (50% females), with anti-NMDAR encephalitis referred by 13 Italian centers (mean age at onset 8 years, range 3-17). Onset was with neurological symptoms in 70%, and with behavioral/psychiatric disturbances in 30%. Most patients developed a severe clinical picture (90%), and 41% experienced medical complications; children 12-18 years old seemed to be more severe and symptomatic than younger patients. All children received first-line immune therapy; second-line treatment was administered to 45%. Relapses occurred in 15%. At last follow-up (mean 23.9 months, range 5-82), 85% patients had modified Rankin Scale (mRS) 0-1; this rate was higher among older patients, and in those receiving first immune therapy within 1 month.

3.2.3 Herpes simplex virus-induced anti-NMDAR encephalitis (systematic literature review). 43 patients with herpes simplex encephalitis (HSE) followed by anti-NMDAR encephalitis were identified in the literature (31 children). Latency between HSE and anti-NMDAR encephalitis was significantly shorter in children than adults (median 24 vs. 40.5 days; p=0.0057). Compared to the HSE phase, anti-NMDAR encephalitis was characterized by significantly higher frequency of movement disorder (2.5% in HSE, vs. 75% in anti-NMDAR encephalitis; p<.0001), and by significantly lower rate of seizures (70% in HSE, vs. 30% in anti-NMDAR encephalitis; p=0.0011). Compared to adults, during anti-NMDAR encephalitis children had significantly more movement disorder (86.7% in children, vs. 40% in adults; p=0.0064) and less psychiatric symptoms (41.9% in children, vs. 90% in adults; p=0.0251). Children also had a slightly higher median mRS than adults during the acute phase of anti-NMDAR encephalitis (5 vs. 4; p=0.0146). During anti-NMDAR encephalitis, 84.6% patients received acyclovir (for ≤7 days in 22.7%; long-term antivirals in 18% only), and 92.7% immune therapy, but none had recurrence of HSE clinically or using CSF HSV-PCR (median follow-up 7 months).

3.3 Modes of use, efficacy and tolerability of individual immune therapeutic agents in different clinical situations in paediatric neurology.

3.3.1 Intravenous immunoglobulin in Sydenham's chorea (systematic literature review). The studies reviewed on intravenous immunoglobulin in Sydenham's chorea demonstrate a short-term benefit in symptomatic improvement. However, they do not clarify an optimum timing and duration for use of intravenous immunoglobulin, and do not provide data on the effect on long-term neurological and psychiatric complications.

3.3.2 Intravenous immunoglobulin in paediatric neurology (single-center retrospective observational study). 196 children received intravenous immunoglobulin for neuroimmunological indications at the Children's Hospital at Westmead, Australia, between 2000 and 2014 (28.1% had Guillain-Barré syndrome) (15.5% of all hospital indications). In total, 1669 intravenous immunoglobulin courses were administered (total 57221 g, median 78 g/patient, range 12-5748 g). Highest median number of courses was in chronic inflammatory demyelinating polyneuropathies, opsoclonus-myoclonus-ataxia, suspected immune-mediated epilepsies and Rasmussen's encephalitis. Adverse reactions occurred in 25.5%, mostly minor. Outcome at follow-up was best in anti-NMDAR encephalitis, Guillain-Barré syndrome and myasthenia gravis, and worst in Rasmussen's encephalitis and epilepsies. The total cost for intravenous immunoglobulin was 2,595,907 American dollars (median $3,538/patient, range $544-260,766). 45.4%-57.1% patients received intravenous immunoglobulin for 'weak' indications or 'not listed' in international guidelines. Some entities frequently treated with intravenous immunoglobulin in current practice, such as anti-NMDAR encephalitis and transverse myelitis, are not listed in most guidelines.

3.3.3 Therapeutic plasma exchange in anti-NMDAR encephalitis (systematic literature review). 71 articles were identified (mostly retrospective), reporting a total of 242 children treated with therapeutic plasma exchange for anti-NMDAR encephalitis (73.2%, 93/127 females; median age at onset 12 years, range 1-18). Median time to immunotherapy was 21 days (range 0-190). In most cases, therapeutic plasma exchange was given with steroids and intravenous immunoglobulin (69.5%, 89/128), or steroids only (18%, 23/128); in a minority, it was associated with intravenous immunoglobulin only (7%, 9/128), or was the only first-line treatment (5.5%, 7/128). In 54.5% (65/119), therapeutic plasma exchange was the third treatment after steroids and intravenous immunoglobulin, in 31.1% (37/119) the second after steroids or intravenous immunoglobulin; only in 14.3% (17/119) was it the first treatment. Second-line immunotherapies were administered in

71.9% (100/139). Higher rates of full/substantial recovery at follow-up were observed with immunotherapy given ≤30 days from onset (69.4%, 25/36) compared to later (59.2%, 16/27), and when therapeutic plasma exchange was associated with steroids (66.7%, 70/105) rather than not (46.7%, 7/15). Significant adverse reactions to therapeutic plasma exchange were reported in 6 patients.

3.3.4 Rituximab in paediatric neuromyelitis optica spectrum disorders (international retrospective observational study). 16 patients treated with at least two courses of rituximab for neuromyelitis optica were included (14 females; mean age 9.6 years, range 1.8-15.3). The patients had a mean of 6.1 events (range 1-11) during a mean follow-up of 6.1 years (range 1.6-13.6), and received a total of 76 rituximab courses (mean 4.7, range 2-9) in 42.6-year cohort treatment. Before rituximab, 62.5% received azathioprine, mycophenolate mofetil or cyclophosphamide. Mean time from rituximab to last documented B cell depletion and first repopulation was 4.5 and 6.8 months respectively, with large inter-patient variability. Earliest repopulations (2.7 and 2.9 months) occurred with the lowest rituximab doses. Significant reduction between pre and post rituximab annualized relapse rate (ARR) was observed (p=0.003). During rituximab, 6 patients were relapse-free, although 21 relapses occurred in 10 patients, including 13 'repopulation', 3 'depletion', and 4 'depletion failure-related relapses'. Of the 13 'repopulation relapses', 4 had CD19 10-50x10^6cells/L, 10 inadequate monitoring (≤1 CD19 in the 4 months before relapses), and 5 delayed re-dosing ≥10 days after repopulation detection.

3.3.5 Mycophenolate mofetil, azathioprine and methotrexate in anti-NMDAR encephalitis (systematic literature review). 76 patients treated with mycophenolate mofetil/azathioprine/methotrexate for paediatric-onset anti-NMDAR encephalitis were included (age range at onset 0.8-18 years; 69.7% females; 49.1% had ≥1 relapse), reported in 37 articles. Mycophenolate mofetil was used in 53.9%, azathioprine in 25%, methotrexate in 15.8%; an additional 5.3% received two among mycophenolate mofetil/azathioprine/methotrexate. Mycophenolate mofetil/azathioprine/methotrexate were not preceded by any second-line therapy (rituximab/cyclophosphamide) in 47.7%, and were administered only after relapses in 46.8%. Among the subgroup treated with mycophenolate mofetil/azathioprine/methotrexate after the first event, relapses occurred in 8.3% only. Time on mycophenolate mofetil/azathioprine/methotrexate

was median 9 months (range 1-48). Median annualised relapse rate was 0.45 (mean 1, range 0-6.67) before mycophenolate mofetil/azathioprine/methotrexate (excluding onset), and 0 (mean 0.06, range 0-1.3) during/after mycophenolate mofetil/azathioprine/methotrexate. Adverse reactions were reported only for mycophenolate mofetil (cytomegalovirus colitis and respiratory infection; grade 3 Common Terminology Criteria for Adverse Events v4.0). Relapse rate was significantly higher in patients started on first immune therapy (any) >30 days after onset (85.7%) compared to those treated early (31.2% (p=0.0272).

3.3.6 Mycophenolate mofetil in paediatric autoimmune and immune-mediated central nervous system conditions (international retrospective observational study). 44 children were included (30/44, 68.2% females). 43.2% (19/44) had proven or suspected autoimmune encephalitis, 31.8% (14/44) autoimmune inflammatory demyelinating CNS diseases, and 25% (11/44) other autoimmune/immune-mediated CNS conditions. Worst mRS was median 4 (range 2-6). Disease course was relapsing in 52.3% (23/44), monophasic in 38.6% (17/44), and chronic/chronic-progressive in 9.1% (4/44). Before mycophenolate mofetil, all patients received first-line (steroids: 44/44, 100%; intravenous immunoglobulin: 23/44, 52.3%; plasma exchange: 14/44, 31.8%) and 38.6% (17/44) second-line immune therapies (cyclophosphamide: 12/44, 27.3%; rituximab: 6/44, 13.6%). Median age at mycophenolate mofetil commencement was 9.3 years (range 1.4-16.4). Mycophenolate mofetil was started at median 9.5 months from onset (range 1-127; ≤6 months in 31.8%, 14/44). In 55% (22/40) of patients, mycophenolate mofetil was started only after ≥2 events had occurred. Median duration of treatment with mycophenolate mofetil was 18 months (mean 23.2, range 0.3-73). Median annualised relapse rate (excluding patients with chronic/chronic-progressive disease) was 0.52 (mean 0.86, range 0-3) before mycophenolate mofetil (excluding first events), and 0 (mean 0.36, range 0-4.64) during mycophenolate mofetil. 20.5% (8/39) patients relapsed during mycophenolate mofetil; compared to patients who did not relapse (31/49, 79.5%), these patients were younger (median age at onset 4.2 years versus 7.6), were more frequently females (8/8, 100% versus 21/31, 67.7%), had lower rate of second-line treatments before mycophenolate mofetil (1/8, 12.5% versus 15/31, 48.4%), a later commencement of mycophenolate mofetil (>6 months after onset in 7/8, 87.5% versus 22/35, 58.1%), and more frequently they were started on mycophenolate mofetil only after ≥2 events had occurred (7/8, 87.5% versus 14/35, 45.2%). Adverse reactions to

mycophenolate mofetil occurred in 18.2% (8/44) of cases (6/8: grade 2, 2/8: grade 3 Common Terminology Criteria for Adverse Events v4.0).

4. Conclusion. The present thesis is a collection of ten works exploring several aspects of the clinical and therapeutic decision-making in paediatric autoimmune and immune-mediated inflammatory conditions. A growing array of immune therapies are becoming available in paediatric neurology, also derived from the experience in immune modulation from other fields of paediatrics and in adult patients. While quality data and definite recommendations are generally lacking, there are common themes emerging, such as the utility of early and aggressive immune therapy in certain clinical situations, such as in autoimmune encephalitis. The use of immune therapy is still characterised by a great heterogeneity between physicians in many neurological conditions, for examples as regards therapeutic plasma exchange and steroid sparers in anti-NMDAR encephalitis, reflecting not only the lack of definite recommendations, but also different treating habits and potential practical difficulties, such as with therapeutic plasma exchange in children and uncooperative patients. Even when recommendations do exist, such as for the use of intravenous immunoglobulin in neurology, current practice is not always adherent to the guidelines, suggesting both the need for greater adherence to existing recommendations and the need for recommendations to be updated to accommodate emerging indications. In other cases, finally, the utility and safety of treatments such as steroid sparing agents warrants further investigations in several fields of paediatric neurology, such as in anti-NMDAR encephalitis. In all cases, both currently accepted and future potential agents have adverse effects, which can be severe. A comprehensive understanding of the therapeutic aspects should not go without the ability to understand each clinical situation in all its facets, taking into considerations not only potential effects, adverse reactions and mechanisms of treatment agents, but also the pathophysiology, the severity of the acute disease, the risk of relapses and of permanent disability, in a complex 'risk-versus-benefit' determination and a tailored approach

LIST OF ACRONYMS AND ABBREVIATIONS

Ab = antibody

AchR = acetylcholine receptor

AED = antiepileptic drugs

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

ANA = antinuclear antibodies

Anti-NMDAR = anti-N-methyl-D-aspartate receptor

ARR = annualised relapse rate

AQP4 = aquaporin-4

AZA = azathioprine

Caspr2 = contactin-associated protein-2

CNS = central nervous system

CRMP5 = collapsin response-mediator protein 5

CSF = cerebrospinal fluid

CTCAE = Common Terminology Criteria for Adverse Events

CYC or CPA = cyclophosphamide

D2R = dopamine-2 receptor

DNET = dysembryoplastic neuroepithelial tumour

DPPX = dipeptidyl-peptidase-like protein-6

EDSS = Kurtzke Expanded Disability Status Scale

EE = epileptic encephalopathy

EEG = electroencephalogram

F = females

FBDS = faciobrachial dystonic seizures

GABAAR = γ-aminobutyric acid-A receptor

GABABR = γ-aminobutyric acid-B receptor

GAD = glutamic acid decarboxylase

GC = glucocorticoid

GlyR = glycine receptor

GR = glucocorticoid receptor

HEK293 = human embryonic kidney cells

HSE = herpes simplex encephalitis

HSV = herpes simplex virus

IL = interleukin

IT = immune therapy

IVIG = intravenous immunoglobulin

IVMP = intravenous methylprednisolone

LE = limbic encephalitis

LGI1 = leucine-rich, glioma-inactivated protein-1

M = males

MG = myasthenia gravis

mGluR5 = metabotropic glutamate receptor 5

MMF = mycophenolate mofetil

MOG = myelin oligodendrocyte glycoprotein

MRI = magnetic resonance imaging

mRS = modified Rankin Scale

MS = multiple sclerosis

MTX = methotrexate

MUSK = muscle-specific tyrosine kinase

n.a. = not available

ON = optic neuritis

OP = oral prednisone

PCR = polymerase chain reaction

PERM = progressive encephalomyelitis with rigidity and myoclonus

RRMS = relapsing-remitting multiple sclerosis

RTX = rituximab

SCLC = small cell lung cancer

SOX1 = Sry-like high mobility group box 1

SPS = stiff-person-syndrome

TNF-α = tumor necrosis factor α

TPE = therapeutic plasma exchange

TPO = thyroid peroxidase

VGCC = voltage-gated calcium channels

VGKC = voltage-gated potassium channel

1. INTRODUCTION

1.1 Context

This PhD thesis is the final result of an interest in the field of paediatric neuroimmunology started during the training in paediatric neurology at the Department of Women's and Children's Health in Padua, Italy (2010-2015), and developed during my PhD at the University of Padua, Italy, and at the Children's Hospital at Westmead, Sydney, Australia (2014-2017).

During my training in paediatric neurology in Padua, I was first exposed to the diagnostic challenges and the therapeutic decision making for children with autoimmune and immune-mediated neurological disease, in a field that was moving forward quickly - as it still is - in terms of disease definition and classification, biomarker identification, and therapeutic possibilities. In particular, the opportunity to take care of the first few patients with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis in our Department during my first years of training ended up being a clinical experience that would stick with me later on. Thereafter, a research interest in paediatric neuroimmunology, also led by my mentor Dr. Stefano Sartori, naturally sprouted, and rooted itself into my PhD project, which started in November 2014. Dr. Stefano Sartori has been sharing with me his broad knowledge in paediatric neurology and neuroimmunology, his intuitions, his enthusiasm and any research opportunities he could. In this context, I also had the invaluable opportunity to spend nearly two years under the supervision of prof. Russell C. Dale in Sydney, Australia, where I gained experience in clinical and research aspects in paediatric neuroimmunology. This deepened and developed the theme of immune therapy, which runs through my thesis. Most important of all - and not irrelevant to the scientific work - in Sydney I was overwhelmed by the generosity and support provided by prof. Russell C. Dale and his peers. I gratefully consider him to be my second mentor.

1.2 Introduction to the content of the thesis

Paediatric neuroimmunology is a rapidly evolving field in a lot of ways. Firstly, clinical-radiological phenotyping and biomarker development have been allowing for re-discussion and re-classification of old clinical entities, and characterisation of new clinical forms. For example, the identification of neuromyelitis optica (NMO) IgG in 2004 [Lennon, 2004] confirmed the clinical suspicion that NMO was a different disease to multiple sclerosis, as initially thought. On the other hand, autoantibodies targeting neuronal cell surface proteins have been identified in the last years in cases of encephalitis which were previously unexplained. The first of this novel class was identified in 2007, targeting the NMDAR [Dalmau, 2007], and was followed by the subsequent identification of antibodies against a vast array of other neuronal surface antigens. Similarly, a new subclass of acquired central nervous system (CNS) demyelinating syndromes is being delineated thanks to the identification of myelin oligodendrocyte glycoprotein (MOG) antibodies [Hacohen, 2015; Hennes, 2017].

Moreover, the expanding field of immunotherapeutics represents the natural counterpart to the efforts in clinical-radiological and biomarker phenotyping in autoimmune and immune-mediated diseases. A rapidly growing armamentarium is indeed now available in this field, especially with regards to the advent of new drugs such as monoclonal antibodies. However, there are some constraints in this context. Namely, the limited knowledge of the pathophysiology for several autoimmune and immune-mediated diseases, as well as of the complete mechanisms of action for many of these immune therapy agents. Besides, since autoimmune and immune-mediated conditions are relatively rare and, as said before, many have been described only recently, literature is lacking of quality, solid data on efficacy and tolerability of immune therapy in these conditions, especially in paediatric age.

In this context, the present PhD thesis is meant to explore the field of clinical and therapeutic decision making in paediatric autoimmune and immune-mediated disease. Specifically, the thesis is articulated through a collection of ten works exploring three main areas, covered in sections 3.1 to 3.3:

- *Section 3.1: available immunotherapeutic agents and their mechanisms of action*;
- *Section 3.2: immune therapy in autoimmune encephalitis*: in particular, investigating the available evidence in the literature on the use of immune therapy in autoimmune encephalitis (section 3.2.1), the clinical characteristics and outcome, also with regards to treatment, in the

Italian cohort of paediatric anti-NMDAR encephalitis (section 3.2.2), and those of the literature cohort of patients with anti-NMDAR encephalitis occurring after herpes virus encephalitis (section 3.2.3);

- *Section 3.3: modes of use, efficacy and tolerability of individual immune therapeutic agents in different clinical situations in paediatric neurology*: intravenous immunoglobulin in Sydenham's chorea (section 3.3.1); intravenous immunoglobulin in paediatric neurology (section 3.3.2); therapeutic plasma exchange in anti-NMDAR encephalitis (section 3.3.3); rituximab in neuromyelitis optica spectrum disorders (section 3.3.4); mycophenolate mofetil, azathioprine and methotrexate in anti-NMDAR encephalitis (section 3.3.5); mycophenolate mofetil in paediatric autoimmune and immune-mediated CNS conditions (section 3.3.6).

References

Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.

Hacohen Y, Absoud M, Deiva K, Hemingway C, Nytrova P, Woodhall M, Palace J, Wassmer E, Tardieu M, Vincent A, Lim M, Waters P. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. Neurol Neuroimmunol Neuroinflamm. 2015 Mar 12;2(2):e81.

Hennes EM, Baumann M, Schanda K, Anlar B, Bajer-Kornek B, Blaschek A, Brantner-Inthaler S, Diepold K, Eisenkölbl A, Gotwald T, Kuchukhidze G, Gruber-Sedlmayr U, Häusler M, Höftberger R, Karenfort M, Klein A, Koch J, Kraus V, Lechner C, Leiz S, Leypoldt F, Mader S, Marquard K, Poggenburg I, Pohl D, Pritsch M, Raucherzauner M, Schimmel M, Thiels C, Tibussek D, Vieker S, Zeches C, Berger T, Reindl M, Rostásy K; BIOMARKER Study Group. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. Neurology. 2017 Aug 29;89(9):900-908.

Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinshenker BG. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 2004 Dec 11-17;364(9451):2106-12.

2. METHODS

The present PhD thesis is articulated into sub-projects that explore the theme of clinical and therapeutic decision making in paediatric autoimmune and immune-mediated disease, as illustrated in sections 3.1 to 3.3.

Study period and setting. The studies were carried out between 2014 and 2017 at the Department of Women's and Children's Health in Padua, Italy, under the supervision of Dr. Stefano Sartori and of Prof. Giorgio Perilongo, and at the Children's Hospital at Westmead, Sydney, Australia, under the supervision of Prof. Russell C. Dale.

Study designs. The study design of the projects include six literature reviews (sections 3.1, 3.2, 3.4, 3.5, 3.7, 3.9) and four original studies with observational retrospective design (sections 3.3, 3.6, 3.8, 3.10). The study designs are detailed below for each individual project:

- *Section 3.1.1: Immune therapeutic agents and their mechanisms of action:* literature review.
- *Section 3.2.1: Autoimmune encephalitis with antibodies targeting neuronal surface antigens:* systematic literature review.
- *Section 3.2.2: Clinical and therapeutic aspects of the Italian cohort of paediatric anti-NMDAR encephalitis*: national retrospective observational study.
- *Section 3.2.3: Herpes simplex virus-induced anti-NMDAR encephalitis:* systematic literature review.
- *Section 3.3.1: Intravenous immunoglobulin in Sydenham's chorea:* systematic literature review.
- *Section 3.3.2: Intravenous immunoglobulin in paediatric neurology*: single-center retrospective observational study.
- *Section 3.3.3: Therapeutic plasma exchange in anti-NMDAR encephalitis:* systematic literature review.
- *Section 3.3.4: Rituximab in neuromyelitis optica spectrum disorders*: international retrospective observational study.
- *Section 3.3.5: Mycophenolate mofetil, azathioprine and methotrexate in anti-NMDAR encephalitis:* systematic literature review.

- *Section 3.3.6: Mycophenolate mofetil in paediatric autoimmune and immune-mediated central nervous system conditions*: international retrospective observational study.

Statistical analysis. Statistical analysis was carried out when appropriate, as specified in the Methods section for each individual study (Section 3.2.3: Herpes simplex virus-induced anti-NMDAR encephalitis; Section 3.3.4: Rituximab in neuromyelitis optica spectrum disorders).

Ethics approval. Ethics committee was involved when appropriate (Section 3.3.2: Intravenous immunoglobulin in paediatric neurology; Section 3.3.4: Rituximab in neuromyelitis optica spectrum disorders).

State of advancement of the projects. Most of the projects have been concluded (sections 3.1.1 to 3.3.4) [Nosadini, 2017; Nosadini, 2015; Sartori, 2015; Nosadini, 2017; Mohammad, 2015; Nosadini, 2016; Suppiej, 2016; Nosadini, 2016], whereas the systematic literature review on mycophenolate mofetil, azathioprine and methotrexate in paediatric anti-NMDAR encephalitis (section 3.3.5) and the original study on children with paediatric CNS autoimmune or immune-mediated inflammatory diseases treated with mycophenolate mofetil (section 3.3.6) are still in progress.

References

Mohammad SS, Nosadini M, Grattan-Smith P, Dale RC. Intravenous immunoglobulin in acute Sydenham's chorea: A systematic review. J Paediatr Child Health. 2015 Dec;51(12):1235-8.

Nosadini M, Alper G, Riney CJ, Benson LA, Mohammad SS, Ramanathan S, Nolan M, Appleton R, Leventer RJ, Deiva K, Brilot F, Gorman MP, Waldman AT, Banwell B, Dale RC. Rituximab monitoring and redosing in pediatric neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm. 2016 Jan 21;3(1):e188.

Nosadini M, Mohammad SS, Corazza F, Ruga EM, Kothur K, Perilongo G, Frigo AC, Toldo I, Dale RC, Sartori S. Herpes simplex virus-induced anti-N-methyl-d-aspartate receptor encephalitis: a systematic literature review with analysis of 43 cases. Dev Med Child Neurol. 2017 Aug;59(8):796-805.

Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother. 2015;15(12):1391-419.

Nosadini M, Mohammad SS, Suppiej A, Sartori S, Dale RC; IVIG in Neurology Study Group. Intravenous immunoglobulin in paediatric neurology: safety, adherence to guidelines, and long-term outcome. Dev Med Child Neurol. 2016 Nov;58(11):1180-1192.

Nosadini M, Sartori S, Sharma S, Dale RC. Immunotherapeutics in Pediatric Autoimmune Central Nervous System Disease: Agents and Mechanisms. Semin Pediatr Neurol. 2017 Aug;24(3):214-228.

Sartori S, Nosadini M, Cesaroni E, Falsaperla R, Capovilla G, Beccaria F, Mancardi MM, Santangelo G, Giunta L, Boniver C, Cantalupo G, Cappellari A, Costa P, Dalla Bernardina B, Dilena R, Natali Sora MG, Pelizza MF, Pruna D, Serino D, Vanadia F, Vigevano F, Zamponi N, Zanus C, Toldo I, Suppiej A. Paediatric anti-N-methyl-D-aspartate receptor encephalitis: The first Italian multicenter case series. Eur J Paediatr Neurol. 2015 Jul;19(4):453-63.

Suppiej A, Nosadini M, Zuliani L, Pelizza MF, Toldo I, Bertossi C, Tison T, Zoccarato M, Marson P, Giometto B, Dale RC, Sartori S. Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review. Brain Dev. 2016 Aug;38(7):613-22.

3. RESULTS

3.1 Immune therapy agents and their mechanisms of action

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Immunotherapeutics in Pediatric Autoimmune Central Nervous System Disease: Agents and Mechanisms

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Beyond the major advances produced by careful clinical-radiological phenotyping and biomarker development in autoimmune central nervous system disorders, a comprehensive knowledge of the range of available immune therapies and a deeper understanding of their action should benefit therapeutic decision-making. This review discusses the agents used in neuroimmunology and their mechanisms of action. First-line treatments typically include corticosteroids, intravenous immunoglobulin, and plasmapheresis, while for severe disease second-line "induction" agents such as rituximab or cyclophosphamide are used. Steroid-sparing agents such as mycophenolate, azathioprine, or methotrexate are often used in potentially relapsing or corticosteroid-dependent diseases. Lessons from adult neuroimmunology and rheumatology could be translated into pediatric autoimmune central nervous system disease in the future, including the potential utility of monoclonal antibodies targeting lymphocytes, adhesion molecules for lymphocytic migration, cytokines or their receptors, or complement. Finally, many agents used in other fields have multiple mechanisms of action, including immunomodulation, with potential usefulness in neuroimmunology, such as antibiotics, psychotropic drugs, probiotics, gut health, and ketogenic diet. All currently accepted and future potential agents have adverse effects, which can be severe; therefore, a "risk-versus-benefit" determination should guide therapeutic decision-making.
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Introduction

There is increasing interest in immune-mediated brain disease. The recent descriptions of autoantibody biomarkers associated with encephalitis and demyelination has put "neuroimmunology" on the map, and as a "treatable group of conditions", they should be high on the differential list of any child with a new presentation or change in neurological function. Immune-mediated brain conditions can be separated according to syndrome such as autoimmune encephalitis, autoimmune demyelination, or autoimmune neuropsychiatric syndrome. Unfortunately, other than autoantibody biomarkers, our ability to define dominant immunopathologic processes in individual patients is limited, and so it is often necessary to consider that multiple immune processes (ie, T cell, B cell, autoantibody, and innate immunity) are operating in individual patients. Indeed, even in immune disorders with pathogenic autoantibodies such as aquaporin-4 (AQP4) antibody–associated neuromyelitis optica, there is strong evidence of the role of B cells, T cells, eosinophils, neutrophils, cytokines, chemokines, as well as

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autoantibodies.[1] Therefore, these disorders are often immunologically complex; and hence, the approach may need to be flexible. Indeed, there are many anecdotal experiences of patients with autoimmune central nervous system (CNS) diseases who do not respond to steroids (glucocorticoids [GCs]), but who do respond to intravenous immunoglobulin (IVIG), and likewise patients who do not respond to cyclophosphamide (CPA) who then respond to rituximab (RTX). Until there are improved molecular techniques to define the immune system in individual patients, it will be necessary to be flexible in therapeutic choices.

This review therefore is intended to help the clinician appreciate the mechanisms of actions of drugs, and to facilitate link the likely dominant pathologic process, the possible immune mechanism, and the mechanisms of drug action (described below and in Table 1). In conditions where there is clear evidence that there is an "autoaggressive" process, and a potentially poor prognosis, then immune suppression is warranted. In other syndromes, such as pediatric acute-onset neuropsychiatric syndromes, where the exact immune mechanism is unclear but an immune dysregulation process seems likely, then immune modulation (±immune suppression) may be indicated if the disease is impairing.

This review therefore discusses agents that are generally considered "first line" such as GCs, IVIG, and therapeutic apheresis (TA) in the treatment of suspected or confirmed autoimmune or inflammatory brain disease. Secondly, we will describe immune suppressants, such as RTX and CPA that are used as "second-line induction or rescue" agents in inflammatory or autoimmune CNS disease. We will also refer to mycophenolate mofetil (MMF) and azathioprine (AZA), which are typically used in GC responsive conditions as "steroid sparers", or early in the disease course when it is considered likely to be immune responsive with high risk of relapse (such as AQP4 antibody–associated neuromyelitis optica spectrum disorders). We will also discuss agents that are used for immune suppression effective in immune-mediated brain disease, such as tacrolimus, and other agents such as the protease inhibitor bortezomib and compounds that modulate signaling (ruxolitinib and other Janus kinase [JAK] inhibitors). In addition, we will briefly review "disease modifying therapies" used in multiple sclerosis.

We will consider new emerging monoclonal therapies that have been developed for the rheumatology or immunology market that target specific lymphocytes (ocrelizumab [OCR], ofatumumab, and alemtuzumab), complement (eculizumab), cytokines or cytokine receptors (tocilizumab, daclizumab and the tumor necrosis factor α [TNF-α] inhibitors infliximab, and adalimumab) or affect lymphocyte adhesion across vessel walls (natalizumab). Other nonmonoclonal compounds that target cytokines will also be reviewed, such as anakinra (anti-IL1) and etanercept (TNF-α inhibitor). All of these agents have potential for use in neuroinflammatory disorders although improved understanding of the underlying immunopathogenesis is essential to make clearer "therapeutic decisions". We will also discuss commonly used licensed drugs that have immune modulatory properties, but their use in immune-mediate brain disease is not well established, which include antibiotics such as minocycline and other macrolides, nonsteroidal anti-inflammatories, psychotropic drugs, and also "naturopathic" agents such as curcumin. These agents lack an evidence base for effect in neuroinflammation, but so do all of the "conventional therapies" described earlier. And finally, it is likely that the role of gut health, gut immunity, and the microbiome will become an increasing focus in immune dysregulation disorders in general.

A General Approach to Therapeutic Decision-Making

Until we have a better understanding of autoimmune and inflammatory CNS disease, it will be necessary to use broad immune suppressive or immune modulatory agents such as GCs or IVIG. For this reason, there is often a "common approach" to the first- and second-line treatment of these conditions, regardless of the specific syndrome. However, in the future, with improved understanding of the pathophysiology of disease, it can be hoped that there will be "targeted" therapies that could be more effective, and hopefully safer (see examples of option in "future therapies" below). The other unaddressed issue surrounds the fact that most therapies target peripheral immune cells or proteins, rather than the immune system in the brain. The role of the blood-brain barrier, and the relative importance of therapies gaining access to the CNS are important yet unanswered issues.

"First-Line Agents" for Classic Neuroinflammation

Glucocorticoids

GCs belong to the class of corticosteroids, which are steroid hormones produced in the adrenal cortex under the regulation of the hypothalamic-pituitary-adrenal axis. Beside GCs, corticosteroids include mineralocorticoids and androgens. GCs act via the nearly ubiquitous glucocorticoid receptor, and play a central role in numerous physiological functions, including homeostasis, inflammation, behavior, metabolism and immune function; GCs also have anti-inflammatory, immunosuppressive, antiproliferative, and vasoconstrictive properties.[2] Intravenous or oral GCs represent the mainstay of acute treatment in the vast majority of autoimmune and immune-mediated neurological conditions,[3-7] in view of their potent and wide actions on the immune system (Table 1).[8] High-dose intravenous methylprednisolone pulses (30/mg/kg) are generally given once daily for 3-5 days in acute diseases, sometimes followed by oral prednisone taper over weeks-months.[3-7] An alternative approach, rather than oral prednisolone taper, is to use "pulses" of GCs, such as monthly (3 days) intravenous methylprednisolone or 3-4 weekly (3 days) of oral dexamethasone.[9] Although most inflammatory disorders are treated with methylprednisolone/dexamethasone or prednisolone, adrenocorticotropic hormone has a role in moderate-severe opsoclonus myoclonus ataxia syndrome.[9] It is possible that the type of GCs

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Table 1 Summary of the Key Modes of Action and Principal Effects of the Main Immune Therapies in Neurologic Diseases

Immune Therapy	Key Mechanisms of Action in Neurologic Diseases	Targets and Effects
Glucocorticoids (GCs) Corticosteroids	*Genomic modes of action* Binding of the liganded GC receptor (GR) to positive (transactivation) or negative (transrepression) GC-response elements (GREs) within the DNA Liganded GR tethering and blocking of transcription factors, without contacting DNA Binding of the liganded GR to composite elements (DNA sequences containing both a GRE and a response element for a distinct transcription factor) *Non-genomic modes of action* GC intercalation into plasma membranes GC binding-mediated dissociation of heatshock proteins and other co-factors from the GR Interaction of the liganded GR with cytoplasmic signaling complexes and the mithocondria[8] *A unified model for GC-mediated regulation of the immune system* Besides immunosuppressive properties of GCs, there are also data supporting an immune-enhancing role of GCs: basal levels of GR signaling would sensitize cells to harmful stimuli, promoting the induction of an inflammatory response upon tissue insult; during the inflammatory state, however, stress-induced (or pharmacological) concentrations of GCs would restrain the immune response, thereby shortening the duration of the immune response[8]	Thymocytes and B cells are sensitive to GC-induced cell death GCs produce a decrease in T-cell activity by targeting dendritic cell,[8] downregulating the expression of MHC class II and of other co-stimulatory molecules and proinflammatory cytokines, and interfering with T cell receptor signaling GCs promote the expression of anti-inflammatory cytokines Pharmacological treatment with GCs is associated with reduced immunoglobulin concentrations, exception made for IgE
Intravenous immunoglobulin (IVIG) Preparation of polyclonal human immunoglobulins made from a pool of healthy donors	*$F(ab')_2$-dependent mechanisms:* Blockade of cell-cell interactions that are mediated by cell-surface receptors Neutralization of cytokines, complement, immune cell receptors and pathogenic circulating autoantibodies[10] *Fc-dependent mechanisms:* Competitive blockade of immune complement binding to low-affinity FcγRs Modulation of activating and inhibitory FcγR expression on innate immune effector cells and B cells Increased autoantibody clearance by FcRn saturation[10]	Antibody binding-mediated effects with neutralization of cytokines, complement, immune cell receptors, and pathogenic circulating autoantibodies

Table 1 (*continued*)

Immune Therapy	Key Mechanisms of Action in Neurologic Diseases	Targets and Effects
Therapeutic apheresis (TA)	*Therapeutic plasma exchange (TPE)*: blood is passed through a medical device separating plasma from other components of blood	Removal of antibodies and immune complexes Possible role on the removal of cytokines, soluble cytokine receptors, and soluble adhesion molecule, although the evidence on this is mixed[19]
Therapeutic plasma exchange and immunoadsorption	*Immunoadsorption (IA)*: plasma of the patient, after separation from the blood, is passed through a device with columns lined with immobilized antibodies or selective antigens, binding selected proteins and removing them from plasma[18]	
Rituximab (RTX) Chimeric B cell-depleting monoclonal anti-CD20 antibody	*B lymphocyte destruction mediated by binding to cell surface CD20 located on the B lymphocytes, through 3 main mechanisms*[23]: *Antibody-dependent cellular cytotoxicity:* Following binding to cells, antibodies recruit innate immune effector cells that express receptors for the Fc portion of the antibodies (FcγRs), which in turn trigger phagocytosis and cause release of cytotoxic substances *Complement-dependent cytotoxicity:* The classical pathway of the complement system is activated by antibody binding. The Fc portion of IgG binds to the complement C1q component, which triggers a proteolytic cascade to generate the membrane attack complex, which is responsible for eliminating target cells. *Induction of direct cell death:* Blocking of various survival signaling pathways; Downregulation of anti-apoptotic Bcl-2 proteins; Activation of the Fas-mediated pathway through upregulation of Fas receptor; Caspase-dependent and independent mechanism *Transient, dose-dependent decrease in T-cell inflammatory and proliferation capacity in response to "foreign" stimuli* (both by depriving B-cell antigen-presenting cells and through its direct effect on T cells)[24]	B cell depletion[23] Transient, dose-dependent T-cell inactivation: decreased inflammatory cytokine production, proliferation capacity and expression of T-cell activation markers[24]
Cyclophosphamide (CPA) Alkylating agent (prodrug of phoshoramide mustard)	Irreversible alkylation of DNA bases, with formation of DNA crosslinks resulting in impaired essential DNA processes such as DNA replication and/or transcription, eventually leading to cell apoptosis[30,31]	Autoimmune effector cells (T cells, B cells, and NK cells) are exquisitely sensitive to high-dose CPA, since aldehyde dehydrogenase (ALDH), the enzyme responsible for detoxification of CPA, is poorly expressed in lymphocytes[30]

Mycophenolate mofetil (MMF) Prodrug of mycophenolic acid (MPA), which acts as an inhibitor of inosine monophosphate dehydrogenase (IMPDH)	Inhibition of inosine monophosphate dehydrogenase (IMPDH), the rate-limiting enzyme in de novo synthesis of guanosine nucleotides[34]	Antiproliferative effects on T and B lymphocytes, monocytes, fibroblasts, endothelial, mesangial and vascular smooth cells Induction of apoptosis in lymphocytes, monocytes Induction of necrosis in lymphocytes Reduction of cytokine production by T lymphocytes, dendritic cells and endothelial cells Reduction of immunoglobulin production by B lymphocytes Reduction of chemotaxis to inflammation sites in monocytes and lymphocytes Inhibition of cell-cell interaction and endothelial adhesion in monocytes, dendritic cells, neutrophils and fibroblasts Other: inhibition of mast cell degranulation, of nitric oxide production by endothelial cells; suppression of fibroblast ability to migrate, adhere and heal wounds; inhibition of extracellular matrix production in human mesangial cells[33]
Azathioprine (AZA) Synthetic purine analog derived from 6-mercaptopurine	Mercaptopurine metabolites are incorporated into replicating DNA, halting replication, as well as blocking the pathway for purine synthesis. Cytostatic and immunosuppressive action[35]	Interference with T and B cell proliferation
Methotrexate (MTX) Antimetabolite, folic acid antagonist	*Inhibition of purine and pyrimidine synthesis (main antitumoral effect)* Inhibition of dihydrofolate reductase (DHFR) decreases tetrahydrofolate (THF) levels, which results in attenuated DNA/protein/lipid methylation Inhibition of thymidylate synthase (TS) interference with DNA synthesis Inhibitionof 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase blocks de novo purine synthesis *Suppression of transmethylation reactions with accumulation of polyamines* *Promotion of adenosine release with adenosine-mediated suppression of inflammation (main anti-inflammatory effect)* The released adenosine diminishes stimulated neutrophil adhesion By increasing intracellular AICAR accumulation, MTX increases adenosine concentration and diminishes leukocyte accumulation in inflammatory exudates[35]	Reduction of antigen-dependent T-cell proliferation, inhibition of T cell activation and suppression of intercellular adhesion molecule expression by T cells; increased CD95 sensitivity of activated T cells Selective downregulation of B cells

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that produces maximal effect is disease and patient dependent, but there is little data to comment on this further.

Intravenous Immunoglobulin

IVIG is a preparation containing polyclonal human G isotype immunoglobulins (IgG) made from a pool of plasma of thousands of healthy blood donors.[10,11] Plasma is obtained either by separation of whole blood or by plasmapheresis, and immunoglobulin is then extracted from other plasmatic proteins via fractionation.

While low-dose IVIG (~0.4 g/kg) is used as a replacement therapy in immune deficiencies, high doses of IVIG (1-2 g/kg) have anti-inflammatory and immunomodulatory actions, and have been used in autoimmune disorders for about forty years.[10] The extensive use of IVIG in clinical practice as an immunomodulatory agent is not mirrored by a comprehensive knowledge of the modes of action of IVIG. In view of the heterogeneity of autoimmune and immune-mediated conditions that respond to IVIG, it is indeed generally believed that IVIG modes of action may be manifold[10] (Table 1). High-dose IVIG is usually given in acute diseases (2 g/kg over 1-5 days),[12] while lower doses (0.4-1 g/kg in 1 day) are given in chronic treatments. However, it is sometimes observed that lower doses (0.4-1 g/kg) fail to produce immune modulation in severe disease, when higher doses (2 g/kg) should be considered, if agreeable to local guidelines. IVIG is an expensive treatment subject to increasing demand, and guidelines regulating IVIG use according to the evidence base have been created in different countries, to ensure its availability for patients who are most likely to benefit from the therapy.[12-17]

Therapeutic Apheresis

TA techniques most used in pediatric neurology include therapeutic plasma exchange (TPE) and immunoadsorption (IA) (Table 1). TPE is a procedure in which blood of the patient is passed through a medical device separating plasma from other components of blood.[18] Centrifugation- or, less frequently, filtration-based devices can be used for TPE.[19] When the plasma is removed, substances with a certain molecular weight or higher are filtrated, and compensation for protein loss is achieved through a replacement solution such as colloid (ie, albumin and/or plasma) or a combination of crystalloid/colloid solution. In IA, plasma of the patient, after separation from the blood, is passed through a device with columns lined with immobilized antibodies or selective antigens, binding selected proteins and removing them from plasma. In contrast to TPE, IA permits a more targeted removal of plasma proteins, allowing those unbound to return to the circulation.[20]

Most commonly the objective of TA is to remove suspected antibodies implicated in the pathogenesis of autoimmune disease, although TPE also works by removing from the circulation large-molecular-weight molecules other than immunoglobulins, such as immune complexes and complements. In acute disease, 5-7 exchanges are usually carried out over 10-14 days. Guidelines on the use of TA have been issued by the American Society for Apheresis every 7 years from 1986 to 2007, and subsequently every 3 years, most recently in 2010, 2013 and lastly in 2016 (Table 2).[18,21]

"Second-Line Induction Agents" for Severe Disease

Rituximab

RTX is a chimeric B cell-depleting monoclonal anticluster of differentiation 20 (CD20) antibody, initially developed to treat lymphoma, comprised of both mouse and human portions (Table 1). CD20 is a B-cell surface differentiation marker found on pre-B and mature B lymphocytes, which is lost as B cells differentiate into plasma cells (plasmablasts and plasmocytes) and is not found on other cell types or free in circulation. CD20 is involved in calcium transportation across cell membrane. The binding of RTX to cell surface CD20 located on the B lymphocytes results in destruction of the lymphocyte by different potential mechanisms, including antibody-dependent cytotoxicity or complement-dependent cytotoxicity, stimulation of apoptosis, or growth arrest.[22,23] Beside B-cell depletion, there are data suggesting that RTX may also induce substantial reversible T-cell depletion, mainly of CD4+ cells.[24,25] Indeed, part of the rapid responses to RTX seen in some patients may be related to direct B cell effects or B cell-T cell interaction effects, rather than "autoantibodies" per se.

RTX treatment regimens vary, although most frequent dose is 375 mg/m^2 weekly for 4 weeks. RTX treatment monitoring is via CD19 count, which should be done monthly after RTX administration,[26,27] as CD19 repopulation over the threshold of 10×10^6 cells/L has been associated to increased risk for relapses in severe autoimmune CNS disease such as AQP4 antibody–positive neuromyelitis optica.[26,28] CD20 is expressed during the midstages of ontogeny and virtually disappears at the plasma cell stage; CD19 expression mirrors CD20 expression and can, therefore, serve as a surrogate marker in patients with circulating RTX.[29]

Cyclophosphamide

CPA is an alkylating agent activated by cytochromes (P450) in the liver, whose active metabolite is phoshoramide mustard (Table 1). Alkylating agents are electrophilic entities that react with nucleophilic moieties of DNA or proteins resulting in the covalent transfer of an alkyl group. CPA cytotoxic effects derive from the ability of phoshoramide mustard to alkylate DNA bases, forming DNA crosslinks both between and within DNA strands (interstrand and intrastrand crosslinkages). This is irreversible and results in impaired essential DNA processes such as DNA replication or transcription, eventually leading to cell apoptosis.[30] The effects of CPA are cell cycle independent; however, as with all alkylating agents, rapidly proliferating cells are most sensitive.[31] Early hematopoietic stem cells are spared from CPA cytotoxicity because of their high levels of aldehyde dehydrogenase, an enzyme that confers resistance to the drug by detoxifying the active metabolite of CPA. Conversely, committed immune effector cells (T cells, B cells, and NK cells) are exquisitely sensitive to high-dose CPA because of

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Table 2 Neurologic Indications for Therapeutic Apheresis According to the Guidelines on the Use of Therapeutic Apheresis of the American Society for Apheresis[18]

Disease	TA Modality	Indication	Category, Grade*	Rationale for TA and Mechanism of Action
Acute disseminated encephalomyelitis (ADEM)	TPE	Steroid refractory	II, 2C	Removal of presumed pathogenic autoantibodies (potential candidate target of autoantibodies: myelin oligodendrocyte glycoprotein)
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome)	TPE	Primary treatment	I, 1A	Removal of autoantibodies damaging the peripheral nerve myelin (molecular mimicry?), and possibly of circulating immune complexes and of complement[18]
		After IVIG (2 g/kg)	III, 2C	
Chronic focal encephalitis (Rasmussen encephalitis)	TPE	–	III, 2C	Removal of presumed pathogenic autoantibodies to neural molecules, that may be produced in the CNS after cytotoxic T cell-mediated neuronal damage
Dermatomyositis/polymyositis	TPE		IV, 2B	Removal of autoantibodies such as ANA, anti-Ro, anti-La, and Sm, anti-ribonucleoprotein, or myositis-specific, that are commonly present, although not specific to the disease
	ECP		IV, 2C	
Hashimoto encephalopathy: steroid-responsive encephalopathy associated with autoimmune thyroiditis†	TPE	–	II, 2C	Removal of presumed pathogenic autoantibodies (anti-thyroid antibodies)
Multiple sclerosis	TPE	Acute CNS inflammatory demyelinating	II, 1B	Removal of presumed pathogenic autoantibodies, and/or immune complexes or modulating immune response[18]
	IA	Acute CNS inflammatory demyelinating	III, 2C	
	TPE	Chronic progressive	III, 2B	
Myasthenia gravis	TPE	Moderate-severe	I, 1C	Removal of autoantibodies (anti-AChR, anti-Musk)
	TPE	Pre-thymectomy	I, 1C	
Neuromyelitis optica spectrum disorders	TPE	Acute	II, 1B	Removal of anti-aquaporin 4 autoantibodies
	TPE	Maintenance	III, 2C	
N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis†	TPE	–	I, 1C	Removal of anti-NMDAR autoantibodies
Paraneoplastic neurological syndromes	TPE	–	III, 2C	Removal of autoantibodies (anti-Hu, anti-CV2/CRMP5, anti-Yo, anti-Tr, and anti-amphiphisin)
	IA	–	III, 2C	
Paraproteinemic demyelinating polyneuropahties/chronic acquired demyelinating polyneuropathies	TPE	Anti-MAG neuropathy	III, 1C	Removal of anti-MAG antibodies
	TPE	Multifocal Motor Neuropathy	IV, 1C	
	TPE	IgG/IgA	I, 1B	
	TPE	IgM	I, 1C	
	TPE	Multiple myeloma	III, 2C	
	IA	IgG/IgA/IgM	III, 2C	
Pediatric autoimmune neuropsychiatric disorders ssociated with streptococcal infections (PANDAS); Sydenham chorea	TPE	PANDAS exacerbation	II, 1B	Removal of (possible pathogenetic) autoantibodies (antineuronal, antibasal ganglia)
	TPE	Sydenham chorea, severe	III, 2B	

Table 2 (*continued*)

Disease	TA Modality	Indication	Category, Grade*	Rationale for TA and Mechanism of Action
Progressive multifocal leukoencephalopathy associated with natalizumab†	TPE	–	I, 1C	Removal of natalizumab, decrease in receptor saturation, restoration of leukocyte transmigration
Stiff-person syndrome	TPE	–	III, 2C	Removal of autoantibodies (anti-GAD)
Voltage-gated potassium channel (VGKC) antibodies	TPE	–	II, 2C	Removal of anti-VGKC autoantibodies
Category[18]	Description			
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other treatments			
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other treatments			
III	Optimum role of apheresis therapy is not established. Decision making should be individualized			
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances			
Recommendation[18]	Description		Methodological quality of supporting evidence	
Grade 1A	Strong recommendation, high-quality evidence		RCTs without important limitations or overwhelming evidence from observational studies	
Grade 1B	Strong recommendation, moderate-quality evidence		RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	
Grade 1C	Strong recommendation, low-quality or very low-quality evidence		Observational studies or case series	
Grade 2A	Weak recommendation, high-quality evidence		RCTs without important limitations or overwhelming evidence from observational studies	
Grade 2B	Weak recommendation, moderate-quality evidence		RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	
Grade 2C	Weak recommendation, low-quality or very low-quality evidence		Observational studies or case series	

ECP: extracorporeal photophoresis. (Modified with permission from Schwartz et al.[18])

*See bottom part of Table 2 for category and grade. (Adapted with permission from the Guidelines on the use of therapeutic apheresis of the American Society for Apheresis.[18])

†Hashimoto encephalopathy, N-methyl-d-aspartate receptor antibody encephalitis, and progressive multifocal leukoencephalopathy associated with natalizumab were the new neurologic diseases included in the last Guidelines on the use of therapeutic apheresis of the American Society for Apheresis.[18]

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their relatively low levels of aldehyde dehydrogenase.[32] CPA dose regimen usually is 750 mg/m^2 intravenously every month for 6 months.

Maintenance Therapy: Steroid-Sparing Drugs

Mycophenolate Mofetil

MMF is a prodrug of mycophenolic acid (MPA). MPA is a fermentation product of *Penicillium brevicompactum* and other analogue fungi, and acts as an inhibitor of inosine monophosphate dehydrogenase (IMPDH).[33] IMPDH is the rate-limiting enzyme in de novo synthesis of guanosine nucleotides, converting inosine monophosphate, produced from adenosine monophosphate by adenosine deaminase, in guanosine monophosphate.[34]

MPA effects on B and T lymphocytes represent the principal mechanism by which MMF exerts immunosuppressive action.[34] This is due to the fact that lymphocytes are more dependent on the synthesis of guanosine nucleotides than other cell types, and IMPDH is required for lymphocytic clonal expansion; moreover, MPA selectively targets the type II isoform of IMPDH, which is expressed in activated lymphocytes, rather than the type I (expressed in most cell types). Therefore, MPA has a more potent cytostatic effect on lymphocytes than other cells.[34] A vast repertoire of cells are targeted by MPA action, and its main effects include antiproliferative and proapoptitic effects, inhibition of chemotaxis, endothelial adhesion, and cell-cell interactions (Table 1).

Azathioprine

AZA is a synthetic purine analog derived from 6-mercaptopurine (Table 1). The AZA molecule contains the following 2 moieties: 6-mercaptopurine and an imidazole derivative. The immunosuppressive action of AZA depends on the synergistic cooperation of relatively weak cytostatic effect of low doses of 6-mercaptopurine and the chemosensitizing effect induced by highly reactive imidazole derivatives.[35] The active metabolites of AZA act by disrupting the function of endogenous purines. Mercaptopurine metabolites are incorporated into DNA, halting replication, as well as blocking the pathway for purine synthesis. AZA thus most strongly affects proliferating cells, such as the T cells and B cells of the immune system.

Methotrexate

Methotrexate (MTX) is an antimetabolite that interferes with the actions of folate in cellular synthesis.[36] MTX antagonizes the enzyme dihydrofolate reductase, resulting in the arrest of the synthesis of tetrahydrofolate and therefore preventing the synthesis of purines and pyrimidines. The major effect of MTX is therefore on more rapidly dividing cell systems, typically the gut lining and bone marrow, and this is the main antitumoral action of MTX.[36] On the contrary, anti-inflammatory actions of MTX are thought to be exerted through multiple mechanisms, especially by increase in extracellular adenosine release (Table 1).[37]

Tacrolimus (FK-506)

Tacrolimus is an immune suppressive agent, a macrolide calcineurin inhibitor that acts by inhibiting the production of interleukin (IL)-2.[38] It is commonly used in organ transplant patients and in some autoimmune diseases, such as ulcerative colitis. Among neurologic conditions, tacrolimus has been shown to be of benefit in Rasmussen encephalitis[39] and neuromyelitis optica.[40] Calcineurin inhibitor cyclophosphamide is another immune suppressant, although concerns about serious adverse events, such as impaired fertility and late development of malignancy, are of greater concern in children than in adults.[41,42]

Other Agents

Bortezomib

Bortezomib is a protease inhibitor, developed for cancer treatment, which inhibits proinflammatory cytokine cascades and reduces plasma cell production and therefore autoantibody production, and has been recently used in adults with anti-*N*-methyl-D-aspartate encephalitis who were refractory to conventional treatment.[43,44]

Oral Agents That Modulate Cell Signaling

JAK is a key enzyme involved in cell signaling and agents targeting JAK (such as ruxolitinib and tofacitinib) have anti-inflammatory properties by reducing cytokine production. These agents are used to treat myelofibrosis, and have emerging roles in the treatment of rheumatoid arthritis, ulcerative colitis and other autoimmune diseases, and may have a role in genetic autoinflammatory disorders.[45,46]

Future Utility of Monoclonal Antibodies

Monoclonal antibodies that have theoretical use in pediatric autoimmune CNS disease have been developed for oncology (ie, RTX), rheumatology (ie, etanercept), or the treatment of adult neurological disease (ie, natalizumab in multiple sclerosis). With improved understanding of pathophysiology and biomarkers, some of these agents could theoretically be used in the future in pediatric autoimmune CNS disease. A few examples demonstrating the potential current and future utility of monoclonal antibodies are described, and listed in Table 3.[27,47-62]

Monoclonal Antibodies That Target Lymphocytes

Ocrelizumab (OCR) is a humanized monoclonal anti-CD20 antibody that has the same therapeutic target as RTX,[51] which has shown efficacy in multiple sclerosis.[47,49,51] Ofatumumab is

Table 3 Monoclonal Antibodies Used in Neurology (Selected Agents)

Monoclonal Antibody	H/h/C	Target and Mechanism of Action	Main Uses in Central Nervous System Autoimmune and Immune-Mediated Conditions
Monoclonal antibodies targeting lymphocytes			
Alemtuzumab	h	*Target*: CD52 (expressed on the cell surface of lymphocytes and at lower levels on monocytes, macrophages, eosinophils, and natural killer [NK] cells) *Mechanism*: Targeting of the CD52 molecule, which is present on the cell surface of lymphocytes and at lower levels on monocytes, macrophages, eosinophils, and natural killer (NK) cells. The exact physiologic function of CD52 is largely unknown but is thought to be involved in T cell activation, cell migration, and induction of regulatory T cells. By binding to CD52 on the cell surface, alemtuzumab causes long-lasting depletion of lymphocytes and monocytes mediated by antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis[53]	FDA-approved for MS EMA-approved for MS patients who have had an inadequate response to ≥2 drugs indicated for the treatment of MS[50-53]
Rituximab	C	*Target*: CD20 (expressed on pre-B and mature B lymphocytes) *Mechanism*: B lymphocyte destruction and transient decrease in T-cell inflammatory and proliferation capacity in response to ''foreign'' stimuli (Table 1)	MS, NMO spectrum disorders, anti-*N*-methyl-D-aspartate receptor encephalitis, opsoclonus myoclonus ataxia syndrome, NPSLE[9,26,49]
Ocrelizumab	h	*Target*: CD20, same epitope as rituximab (expressed on pre-B and mature B lymphocytes) *Mechanism*: Depletion of CD20 expressing B-cells through antibody-dependent cell-mediated phagocytosis and cytotoxicity, as well as complement-mediated cytolysis[50]	Under consideration for approval for MS by the FDA and the EMA[47,50-53]
Ofatumumab	H	*Target*: CD20, different epitope as rituximab andocrelizumab (expressed on pre-B and mature B lymphocytes) *Mechanism*: pronounced complement-mediated cytotoxicity in vitro	Relapsing-remitting MS. Safer choice than natalizumab in JC-virus positive patients[51,52]
Monoclonal antibodies targeting complement			
Eculizumab	h	*Target*: complement protein C5 *Mechanism*: Targeting of the cleavage of C5, preventing the release of C5a and activation of the terminal complement pathway	NMO spectrum disorders[48]
Monoclonal antibodies targeting lymphocyte adhesion			
Natalizumab	h	*Target*: α4 integrin (a component of the very late antigen (VLA)-4 present on lymphocytes) *Mechanism*: Inhibition of lymphocyte migration across the blood-brain barrier by blocking a4 integrin, a component of the very late antigen (VLA)-4 present on lymphocytes, and thereby inhibiting interaction between VLA-4 and the ligand vascular cell adhesion molecule (VCAM) on endothelial cells[53]	FDA-approved for relapsing MS EMA-approved as a second-line treatment in patients with highly active relapsing-remitting MS in whom the disease remains active despite appropriate treatment with ≥1 other DMT or as first treatment in patients with severe disease[53]
Monoclonal antibodies targeting cytokines or cytokine receptors			
Tocilizumab	h	*Target*: IL-6 receptor *Mechanism*: Binding to the IL-6 binding site of human IL-6 receptor and competitively inhibits IL-6 signaling. Tocilizumab ameliorates inflammatory manifestations and normalizes acute phase protein levels[58]	Autoimmune encephalitis refractory to rituximab,[59] NMO[60]

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Daclizumab	h	*Target*: α subunit (CD25) of the IL-2 receptor *Mechanism*: Results of blockage of CD25[62]: on T cells, decreases stimulation of autoreactive T cells by autocrine IL-2; increased availability of soluble IL-2 to the cells carrying intermediate-affinity IL-2 receptor, such as CD56 bright NK cells, leads to an expansion of this cell population; on dendritic cells, prevents a "trans-presentation" of this α chain to T cells carrying intermediate affinity IL-2 receptor and thus formation of high-affinity IL-2 receptor, which would result in T-cell stimulation; results in a reduction of lymphoid tissue inducers in the CNS.	MS[61,62]
TNF-α inhibitors (Infliximab, Adalimumab)	C (Infliximab) H (Adalimumab)	*Target*: Tumor necrosis factor α (TNF-α) *Mechanism*: Prevention of the binding of TNF-α to its receptors, resulting in neutralization of TNF-α proinflammatory effects (which include induction of proinflammatory cytokines, enhancement of leukocyte migration, proliferation of immune cells, and induction of acute phase reactants and tissue damage)	Infliximab: Neurosarcoidosis,[64] limbic encephalitis[65] Adalimumab: Rasmussen encephalitis[66]

C, chimeric; CD, cluster of differentiation; DMT, disease-modifying therapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; H, human; h, humanized; JC, John Cunningham; MS, multiple sclerosis; NK, natural killer; NMO, neuromyelitis optica; NPSLE, neuropsychiatric systemic lupus erythematosus; VLA, very late antigen.

a human monoclonal anti-CD20 antibody that binds to an epitope distinct from that of OCR or RTX, and appears to be effective in multiple sclerosis.[50,51]

Alemtuzumab was developed for blood cancer indications and targets CD52, a mature lymphocyte antigen, consisting of a glycoprotein expressed on the surface of different leukocyte populations, including T lymphocytes, B lymphocytes, and natural killer cells.[51] Alemtuzumab is highly effective at reducing relapse in multiple sclerosis, but has a high rate of adverse events, including thyroid autoimmune disease.[53]

Monoclonal Antibodies That Target Complement

Eculizumab is a monoclonal antibody that targets complement protein C5. Antibody-mediated complement cytotoxicity is evident in the pathology of neuromyelitis optica, and an open-label pilot study of eculizumab in patients with severe neuromyelitis optica showed a reduction in relapse rate.[48]

Monoclonal Antibodies That Target Lymphocyte Adhesion Across Vessel Walls

Natalizumab is a humanized monoclonal antibody that targets α-4 integrin, an essential adhesion molecule expressed on the surface of lymphocytes, involved in lymphocyte trafficking in to the CNS. Natalizumab is highly effective in the treatment of multiple sclerosis.[54] The major adverse event is the risk of progressive multifocal leukoencephalopathy due to John Cunningham virus, but there is now John Cunningham serological screening that can provide relative risk analysis.

Monoclonal Antibodies and Other Biologics That Target Cytokines or Cytokine Receptors

Anakinra is an IL-1 receptor antagonist therefore blocking action of IL-1, and is used to treat rheumatoid arthritis and neonatal-onset multisystem inflammatory disease, a genetic autoinflammatory disorder associated with alteration in IL-1 β cytokine.[55] Recent reports show that the potential effect of anakinra is the treatment of febrile infection-related epilepsy syndrome, associated with reduction in proinflammatory cytokines.[56] Tocilizumab is a monoclonal antibody that targets IL-6 receptor and inhibits binding of IL-6 to IL-6 receptor. IL-6 is a pleitropic cytokine central to many proinflammatory pathways used to treat rheumatoid arthritis,[57] and has recently been shown to be useful as rescue treatment in RTX non-responsive adults with autoimmune encephalitis, and neuromyelitis optica.[58,59] Daclizumab is a monoclonal antibody that selectively binds to the IL-2 receptor α-chain. It has been found useful as a second-line treatment for multiple sclerosis.[60,61]

TNF-α inhibitors include infliximab and adalimumab, used in Crohn disease, rheumatoid arthritis and other rheumatological conditions.[62] These monoclonal antibodies target the cytokine TNF-α, blocking its proinflammatory action. The use of infliximab has been reported in neurosarcoidosis[63] and, more rarely, in limbic encephalitis,[64] while recently

adalimumab has shown good efficacy in terms of seizure reduction in Rasmussen encephalitis.[65] Etanercept, another TNF-α inhibitor, is a circulating dimeric fusion protein composed of the extracellular portion of human soluble TNF-α receptor fused with the Fc portion of human immunoglobulin G1. Opportunistic infections and tuberculosis can be reactivated with the use of TNF-α inhibitors, and tuberculosis should be screened for before prescribing it. There may also be increased risk of malignancies.[66]

Disease Modifying Drugs for Multiple Sclerosis

Interferon-β and glatiramer acetate are first-line immunomodulatory disease modifying therapies used for the treatment of multiple sclerosis in children.[67] These therapies have been developed based on animal models of multiple sclerosis. Interferon acts through specific receptors to regulate signaling cascades, and its effect is mediated through the inhibition of autoreactive T cells and proinflammatory cytokines, reduction of lymphocyte migration, and induction of anti-inflammatory mediators. Glatiramer acetate acts by inhibiting specific effector T lymphocytes and influencing antigen-presenting cells and suppressor T lymphocytes.[68]

Fingolimod is a second-line drug, which modulates the sphingosine-1-phosphate receptor and sequesters lymphocytes in lymph nodes, preventing them from contributing to the immune pathology. Teriflunomide is an oral de novo inhibitor of the dihydroorotate dehydrogenase enzyme involved in pyrimidine synthesis. Teriflunomide exerts anti-inflammatory effects, possibly through reduction of activated lymphocytes in the CNS.[68] There is paucity of data on the use of fingolimod and teriflunomide in pediatric multiple sclerosis, although results of studies are awaited. Alemtuzumab, natalizumab and other monoclonal antibodies mainly used in multiple sclerosis are described earlier.

Other Immune Modulation Agents

Many drugs used in everyday medical practice have immune modulatory effects that are underappreciated or unrecognized. Some of these agents could be useful in the treatment of immune dysregulation syndromes.

Many antibiotics have proven anti-inflammatory or immune modulatory properties, and are used as prophylaxis for chronic inflammatory lung disease, such as cystic fibrosis and chronic dermatitis.[69] The anti-inflammatory and immune modulatory properties of macrolides such as erythromycin and azithromycin are manifold, and other antibiotics also likely have similar properties.[70] It is possible that these anti-inflammatory properties are the cause of effect in infection provoked neuropsychiatric syndromes,[71] rather than antimicrobial actions, although this hypothesis is unproven.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have, as the name suggests, anti-inflammatory properties and may have adjunctive roles in chronic inflammation, if tolerated.[72] Other immunomodulatory agents used in rheumatology include hydroxychloroquine, sulfasalazine, and leflunamide,[73] and have theoretical utility in immune brain disease.

Many drugs used in psychiatry such as the serotonin reuptake inhibitors SSRIs[74] and neuroleptics[75] have anti-inflammatory properties observed for decades. The anti-inflammatory mechanism of action of these psychotropic drugs is likely complex, but it is interesting that dopamine receptors and serotonin receptors exist on the cell surface of lymphocytes, and have cell signaling properties.[76,77] Serotonin reuptake inhibitor and neuroleptics also have potential anti-inflammatory effects on microglia, the resident immune cells of the CNS.[74]

The role of the gut-immune-brain interaction,[78] and the role of the microbiome in multiple sclerosis and other autoimmune diseases is an area of active interest.[79] Probiotics, and other gut health management will likely be an emerging area of attention in chronic autoimmune CNS conditions.[80] The utility of fecal transplantation, used in the treatment of gastrointestinal diseases, has recently been hypothesized and investigated in autoimmune neuropsychiatric disorders.[81] Along these lines, the ketogenic diet has anti-inflammatory properties, among other mechanisms of action, and requires further attention in febrile infection-related epilepsy syndrome and other immune brain disease.[82] Naturopathic agents and foods also have active ingredients with anti-inflammatory properties such as curcumin.[83] Vitamin D is recognized as a major factor related to autoimmune diseases and its deficiency represents a risk factor for these conditions.[84] Because of the high prevalence of vitamin D insufficiency or deficiency in patients with multiple sclerosis, type 1 diabetes mellitus and systemic lupus erythematosus, vitamin D supplementation has been considered a prospective candidate for the treatment of such autoimmune diseases.[85]

Another area of interest and potential benefit is the therapeutic use of helminths. Parasitic helminths have been shown to have the ability to alter or suppress the host's immune responses, which could be beneficial to the host by helping control excessive inflammatory responses.[86] Animal models and preclinical trials have suggested a beneficial effect of helminth infections on inflammatory bowel conditions, multiple sclerosis,[87] asthma and atopy.

Extracellular vesicles (EVs) represent a newborn area of investigation in neuroimmunology. EVs are membrane-surrounded structures released by most cell types. From the therapeutic perspective, the most promising cellular sources of EVs are mesenchymal stem cells, which are easy to obtain and maintain.[88] Mesenchymal stem cells-EVs have been demonstrated to have immunosuppressive effects on B lymphocytes, and immunomodulatory actions on B and T cells in vitro.[89] Therefore, EVs are currently being investigated as a novel therapeutic approach for treating brain inflammatory-related diseases of CNS such as Parkinson disease, Alzheimer disease, multiple sclerosis, amyotrophic lateral sclerosis, meningitis, brain, spinal cord, and peripheral nerve injury and brain tumors.[88]

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Safety

Although some of the monoclonal antibodies provide great excitement as "targeted" immune therapies, it is important to remind clinicians that agents developed for specific indications may not work in other diseases, or even be detrimental. For example, disease modifying therapies used in multiple sclerosis can make neuromyelitis optica worse. And drugs developed for adults with rheumatological disease may have different effects and adverse effects in children with brain disease. All immune suppressive drugs run a risk of infusion related adverse events, immune suppressive side effects such as infection, viral reactivation, and increased risk of neoplasia, as well as drug specific adverse events. Therefore, a "risk versus benefit" determination must be considered in all therapeutic decision making.[90]

Clinical Implications

A more comprehensive knowledge of the range of available immune therapies and a deeper understanding of their modes of action should help the clinician in therapeutic decision-making, according to the prevalent pathophysiological mechanism. Although some immune treatments are widely used and their efficacy and safety profile in pediatric neurology is relatively well understood, a plethora of new treatments are currently being investigated and represent an exciting future horizon in the field of pediatric neuroimmunology. The relative rarity of many of these conditions emphasize the need for multicenter cohorts in order to obtain reliable data on the real effectiveness and tolerability of these new compounds. Only with improved biological understanding of disease, and reproducible biomarkers examining immunogenetic, proteomic, transcriptomic, microbiomic factors, will we be able to truly translate the potential promise of these drugs into clinical practice. Until then, careful consideration and "risk versus benefit" therapeutic decisions based on the disease severity and natural history will be essential, but the clinician should not be "disempowered by complexity" as "empiric" trials of immune therapy in seronegative immune CNS syndromes can reduce disability or be life-saving.

References

1. Jarius S, Wildemann B, Paul F: Neuromyelitis optica: Clinical features, immunopathogenesis and treatment. Clin Exp Immunol 176:149-164, 2014
2. Hapgood JP, Avenant C, Moliki JM: Glucocorticoid-independent modulation of GR activity: Implications for immunotherapy. Pharmacol Ther 165:93-113, 2016
3. Kimbrough DJ, Fujihara K, Jacob A, et al: Treatment of neuromyelitis optica: Review and recommendations. Mult Scler Relat Disord 1:180-187, 2012
4. McKeon A: Paraneoplastic and other autoimmune disorders of the central nervous system. Neurohospitalist 3:53-64, 2013
5. Nosadini M, Mohammad SS, Ramanathan S, et al: Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother 15:1391-1419, 2015
6. Lancaster E: The diagnosis and treatment of autoimmune encephalitis. J Clin Neurol 12:1-13, 2016
7. Dale RC, Gorman MP, Lim M: Autoimmune encephalitis in children: clinical phenomenology, therapeutics, and emerging challenges. Curr Opin Neurol 30:334-344, 2017
8. Cain DW, Cidlowski JA: Immune regulation by glucocorticoids. Nat Rev Immunol 17:233-247, 2017
9. Pranzatelli MR, Tate ED: Trends and tenets in relapsing and progressive opsoclonus-myoclonus syndrome. Brain Dev 38:439-448, 2016
10. Lünemann JD, Nimmerjahn F, Dalakas MC: Intravenous immunoglobulin in neurology—mode of action and clinical efficacy. Nat Rev Neurol 11:80-89, 2015
11. Chaigne B, Mouthon L: Mechanisms of action of intravenous immunoglobulin. Transfus Apher Sci 56:45-49, 2017
12. Nosadini M, Mohammad SS, Suppiej A, et al: Intravenous immunoglobulin in paediatric neurology: safety, adherence to guidelines, and long-term outcome. Dev Med Child Neurol 58:1180-1192, 2016
13. Orange JS, Hossny EM, Weiler CR, et al: Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 117: S525-S553, 2006
14. Feasby T, Banwell B, Benstead T, et al: Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfus Med Rev 21:S57-S107, 2007
15. Elovaara I, Apostolski S, van Doorn P, et al: EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. Eur J Neurol 15:893-908, 2008
16. Wimperis J, Lunn M, Jones A, et al.: Clinical guidelines for immunoglobulin use (ed 2 update), 2011. Available at: https://www.gov.uk/government/publications/clinical-guidelines-for-immunoglobulin-use-second-edition-update.
17. National Blood Authority Australia, Criteria for the clinical use of intravenous immunoglobulin in Australia (ed 2), July 2012. Available at: http://www.blood.gov.au/ivig-criteria.
18. Schwartz J, Padmanabhan A, Aqui N, et al: Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: The seventh special issue. J Clin Apher 31:149-162, 2016
19. Reeves HM, Winters JL: The mechanisms of action of plasma exchange. Br J Haematol 164:342-351, 2014
20. Dubey D, Blackburn K, Greenberg B, et al: Diagnostic and therapeutic strategies for management of autoimmune encephalopathies. Expert Rev Neurother 16:937-949, 2016
21. Ward DM: Conventional apheresis therapies: A review. J Clin Apher 26:230-238, 2011
22. Selewski DT, Shah GV, Mody RJ, et al: Rituximab (rituxan). AJNR Am J Neuroradiol 31:1178-1180, 2010
23. Abulayha A, Bredan A, El Enshasy H, Daniels I: Rituximab: modes of action, remaining dispute and future perspective. Future Oncol 10: 2481-2492, 2014
24. Stroopinsky D, Katz T, Rowe JM, et al: Rituximab-induced direct inhibition of T-cell activation. Cancer Immunol Immunother 61: 1233-1241, 2012
25. Mélet J, Mulleman D, Goupille P, et al: Rituximab-induced T cell depletion in patients with rheumatoid arthritis: association with clinical response. Arthritis Rheum 65:2783-2790, 2013
26. Nosadini M, Alper G, Riney CJ, et al: Rituximab monitoring and redosing in pediatric neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm 3:e188, 2016
27. Dale RC, Brilot F, Duffy LV, et al: Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 83:142-150, 2014
28. Pellkofer HL, Krumbholz M, Berthele A, et al: Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. Neurology 76:1310-1315, 2011
29. Pescovitz MD: Rituximab, an anti-cd20 monoclonal antibody: History and mechanism of action. Am J Transplant 6:859-866, 2006
30. Puyo S, Montaudon D, Pourquier P: From old alkylating agents to new minor groove binders. Crit Rev Oncol Hematol 89:43-61, 2014

31. Ahlmann M, Hempel G: The effect of cyclophosphamide on the immune system: implications for clinical cancer therapy. Cancer Chemother Pharmacol 78:661-671, 2016
32. Brodsky RA: High dose cyclophosphamide treatment for autoimmune disorders. ScientificWorldJournal 2:1808-1815, 2002
33. Zizzo G, De Santis M, Ferraccioli GF: Mycophenolic acid in rheumatology: Mechanisms of action and severe adverse events. Reumatismo 62:91-100, 2010
34. Allison AC, Eugui EM: Mycophenolate mofetil and its mechanisms of action. Immunopharmacology 47:85-118, 2000
35. Hoffmann M, Rychlewski J, Chrzanowska M, Hermann T: Mechanism of activation of an immunosuppressive drug: azathioprine. Quantum chemical study on the reaction of azathioprine with cysteine. J Am Chem Soc 123:6404-6409, 2001
36. Bateman DN, Page CB: Antidotes to coumarins, isoniazid, methotrexate and thyroxine, toxins that work via metabolic processes. Br J Clin Pharmacol 81:437-445, 2016
37. Tian H, Cronstein BN: Understanding the mechanisms of action of methotrexate: Implications for the treatment of rheumatoid arthritis. Bull NYU Hosp Jt Dis 65:168-173, 2007
38. Zeevi A, Duquesnoy R, Eiras G, et al: Immunosuppressive effect of FK-506 on in vitro lymphocyte alloactivation: synergism with cyclosporine A. Transplant Proc 19:40-44, 1987
39. Bien CG, Tiemeier H, Sassen R, et al: Rasmussen encephalitis: Incidence and course under randomized therapy with tacrolimus or intravenous immunoglobulins. Epilepsia 54:543-550, 2013
40. Tanaka M, Kinoshita M, Tanaka K: Corticosteroid and tacrolimus treatment in neuromyelitis optica related disorders. Mult Scler 21:669, 2015
41. Chiang LM, Darras BT, Kang PB: Juvenile myasthenia gravis. Muscle Nerve 39:423-431, 2009
42. Andrews PI: Autoimmune myasthenia gravis in childhood. Semin Neurol 24:101-110, 2004
43. Behrendt V, Krogias C, Reinacher-Schick A, et al: Bortezomib treatment for patients with anti-*N*-methyl-D-aspartate receptor encephalitis. JAMA Neurol 73:1251-1253, 2016
44. Scheibe F, Prüss H, Mengel AM, et al: Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis. Neurology 88:366-370, 2017
45. O'Shea JJ, Kontzias A, Yamaoka K, et al: Janus kinase inhibitors in autoimmune diseases. Ann Rheum Dis 72:ii111-ii115, 2013
46. Hodecker SC, Stellmann JP, Rosenkranz SC, et al: Ruxolitinib treatment in a patient with neuromyelitis optica: A case report. Neurol Neuroimmunol Neuroinflamm 4:e328, 2017
47. Kappos L, Li D, Calabresi PA, O'Connor P, et al: Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 378:1779-1787, 2011
48. Pittock SJ, Lennon VA, McKeon A, et al: Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. Lancet Neurol 12:554-562, 2013
49. Montalban X, Hauser SL, Kappos L, et al: Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 376:209-220, 2017
50. Bittner S, Ruck T, Wiendl H, et al: Targeting B cells in relapsing-remitting multiple sclerosis: From pathophysiology to optimal clinical management. Ther Adv Neurol Disord 10:51-66, 2017
51. Collongues N, Michel L, de Seze J: Biotherapy in inflammatory diseases of the CNS: Current knowledge and applications. Curr Treat Options Neurol 19:19, 2017
52. Blinkenberg M, Soelberg Sørensen P: Monoclonal antibodies for relapsing multiple sclerosis: A review of recently marketed and late-stage agents. CNS Drugs 31:357-371, 2017
53. Coles AJ, Twyman CL, Arnold DL, et al: Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 380:1829-1839, 2012
54. Polman CH, O'Connor PW, Havrdova E, et al: A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 354:899-910, 2006
55. Lovell DJ, Bowyer SL, Solinger AM: Interleukin-1 blockade by anakinra improves clinical symptoms in patients with neonatal-onset multisystem inflammatory disease. Arthritis Rheum 52:1283-1286, 2005
56. Kenney-Jung DL, Vezzani A, Kahoud RJ, et al: Febrile infection-related epilepsy syndrome treated with anakinra. Ann Neurol 80: 939-945, 2016
57. Nishimoto N, Terao K, Mima T, et al: Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood 112:3959-3964, 2008
58. Lee WJ, Lee ST, Moon J, et al: Tocilizumab in autoimmune encephalitis refractory to rituximab: An institutional cohort study. Neurotherapeutics 13:824-832, 2016
59. Araki M, Matsuoka T, Miyamoto K, et al: Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: A pilot study. Neurology 82:1302-1306, 2014
60. Gorman MP, Tillema JM, Ciliax AM, et al: Daclizumab use in patients with pediatric multiple sclerosis. Arch Neurol 69:78-81, 2012
61. Preiningerova JL, Vachova M: Daclizumab high-yield process in the treatment of relapsing-remitting multiple sclerosis. Ther Adv Neurol Disord 10:67-75, 2017
62. Feldmann M: Development of anti-TNF therapy for rheumatoid arthritis. Nat Rev Immunol 2:364-371, 2002
63. Cohen Aubart F, Bouvry D, Galanaud D, et al: Long-term outcomes of refractory neurosarcoidosis treated with infliximab. J Neurol 264:891-897, 2017
64. Kondo T, Fukuta M, Takemoto A, et al: Limbic encephalitis associated with relapsing polychondritis responded to infliximab and maintained its condition without recurrence after discontinuation: a case report and review of the literature. Nagoya J Med Sci 76:361-368, 2014
65. Lagarde S, Villeneuve N, Trébuchon A, et al: Anti-tumor necrosis factor alpha therapy (adalimumab) in Rasmussen's encephalitis: An open pilot study. Epilepsia 57:956-966, 2016
66. Bongartz T, Sutton AJ, Sweeting MJ, et al: Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. J Am Med Assoc 295:2275-2285, 2006
67. Chitnis T, Tenembaum S, Banwell B, et al: Consensus statement: Evaluation of new and existing therapeutics for pediatric multiple sclerosis. Mult Scler 18:116-127, 2012
68. Chitnis T: Disease-modifying therapy of pediatric multiple sclerosis. Neurotherapeutics 10:89-96, 2013
69. Amsden GW: Anti-inflammatory effects of macrolides—An underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? J Antimicrob Chemother 55:10-21, 2005
70. Labro MT: Antibiotics as anti-inflammatory agents. Curr Opin Investig Drugs 3:61-68, 2002
71. Murphy TK, Brennan EM, Johnco C, et al: A double-blind randomized placebo-controlled pilot study of azithromycin in youth with acute-onset obsessive-compulsive disorder. J Child Adolesc Psychopharmacol 2017. doi: 10.1089/cap.2016.0190. [Epub ahead of print]
72. Ajmone-Cat MA, Bernardo A, Greco A, Minghetti L: Non-steroidal anti-inflammatory drugs and brain inflammation: Effects on microglial functions. Pharmaceuticals (Basel) 3:1949-1965, 2010
73. Her M, Kavanaugh A: Advances in use of immunomodulatory agents—A rheumatology perspective. Nat Rev Gastroenterol Hepatol 12:363-368, 2015
74. Tynan RJ, Weidenhofer J, Hinwood M, et al: A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. Brain Behav Immun 26:469-479, 2012
75. Al-Amin MM, Nasir Uddin MM, Mahmud Reza H: Effects of antipsychotics on the inflammatory response system of patients with schizophrenia in peripheral blood mononuclear cell cultures. Clin Psychopharmacol Neurosci 11:144-151, 2013
76. Levite M: Dopamine and T cells: dopamine receptors and potent effects on T cells, dopamine production in T cells, and abnormalities in the

ARTICLE IN PRESS

dopaminergic system in T cells in autoimmune, neurological and psychiatric diseases. Acta Physiol 216:42-89, 2016
77. Ahern GP: 5-HT and the immune system. Curr Opin Pharmacol 11:29-33, 2011
78. Carabotti M, Scirocco A, Maselli MA, Severi C: The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol 28:203-209, 2015
79. Jangi S, Gandhi R, Cox LM, et al: Alterations of the human gut microbiome in multiple sclerosis. Nat Commun 7:12015, 2016
80. Fleming JO, Isaak A, Lee JE, et al: Probiotic helminth administration in relapsing-remitting multiple sclerosis: A phase 1 study. Mult Scler 17:743-754, 2011
81. Evrensel A, Ceylan ME: Fecal microbiota transplantation and its usage in neuropsychiatric disorders. Clin Psychopharmacol Neurosci 14:231-237, 2016
82. Dupuis N, Curatolo N, Benoist JF, Auvin S: Ketogenic diet exhibits anti-inflammatory properties. Epilepsia 56:e95-e98, 2015
83. Menon VP, Sudheer AR: Antioxidant and anti-inflammatory properties of curcumin. Adv Exp Med Biol 595:105-125, 2007
84. Ramagopalan SV, Goldacre R, Disanto G, et al: Hospital admissions for vitamin D related conditions and subsequent immune-mediated disease: record-linkage studies. BMC Med 11:171, 2013
85. Yang CY, Leung PS, Adamopoulos IE, Gershwin ME: The implication of vitamin D and autoimmunity: A comprehensive review. Clin Rev Allergy Immunol 45:217-226, 2013
86. Helmby H: Human helminth therapy to treat inflammatory disorders—where do we stand? BMC Immunol 16:12, 2015
87. Tanasescu R, Constantinescu CS: Helminth therapy for MS. Curr Top Behav Neurosci 26:195-220, 2015
88. Koniusz S, Andrzejewska A, Muraca M, et al: Extracellular vesicles in physiology, pathology, and therapy of the immune and central nervous system, with focus on extracellular vesicles derived from mesenchymal stem cells as therapeutic tools. Front Cell Neurosci 10:109, 2016
89. Del Fattore A, Luciano R, Pascucci L, et al: Immunoregulatory Effects of Mesenchymal Stem Cell-Derived Extracellular Vesicles on T Lymphocytes. Cell Transplant 24:2615-2627, 2015
90. Dale RC, Nosadini M, Lim M: Therapeutic decision making in autoimmune and inflammatory disorders of the central nervous system in children. JICNA 16:11, 2016

3.2 Immune therapy in autoimmune encephalitis

3.2.1 Systematic literature review of immune therapy in autoimmune encephalitis

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Immune therapy in autoimmune encephalitis: a systematic review

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EXPERT REVIEWS

Immune therapy in autoimmune encephalitis: a systematic review

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We have reviewed the literature of immune therapy in autoimmune encephalitis associated with antibodies to cell surface antigens including N-methyl-D-aspartate receptor (NMDAR), leucine-rich, glioma-inactivated protein-1 (LGI1), contactin-associated protein-2 (Caspr2), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), γ-aminobutyric acid-A receptor (GABAAR), γ-aminobutyric acid-B receptor (GABABR), Glycine R and other rarer antigens. Most studies are retrospective cohorts, and there are no randomised controlled trials. Most clinicians use first-line therapy (steroids, intravenous immunoglobulin, plasma exchange), and if severe or refractory, second-line therapy (rituximab, cyclophosphamide). When present, tumours should be removed. There are common therapeutic themes emerging. Firstly, patients given immune therapy do better and relapse less than patients given no treatment. Secondly, patients given early treatment do better. And thirdly, when patients fail first-line therapy, second-line therapy improves outcomes and reduces relapses. Given the retrospective uncontrolled data, the literature has inherent bias, including severity and reporting bias.

Keywords: Autoimmune encephalitis • antibodies to neuronal cell surface antigens • immune therapy • treatment • limbic encephalitis • NMDAR • LGI1 • Caspr2 • AMPAR

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Autoantibodies against neuronal antigens were first recognized in patients with acquired neurological syndromes and tumors distant to the nervous system. These paraneoplastic syndromes include limbic encephalitis, brainstem encephalitis, cerebellar ataxia and peripheral neuropathy, among others, and are often associated with onconeuronal antibodies, which target intracellular antigens, including Hu, Yo, Ri, Ma2, CV2/CRMP5, amphiphysin and glutamic acid decarboxylase (GAD). These onconeuronal antibodies cannot access the antigen under physiological circumstances, and neuronal tissues from these patients show prevalent infiltration by T lymphocytes. Moreover, experimental studies after immunization with the antigen Hu did not cause neurological disease in mice, and response to immune therapy is poor in these paraneoplastic disorders.[1–4] Therefore, onconeuronal autoantibodies are considered biomarkers for the presence of tumors rather than pathogenic mediators of neurological disease [5] and should motivate the search for an associated malignancy.

More recently, autoantibodies targeting neuronal cell surface proteins have been identified in cases of encephalitis that were previously unexplained. The first of this novel class was identified in 2007 and targeted the *N*-methyl-D-aspartate receptor (NMDAR).[6] Subsequently, antibodies were identified against the glycine receptor (GlyR),[7] the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR),[8] the leucine-rich, glioma-inactivated protein-1 (LGI1), the contactin-associated protein-2 (Caspr2),[9,10] the γ-aminobutyric acid-A receptor (GABAAR) and γ-aminobutyric acid-B receptor (GABABR),[11,12] the metabotropic glutamate receptor 5 (mGluR5),[13] the dopamine-2 receptor (D2R),[14] the dipeptidyl-peptidase-like protein-6 (DPPX),[15] and the IgLON5.[16] The presence of tumor varies, with some antibodies commonly associated with

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tumors, whereas in other antibody-associated syndromes tumors are rare or absent.[17] Disease onset can be at any age and is often more acute or subacute than in classic paraneoplastic syndromes, which tend to be more insidious [5], although the clinical distinction between onconeuronal and cell surface antibody syndromes may be challenging at presentation, especially in patients with limbic encephalitis. Similarly, significant overlap between different types of encephalitis with neuronal surface antibodies exists at onset,[17] as behavioral and psychiatric changes, seizures, memory deficits and sleep disturbances may be common features. The two most frequent clinical syndromes are anti-NMDAR encephalitis, a multiphasic disease with behavioral and psychiatric changes, movement disorders, seizures, hyporesponsive state and dysautonomia, [6] and limbic encephalitis, characterized by confusion, agitation, memory loss and seizures, which can be associated with various antibodies, including anti-LGI1, anti-AMPAR and anti-GABABR. In view of the relative rarity of these conditions, and as the discovery of these neuronal surface antibodies is quite recent, the spectrum of the clinical syndromes and the best treatment approach is yet to be defined. These cell surface antibody syndromes have in common the presence of serum and cerebrospinal fluid (CSF) autoantibodies, predominantly IgG, which bind to the extracellular domain of cell surface antigens that are important to neuronal function. Three antibody assays were initially used to define the presence of neuronal surface antibodies in patients' serum and CSF: demonstration of antibody binding to fixed brain sections, to the surface of cultured live neurons, and to the surface of human embryonic kidney (HEK293) cells transfected with specific antigens.[18,19] This approach has been simplified, and cell-based assays using HEK293 cells currently represent the commonly available technique used for diagnosis, although assays involving all three techniques improve the diagnostic specificity and are commonly used in novel antibody discovery, and CSF is generally considered more specific than serum.[4,20] Unlike the onconeuronal antibodies, the neuronal cell surface autoantibodies can reach their target protein in the absence of cell damage and influence the antigen function or cause antigen internalization, and therefore, are potentially pathogenic.[4,21] Most importantly, autoimmune encephalitis associated with neuronal surface antibodies are generally more likely to respond to immune therapy, resulting in good recovery in up to 70–80% of cases.[20,22] No randomized controlled trials in autoimmune encephalitis have been published, and available evidence is mostly based on retrospective data. The treatment of these conditions is similar to other autoimmune disorders of the central nervous system (CNS). First-line immune therapies generally consist of corticosteroids (intravenous and oral), sometimes with intravenous immunoglobulin (IVIG) and/or plasma exchange (PE). Second-line treatments are usually administered when the first-line therapies fail to produce adequate benefit, or when the disease is known to be severe or relapsing, and typically include rituximab, cyclophosphamide, azathioprine, mycophenolate mofetil or others.

We conducted a systematic review on immune therapy in autoimmune encephalitis with neuronal surface antibodies to appreciate the use and type of immune treatment, its efficacy and the available evidence on the possible benefit of early and aggressive treatment.

Box 1. Modified Rankin scale description.[23]

Modified Rankin scale score	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Modified Rankin scale is a neurological disability score often used to describe outcome in the articles included in this review.

The autoimmune encephalitis syndromes are presented in turn and defined by the autoantibody. The literature search was conducted in September 2015, and the search strategy varied according to each syndrome and is stated in the text, with only larger cohorts described in the more common syndromes. The reporting of different findings and outcomes is variable, and the number of patients with available data is reported in the text and tables. Similarly, the reported outcome measures are variable, with modified Rankin scale (mRS) (Box 1) [23] or qualitative descriptions of outcome used in most instances.

Anti-NMDAR antibodies

Epidemiology and clinical features

Encephalitis associated with autoantibodies against the NMDAR was first described in 2007 in women with ovarian teratoma [6] and has subsequently been reported also in children and in both genders. The proportion of paraneoplastic cases varies according to the age and appears to be considerably lower in pediatric series (2.2–7.7%) [24–27] than in series including adults (20.4–59.2%).[18,28,29] The frequency of anti-NMDAR encephalitis surpassed that of individual viral etiologies in the California Encephalitis Project.[30] The disorder is characterized by a multistage course that progresses from behavioral or psychiatric disturbances, memory deficits, seizures and language disintegration into a state of unresponsiveness with catatonic features, movement disorders and autonomic instability.[31] The disease course is often prolonged up to several months, and while a proportion of patients recover fully, in sporadic reports even without immune therapy,[32]

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many have behavioral, cognitive or neurological sequelae of varying severity. Immune therapy appears to yield a more favorable outcome,[28] but although treatment strategies have been suggested in adults,[31] to date there is no established therapeutic algorithm.

We searched for articles with >30 cases each and treatment details on patients with anti-NMDAR encephalitis, and the authors included in this review eight papers published between 2008 and 2015 (Table 1).[18,24–29,33] One of the articles is a prospective population-based study,[26] while all the others are retrospective noncontrolled series. The articles report a total of 905 patients (726/905, 80.2% females), 577 of which were described in one large case series by Titulaer and colleagues. [29] The age at disease onset ranged between 0.7 and 85 years, although most cases were children, adolescents and young adults (427/905, 47% ≤18 years).

Treatment

Most patients received immune therapy (766/829, 92.4%). According to available data, steroids were administered in 83.3% (634/761) of patients, IVIG in 66% (502/761) and PE in 31.1% (244/761). In the large case series by Titulaer et al., steroids and IVIG were often given together (202/462, 44%) [29]. Second-line immune therapies were administered in about a third of cases with available information (229/684, 33.5%): rituximab in 23.5% (195/828), cyclophosphamide in 14.5% (120/828) and other immune therapies in 8.9% (74/828) (azathioprine, mycophenolate mofetil, methotrexate or tacrolimus). Management of anti-NMDAR encephalitis is challenging, and symptomatic treatment often focuses on sedation and improving sleep–wake cycle, and patients appear to have a high rate of adverse events to neuroleptics.[34]

Immune therapy versus no immune therapy

Results in the reviewed articles suggest that the use of immune therapy is associated with a better outcome. In particular, within the non-paraneoplastic group in the cohort described by Irani and colleagues, those patients administered no immune therapy did significantly worse than those who were treated ($p < 0.0001$).[28] In the large case series by Titulaer,[29] 29% of the 29 patients who received no surgery and no immune therapy had a poor outcome (mRS 3–6) as opposed to 21.3% of the total cohort (n = 501). Moreover, the use of immune therapy in the initial episode of encephalitis was associated with a lower frequency of relapses ($p = 0.038$).[29]

Timing of immune therapy

Several observations in the reviewed articles also suggest that early commencement of immune therapy favors a better neurological outcome. In particular, improvement of mRS score was associated with early (<40 days) administration of immune therapies in non-paraneoplastic patients ($p < 0.0001$).[28] Similarly, early treatment was a predictor of good outcome (mRS 0–2) ($p < 0.0001$) in the cohort described by Titulaer. [29] In children with anti-NMDAR encephalitis treated with

Table 1. Summary of the literature review on the treatment of anti-NMDAR encephalitis (only cohorts >30 patients were included). [18,24–29,33]

	Dalmau [18]	Florance [33]	Irani [28]	Titulaer [29]	Dale [24]	Hacohen [25]	Wright [26]	Zekeridou [27]
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Population-based	Retrospective
No. of patients	100	32	44	577[‡]	39	46	31	36
Clinical description (No. of females)	100/100: anti-NMDAR encephalitis (F: 91/100, 91%)	32/32: anti-NMDAR encephalitis (F: 26/32, 81.2%)	44/44: anti-NMDAR encephalitis (F: 31/44, 70.4%)	577/577: anti-NMDAR encephalitis (F: 468/577, 81.1%)	39/39: anti-NMDAR encephalitis treated with rituximab (F: 29/39, 74.3%)	28/46: anti-NMDAR encephalitis 18/46: other anti-NMDAR antibody associated CNS disorders (F: 32/46, 69.6%)	24:31: anti-NMDAR encephalitis 7/31: partial phenotype without encephalopathy (F: 23/31, 74.2%)	36/36: anti-NMDAR encephalitis (F: 26/36, 72.2%)
Median age at onset (range)	23 years (5–76) (22/100 children)	14 years (1.9–18) (32/32 children)	22.5 years (median in F 22, in M 23; range 2–59) (no. of children n.a.)	21 years (0.7–85) (211/577 children)	8.7 years (1.6–17) (39/39 children)	10.5 years (1–18) (46/46 children)	8 years (2–17) (31/31 children)	10.9 years (1.2–17.2) (36/36 children)

(continued)

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Table 1. Summary of the literature review on the treatment of anti-NMDAR encephalitis (only cohorts >30 patients were included). [18,24–29,33] (continued).

	Dalmau [18]	Florance [33]	Irani [28]	Titulaer [29]	Dale [24]	Hacohen [25]	Wright [26]	Zekeridou [27]
Tumor	58/98 (59.2%)	8/32 (25%)	9/44 (20.4%)	220/577 (38.1%)	3/39 (7.7%)	1/46 (2.2%)	1/31 (3.2%)	1/36 (2.8%)
Immune therapy[†]	92/100 (92%)	30/31 (96.8%)	35/44 (79.5%)	462/501 (92.2%)	39/39 (100%)[§]	41/46 (89.1%)	31/31 (100%)	36/36 (100%)
First-line	n.a.	30/31 (96.8%)	n.a.	462/501 (92.2%)	n.a.	41/46 (89.1%)	31/31 (100%)	36/36 (100%)
Steroids	76/100 (76%)	n.a.	33/44 (75%)	421/501 (84%)	37/39 (94.9%)	36/46 (78.3%)	31/31 (100%)	n.a.
IVIG	62/100 (62%)	n.a.	15/44 (34.1%)	346/501 (69.1%)	34/39 (87.2%)	23/46 (50%)	22/31 (71%)	n.a.
Plasma exchange	34/100 (34%)	n.a.	13/44 (29.5%)	163/501 (32.5%)	11/39 (28.2%)	14/46 (30.4%)	9/31 (29%)	n.a.
Second-line	n.a.	7/31 (22.6%)	n.a.	134/501 (26.7%)	39/39 (100%)	10/46 (21.7%)	10/31 (32.2%)	29/36 (80.5%)
Rituximab	10/100 (10%)	6/31 (19.3%)	2/44 (4.5%)	101/501 (20.1%)	39/39 (100%)	5/46 (10.9%)	6/31 (19.3%)	26/36 (80.5%)
Cyclophosphamide	9/100 (9%)	5/31 (16.1%)	4/44 (9.1%)	81/501 (16.2%)	8/39 (20.5%)	2/46 (4.3%)	6/31 (19.3%)	5/36 (13.9%)
Other:	1/100 (AZA) (1%)	0/31 (0%)	1/44 (2.3%) AZA 1/44 (2.3%) MMF 23/44 (52.3%) combination of the above	31/501 (6.2%) AZA, MMF, methotrexate or tacrolimus	4/39 (10.2%) MMF or AZA	5/46 (10.9%) MMF 1/46 (2.2%) AZA	1/31 (3.2%) MMF	1/36 (2.8%) MMF 5/36 (13.9%) AZA
Median length of follow-up (range)	17 months (1–194)	4.5 months (2–14.5)	16 months (3.6–121)	24 months (4–186)	1.3 years (0.4–4.5) (post rituximab)	30 months (6–60)	12 months in all patients	12 and 24 months in 35/36 and 31/36 patients, respectively
No. of patients who relapsed	15/100 (15%)	n.a.	10/44 (22.7%)	45/501 (9%)	n.a.	15/46 (32.6%)	7/31 (22.6%)	3/36 (8.3%)
Outcome	mRS 0: 47/100 (76%) mRS 1–2: 28/100 (28%) mRS 3–5: 18/100 (18%) mRS 6: 7/100 (7%)	Full recovery: 9/31 (29%) Substantial improvement: 14/31 (45.2%) Limited improvement: 8/31 (25.8%)	n.a.	mRS 0–2: 394/501 (78.6%) mRS 3–5: 77/501 (15.4%) mRS 6: 30/501 (6%)	mRS 0: 7/39 (17.9%) mRS 1–5: 30/39 (76.9%) mRS 6: 2/39 (5.1%)	Full recovery: 15/46 (32.6%) mRS 1–5: 31/46 (67.4%)	Full recovery: 19/30 (63.3%) Partial recovery: 10/30 (32.2%) No recovery: 1/30 (3.2%)	In the first 24 months: mRS 0: 20/36 (55.5%) mRS 1–2: 10/36 (27.8%) mRS 3–5: 5/36 (13.9%) mRS 6: 1/36 (2.8%)

[†]At first episode.
[‡]Data on treatment and outcome available only in 501/577 patients with follow-up ≥4 months [29].
[§]The immune therapy listed refers only to the medications received before rituximab [24].
AZA: Azathioprine; F: Females; IVIG: Intravenous immunoglobulin; M: Males; MMF: Mycophenolate mofetil; mRS: Modified Rankin scale; n.a.: Not available; NMDAR: *N*-methyl-D-aspartate receptor.

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rituximab, patients who received rituximab early (≤0.1 year) did better than patients treated late (>0.1 year) (mRS 0–2: 92% vs. 57.1%).[24] Similarly, in a recent collation of 80 pediatric patients from 34 published articles, the median time from symptom onset to initiation of treatment was shorter in children who recovered completely compared to those who had not recovered completely at follow-up (15 vs. 21 days) (p = 0.014).[35] In a recent French series in the pediatric age group, the authors observed that treatment delay has tended to become shorter over time (2007–2012) [27], inferring that there seems to be improved recognition of the disease, that allows for expedited diagnosis and commencement of appropriate therapy. In paraneoplastic patients, limited data also suggest a better outcome in patients with early tumor removal.[18]

Second-line immune therapy

The use of second-line immune therapies also appears to be beneficial. In the article by Titulaer, of 221 patients who did not improve with first-line treatment, the patients who received second-line immune therapy (125/221, 57%) had a better outcome (mRS 0–2) than those who did not (p = 0.012) [29]. In the same paper, the introduction of second-line therapy in 15 patients who had multiple attacks reduced the likelihood of further relapses (p = 0.024). On the other hand, in the French series by Zekeridou [27], the authors observed that despite a high rate of use of second-line immune therapy (80.6%, 29/36, mostly rituximab) the outcome in their cohort was very similar to the outcome reported in other series with lower rate of second-line treatment. In this same series, first-line treatment only, rather than second-line therapy, was associated with good outcome in univariate analysis (p = 0.01). Though this was not confirmed in multivariate analysis, and this finding may be influenced by a "severity bias," as second-line therapy is more commonly used in patients with severe disease. In a recent small series of three children with anti-NMDAR encephalitis who did not respond to first- and second-line (rituximab, azathioprine) treatments, the authors suggest that intrathecal treatment with methotrexate and methylprednisolone may be a useful add-on therapy in refractory disease.[36]

Outcome

Relapses occurred in 11.2% of patients (85/758), and 5.1% patients died (40/783). A considerable reduction in relapse rate occurred over time, from 15% in a cohort reported in 2008 [18] to 9% in 2013 [29]. Similarly, the rate of severe deficits or death at follow-up (mRS 3–6) dropped from 25% to 21.3% in these series, possibly due to earlier and more aggressive therapy with increased disease recognition over this time.

The variable measures used for outcome at follow-up and the heterogeneous follow-up duration (range 1–186 months) (Table 1) partly hamper the comparison of outcome between different series, especially in view of the fact that patients continue to improve for up to 18 months after symptom onset [29]. In the largest study by Titulaer and colleagues, at a median follow-up of 24 months (range 4–186), 78.6% (394/501) patients had an mRS of 0–2, 15.4% (77/501) an mRS of 3–5 and 6% (30/501) died [29].

Anti-LGI1 antibodies

Epidemiology and clinical features

In 2010, two independent groups demonstrated that LGI1 and Caspr2 represent the major targets of voltage-gated potassium channel (VGKC) antibodies.[9,10,37] Limbic encephalitis is the predominant clinical syndrome associated with anti-LGI1 antibodies, often in association with hyponatremia. Morvan's syndrome and acquired neuromyotonia have also been described, sometimes with overlapping phenotypes.[10] Detection of anti-LGI1 antibodies has also been reported in patients with exclusive or predominant seizure presentation.[38,39] A distinctive type of seizure, faciobrachial dystonic seizures (FBDS), has been described in association with anti-LGI1 antibodies, and it commonly precedes the onset of limbic encephalitis, representing an important diagnostic clue.[39,40] Other reported atypical manifestations associated with anti-LGI1 antibodies include progressive encephalomyelitis with rigidity and myoclonus (PERM), [41] isolated chorea,[42] hemianesthesia [43] and neurocardiac prodromes.[44,45] The association with tumor is rare, and it has been reported respectively in 0% and 11% of patients in the two largest case series (lung tumor, thyroid tumor, renal cell tumor, ovarian teratoma, thymoma).[9,10]

Eight articles published between 2010 and 2014 reporting ≥4 patients with anti-LGI1 encephalitis were included in this review (Table 2).[9,10,38,39,46–49] One of the papers is a prospective series,[39] whereas all the others are retrospective. The articles report a total of 168 patients, predominantly males (107/168, 63.7%), all adults (age range 28–92 years). While the clinical phenotype of the patients is of limbic encephalitis in most of the articles, seizures are the predominant feature in two papers. Cognitive impairment, confusion, memory problems and/or psychiatric issues are also common.[38,39] Additional antibodies were detected in 4% (4/99) of patients with available information (anti-Caspr2, anti-contactin-2).

Treatment

97.2% (103/106) of the patients with available information received immune therapy at the first episode of disease. First-line treatments were administered in 97.1% (102/105): steroids in 89.5% (94/105), IVIG in 50% (53/106) and PE in 14.1% (15/106). Second-line therapies were used in a limited proportion of cases (28/105, 26.7%): rituximab in 11.4% (12/105), cyclophosphamide in 1.9% (2/105), mycophenolate mofetil in 9.5% (10/105), azathioprine in 7.6% (8/105) and tacrolimus in 1.9% (2/105).

Immune therapy versus no immune therapy

Inadequate data are available on the outcome of the 2.8% (3/106) patients who did not receive immune therapy. However, in the prospective series of 10 patients with FBDS, [39] >20% reduction in FBDS was noted within the first month of immune therapy in nine cases who were refractory to antiepileptic agents for a median of 30 days (range 11–200)

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Table 2. Summary of the literature review on the treatment of anti-LGI1 encephalitis (only cohorts ≥4 patients were included) [9,10 38,39,46–49].

	Lai [9]	Irani [10]	Quek [38]	Irani [39]	Shin [46]	Irani [47]	Malter [48]	Wegner [49]
Study design	Retrospective	Retrospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	57	55	14	9	14	6	9	4
Clinical description (no. of females)	57/57: LE (seizures in 42/57, hyponatremia in 28/47) (F: 20/57, 35.1%)	49/55: LE 2/55: Morvan's syndrome 1/55: neuromyotonia 1/55: epilepsy 2/55: undefined diagnosis (F: 18/55, 32.7%)	10/14: predominant seizure presentation, with cognitive, psychiatric, personality or other changes 4/14: exclusive seizure presentation (F: 6/14, 42.8%)	9/9: faciobrachial dystonic seizures (cognitive impairment in 8/10) (F: 5/10, 50%)[†]	14/14: suspected autoimmune encephalitis (seizures in 14/14, memory impairment, confusion and/or abnormal behavior in 12/14) (F: 6/14, 42.8%)	6/6: LGI1-associated encephalopathy (F: 4/6, 66.7%)	9/9: LE (seizures in 9/9, memory deficits in 8/9) (F: 3/9, 33.3%)	4/4: LE (psychiatric symptoms in 1/4, cognitive deficits in 4/4/, focal seizures in 4/4) (F: 0/4, 0%)
Median age at onset (range)	60 years (30–80)	Adults (median and range n.a.)	60.5 years (39–74)	68 years (28–92)[‡]	60.5 years (41–78)	65 years (48–73)	55 years (32–67)	68 years (interquartile range 61–72.7)
Tumor	6/53 (11.3%): –1/53: lung –2/53: thyroid –1/53: renal cell –1/53 ovarian teratoma –1/53: thymoma	0/55 (0%)	n.a.	1/10 (1%) –1/10: multiple endocrine neoplasia type 1	1/14 (7.1%) –1/14: renal cell carcinoma	n.a.	0/9 (0%)	0/4 (0%)
Additional antibody	1/55 (1.8%) –1/55: Caspr2	n.a.	1/14 (7.1%) (type of antibody n.a.)	2/9 (22.2%) –1/9: Caspr2 –1/9: contactin-2	0/12 (0%)	n.a.	0/9 (0%)	n.a.
Immune therapy[†]	48/50 (96%)	n.a.	14/14 (100%)	9/9 (100%)	13/14 (92.8%)	6/6 (100%)	9/9 (100%)	4/4 (100%)
First-line	48/50 (96%)		13/13 (100%)	9/9 (100%)	13/14 (92.8%)	6/6 (100%)	9/9 (100%)	4/4 (100%)
Steroids	42/50 (84%)		12/13 (92.3%)	9/9 (100%)	13/14 (92.8%)	5/6 (80%)	9/9 (100%)	4/4 (100%)
Intravenous immunoglobulin	31/50 (62%)		4/13 (30.8%)	4/10 (40%)	8/14 (57.1%)	4/6 (66.7%)	0/9 (0%)	2/4 (50%)
PE	3/50 (6%)		3/13 (23.1%)	1/10 (10%)	1/14 (7.1%)	3/6 (50%)	0/9 (0%)	4/4 (100%)
Second-line	6/50 (12%)		11/13 (84.6%)	0/9 (0%)	5/14 (35.7%)	6/6 (100%)	0/9 (0%)	1/4 (25%)
Rituximab	3/50 (6%)		0/13 (0%)	0/9 (0%)	3/14 (21.4%)	6/6 (100%)	0/9 (0%)	0/4 (0%)

(*continued*)

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Table 2. Summary of the literature review on the treatment of anti-LGI1 encephalitis (only cohorts ≥4 patients were included) [9,10,38,39,46–49]. (continued).

	Lai [9]	Irani [10]	Quek [38]	Irani [39]	Shin [46]	Irani [47]	Malter [48]	Wegner [49]
Cyclophosphamide	0/50 (0%)		0/13 (0%)	0/9 (0%)	1/14 (7.1%)	0/6 (100%)	0/9 (0%)	1/4 (25%)
Other:	2/50 (4%) AZA		9/13 (69.2%) mycophenolate mofetil 4/13 (30.8%) AZA	0/9 (0%)	2/14 (14.3%) AZA 2/14 (14.3%) Tacrolimus	1/6 (16.7%) mycophenolate mofetil	0/9 (0%)	0/4 (0%)
Median length of follow-up (range)	18 months after initial immune therapy (2–60) (data available in 33/57)	>36 months	7.5 months (2–48) (data available in 12/14)	17.7 months (6–29.7)	4.5 months (1–24) (data available in 12/14)	34.2 months (17.9–92.1)	39.8 months (12.4–71.8)	23 months (20–37)
No. of patients who relapsed	6/33 (18.2%)	n.a.	3/14 (21.4%)	4/10 (40%)[‡]	2/13 (15.4%)	1/6 (16.7%)	0/9 (0%)	0/4 (0%)
Outcome	Full recovery: 12/50 (24%) Mild disability: 27/50 (54%) Moderate disability: 8/50 (16%) Death: 3/50 (6%)	mRS were significantly reduced after treatments ($p < 0.0001$). Death: 1/55 (1.8%) (unrelated to the clinical syndrome)	Seizure freedom: 11/13 (84.6%) Seizure improvement: 2/13 (15.4%)	All returned to their baseline, although typically without complete normalization of formal neuropsychology testing scores	mRS 0: 6/12 (50%) mRS 1: 3/12 (25%) mRS 2: 2/12 (16.7%) mRS 5: 1/12 (8.3%)	mRS 1: 3/6 (50%) mRS 2: 3/6 (50%)	Seizure free: 8/9 (88.9%) Memory deficits: 6/8 (75%) • –3/8 (37.5%): figural + verbal • –2/8 (25%): figural • –1/8 (12.5%): verbal	mRS 0: 2/4 (50%) mRS 1: 1/4 (25%) mRS 3: 1/4 (25%)

[†]At first episode.
[‡]Including one patient negative for LGI1, Caspr2 and contactin-2 (voltage-gated potassium channel-complex antibodies 377 pM) [39].
AZA: Azathioprine; Caspr2: Contactin-associated protein-2; F: Females; LE: Limbic encephalitis; LGI1: Leucine-rich, glioma-inactivated protein-1; mRS: Modified Rankin scale; n.a.: Not available; PE: Plasma exchange.

(p = 0.006). The addition of corticosteroids was associated with cessation of FBDS within 1 week in 30% (3/10) of patients, and within 2 months in 60% (6/10). Moreover, the eight cases who initially received antiepileptic drugs or no treatment all developed cognitive impairment, whereas the two who received early immune therapy did not develop cognitive impairment (p = 0.02). As regards the type of immune therapy, Shin and colleagues observed that the subgroup of patients initially treated with concurrent steroids and IVIG had a better outcome and higher rate of complete recovery (mRS 0) than the subgroup who initially received only steroids (p = 0.042).[46]

Timing of immune therapy

Time to return to an mRS of 1 significantly correlated with time to administration of immune therapy (p = 0.03) (but not time to antiepileptic drug administration, p = 0.10) in the series by Irani.[39] In the paper by Shin and coworkers, good outcome (mRS ≤1) was reported in the patients who started immune therapy early (≤1 month) (p = 0.058).[46] By contrast, Malter and colleagues found no correlation between time to immune therapy, and seizure and memory outcomes.[48]

Second-line immune therapy

Data on the benefit of second-line immune therapy are limited. In a recent series of six patients with anti-LGI1 antibody-associated encephalopathy,[47] rituximab produced clear benefit in both mRS and FBDS frequency in one patient after failed readministration of steroids, and this effect was reproduced at relapse. Possible improvement with rituximab was observed in two additional patients after steroids and IVIG (respectively in verbal memory, and in cognitive function and emotional lability). In the remaining three patients, rituximab appeared to have no or marginal clinical benefit in reducing seizure frequency or the mRS score. In contrast, the most consistent reductions in seizure frequency were associated with steroids or IVIG, and mRS improvement appeared to be most consistently associated with corticosteroids. Among the 13 cases reported by Shin et al. [46], two patients had three relapses, both of whom were initially treated with corticosteroids only; the addition of rituximab and tacrolimus led to a cessation of any further relapse in one of the two patients. Another recent article reports that rituximab was associated with long-term remission of all symptoms in two patients with anti-LGI1 encephalitis after inefficacy of first-line treatments (15 and 56 months follow-up, respectively).[50]

Patients who received second-line immune treatments had a higher relapse rate than patients treated with first-line only (6/23, 26.1% vs. 6/32, 18.7%), and lower rates of good outcome (mRS 0 or seizure freedom: 10/23, 43.5% vs. 26/30, 86.7%), although this may be related to "severity bias."[38,39,46–49]

Outcome

The natural history of anti-LGI1 encephalitis is variable, with spontaneous complete recovery possible without immune therapy,[51] although death has also been described.[9] Length of follow-up ranged between 2 and 92.1 months in the cohorts (Table 2). Rate of good outcome (full recovery or mRS 0) was 27.8% (20/72) in the studies using neurological status as an outcome measure.[9,46,49] 86.4% (19/22) patients were seizure-free in the studies using seizure status as the main outcome measure [38,48]. Relapses occurred in 18% patients (16/89), and death in 2.5% (4/158) patients.

Anti-Caspr2 antibodies

Epidemiology and clinical features

Caspr2 is a cell adhesion molecule that clusters VGKCs (Kv1.1/1.2) at the juxtaparanodes of the nodes of Ranvier in both the peripheral and the CNS. In one of the two original series that led to its identification as one of the major targets of anti-VGKC antibodies,[10] over a third of anti-Caspr2 patients had limbic encephalitis (7/19, 36.8%); however, seizures were less common than in cases with positive anti-LGI1 antibodies. Neuromyotonia, neuropathic pain, insomnia, dysautonomia and weight loss were more frequent in patients with anti-Caspr2 antibodies. Subsequent series have confirmed the association of anti-Caspr2 antibodies with both central and peripheral neurological manifestations, including encephalopathy, seizures, limbic encephalitis, [52–54] cerebellar ataxia,[55,56] Morvan's syndrome [9,57,58] and peripheral nerve hyperexcitability [9,59]. The association with tumor has been reported in up to 52.4% of cases, especially thymoma [10,57,60]. Additional antibodies have been described in up to 85.7% of patients (anti-VGKC, anti-LGI1, anti-MUSK, anti-AchR, etc.).[57,59]

Six articles reporting ≥5 patients with anti-Caspr2 antibodies, published between 2010 and 2015, were included in this review (Table 3).[10,53–55,57,59] A total of 71 patients are described in these papers (31/86, 36% females), with age at onset ranging between 8 and 77 years (1/67, 1.5% children).

Treatment

The majority of patients with adequate information received immune therapy (37/40, 92.5%), and first-line treatments were administered in 85.7% (18/21): steroids in 61.9% (13/21), IVIG in 38.1% (8/21) and PE in 14.3% (3/21). Second-line therapies were administered in 28.6% (6/21): rituximab in 14.3% (3/21), cyclophosphamide in 4.8% (1/21), mycophenolate mofetil and cyclosporine in 9.5% (2/21) each.

Immune therapy versus no immune therapy

In a recent series, all four patients who received immune therapy had good recovery (mRS 0–1), whereas the only patient not treated had a poor outcome (mRS 4) [54]. In the series by Lancaster et al. [59], the two patients who did not receive immune therapy had a worse outcome (full recovery: 0/2, 0%; severe sequelae: 1/2, 50%) than the patients who did receive immune therapy (full recovery: 2/8, 25%; severe sequelae: 1/8, 12.5%). In the series by Irani et al., all patients received immune therapy, but mRS was significantly reduced post-treatment only in the patients without tumor, whereas four of the six patients with tumor died [10].

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Table 3. Summary of the literature review on the treatment of anti-Caspr2 autoimmunity (only cohorts ≥5 patients were included). [10,53–55,57,59]

	Irani [10]	Lancaster [59]	Becker [55]	Irani [57]	Pinatel [53]	Sunwoo [54]
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	19	8	12‡	21	7	5
Clinical description (no. of females)	7/19: LE 3/19: Morvan's syndrome 7/19: neuromyotonia 2/19: epilepsy only (F: 3/19, 15.8%)	5/8: encephalopathy or seizures + neuropathy or peripheral nerve hyperexcitability (3 also had myasthenia gravis, bulbar weakness, or symptoms that initially suggested motor neuron disease) 2/8: encephalopathy or seizures 1/8: isolated peripheral nerve hyperexcitability (F: 1/8, 12.5%)	9/12: cerebellar ataxia 3/12: controls (F: 8/9, 88.9%)	21/21: Morvan's syndrome (F: n.a.)	7/7: LE (F: 0/7, 0%)	2/5: isolated seizures 1/5: encephalopathy and seizures 1/5: encephalopathy, behavioral changes, insomnia, seizures 1/5: encephalopathy, dysarthria, insomnia, PNS symptoms (F: 2/5, 40%)
Median age at onset (range)	Range 44–77 years (median n. a.)	60.5 years (46–77)	58 years (35–76) (data available in 9/13)	Adults (median and range n. a.)	64 years (60–73)	43.5 years (8–65) (1 child)
Tumor	6/19 (31.6%): –5/19: thymomas –1/19: endometrial adenocarcinoma	1/8 (12.5%): –1/8: History of low-grade bladder cancer	0/9 (0%)	11/21 (52.4%) –10/21: thymomas –1/21: small cell lung cancer	3/7 (42.8%): –2/7: prostate cancer –1/7: thyroid cancer	0/5 (0%)
Additional antibody	n.a.	6/7 (85.7%): –4/7: VGKC –1/7: VGKC, MUSK, AchR –1/7: VGKC, AchR, GAD	2/6 (33.3%): –1/6: ANA –1/6: thyroid antibody, VGKC complex	15/21 (71.4%): –15/21: LGI1	0/7 (0%)	0/5 (0%)
Immune therapy†	19/19 (100%)	6/8 (75%)	1/1 (100%)	n.a.	7/7 (100%)	4/5 (80%)
First-line	n.a.	6/8 (75%)	1/1 (100%)		7/7 (100%)	4/5 (80%)
Steroids		5/8 (62.5%)	0/1 (0%)		4/7 (57.1%)	4/5 (80%)
Intravenous immunoglobulin		2/8 (25%)	1/1 (100%)		2/7 (28.6%)	3/5 (60%)
Plasma exchange		2/8 (25%)	0/1 (0%)		1/7 (14.3%)	0/5 (0%)
Second-line	n.a.	3/8 (37.5%)	1/1 (100%)		1/7 (14.3%)	1/5 (20%)
Rituximab		3/8 (37.5%)	0/1 (0%)		0/7 (0%)	0/5 (0%)
Cyclosporine		1/8 (12.5%)	0/1 (0%)		0/7 (0%)	0/5 (0%)

(*continued*)

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Table 3. Summary of the literature review on the treatment of anti-Caspr2 autoimmunity (only cohorts ≥5 patients were included). [10,53–55,57,59] (continued).

	Irani [10]	Lancaster [59]	Becker [55]	Irani [57]	Pinatel [53]	Sunwoo [54]
Other:		1/8 (12.5%) Cyclosporine	1/1 (100%) Cyclosporine		1/7 (14.3%) mofetil mycophenolate	1/5 (20%) mofetil mycophenolate
Median length of follow-up (range)	n.a.	8 months (6–84)	n.a.	n.a.	n.a.	8 months (3–18)
No. of patients who relapsed	n.a.	n.a.	0/1 (0%)	n.a.	n.a.	0/5 (0%)
Outcome	mRS were reduced by immune therapy ($p = 0.001$ in the patients without tumor), except in the 6 cases with tumors, 4 of whom died mRS 6: 4/19 (21%)	Full recovery: 2/8 (25%) Mild neurological sequelae: 4/8 (50%) Severe neurological sequelae: 2/8 (25%)	mRS 3: 1/1 (100%)	n.a.	n.a.	mRS 0: 2/5 (40%) mRS 1: 2/5 (40%) mRS 4: 1/5 (20%) Seizure-free: 3/4 (75%) Seizure reduction: 1/4 (25%)

†At first episode.
‡Clinical data available in 9/12 patients, and therapeutic and outcome data in 1/12 only [55].
F: Females; LE: Limbic encephalitis; mRS: Modified Rankin scale; VGKC: Voltage-gated potassium channels; AchR: Acetilcholine receptor; ANA: Antinuclear antibodies; GAD: Glutamic acid decarboxylase; MUSK: Muscle-specific tyrosine kinase; LGI1: Leucine-rich, glioma-inactivated protein 1.

Second-line immune therapy

In the combined cohorts, patients who did not receive second-line immune therapy had a worse outcome than those who did (mRS ≥3: 3/9, 33.3% vs. 1/7, 14.3%). Two case reports in 2013 described beneficial effect with B-cell-depleting therapies (rituximab and tocilizumab) in one patient with Morvan's syndrome and one with epilepsy, dysarthria and paroxysmal kinesigenic dyskinesia, respectively.[58,61]

Outcome

The follow-up data are limited. In general, relapse appears uncommon, and full recovery occurred in about one-fourth of patients, whereas 12.1% died (4/33 with adequate information).

Anti-AMPAR antibodies

Epidemiology and clinical features

Autoantibodies against the GluA1 or GluA2 subunits of AMPAR were first described in 2009 [8]. AMPAR is an ionotropic glutamate receptor important for synaptic plasticity, memory and learning.[62] While the initial clinical description in the first 10 patients with anti-AMPAR encephalitis was of limbic encephalitis,[8], subsequent identification of new cases led to a phenotype expansion to include multifocal/diffuse encephalopathy, hyponatremia, limbic encephalitis preceded by motor deficits or a predominantly psychiatric syndrome.[63] The disorder is paraneoplastic in 63–70% of cases,[8,63] and it has been described in association with small cell lung cancer, thymoma, breast and ovarian cancer. However, the condition is rare and further clinical descriptions will help define the spectrum of disease.

A literature search for all articles reporting patients with anti-AMPAR encephalitis led to the identification of eight articles published between 2009 and 2015, reporting a total of 43 patients (Table 4) (32/43, 74.4% females), all adults (age range 23–87 years).[8,63–69] All articles are retrospective; four reported an individual patient,[64,66,68,69] two were small series describing 4 and 3 patients, respectively,[65,67] and only two were larger cohorts reporting 10 and 22 patients, respectively.[8,63] Most of the cases with available information were positive for anti-GluA2 antibodies (19/37, 51.3%), or for both anti-GluA1 and anti-GluA2 antibodies (11/37, 29.7%), whereas a minority for anti-GluA1 antibodies only (7/37, 18.9%). In the 20 cases with available paired CSF and serum samples, antibodies were found in the CSF in all cases (20/20) and in serum in 75% (15/20) [63–66]. 25.6% of patients had other antibodies (10/39), and in the largest series the authors observed that these additional autoantibodies often dictated the clinical phenotype, and that in the patients with cancer and onconeuronal or tumor-related antibodies the median survival was significantly shorter than those patients with cancer but without additional onconeuronal antibodies ($p = 0.009$) [63].

Treatment

Most of the patients received immune therapy during the first episode of disease (40/42, 95.2%). Steroids were administered in 80.9% patients (34/42), IVIG in 52.4% (22/42) and PE in

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Table 4. Summary of the literature review on the treatment of anti-AMPAR encephalitis (all available cohorts were included).[8,63–69]

	Lai [8]	Bataller [64]	Graus [65]	Wei [66]	Höftberger [63]	Dogan Onugoren [67]	Elamin [68]	Li [69]
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	10	1	4	1	22[‡]	3	1	1
Clinical description (no. of females)	10/10: LE (F: 9/10, 90%)	1/1: LE (F: 1/1, 100%)	2/4: LE 2/4: other encephalitis with psychosis (F: 4/4, 100%)	1/1: encephalitis (F: 1/1, 100%)	12/22: LE 8/22: limbic dysfunction with multifocal/diffuse encephalopathy 1/22: LE preceded by motor deficits 1/22: psychosis (F: 14/22, 63.6%)	3/3: LE (F: 1/3, 33.3%)	1/1: encephalitis (F: 1/1, 100%)	1/1: encephalitis (F: 1/1, 100%)
Median age at onset (range)	60 years (38–87)	67 years	59 years (51–71)	30 years	62 years (23–81)	61 years (61–62)	73 years	47 years
Tumor	7/10 (70%): –2/10: breast cancer –1/10: thymic carcinoma –1/10: thymoma –1/10: malignant thymoma –1/10: non-SCLC –1/10: SCLC	1/1 (100%): –1/1: adenocarcinoma	3/4 (75%) –2/3: SCLC –1/3: malignant thymoma	0/1 (0%)	14/22 –5/22: SCLC –4/22: thymoma –2/22: breast cancer –2/22: ovarian teratoma –1/22: lung cancer	1/3 (33.3%) –1/3: ovarian adenocarcinoma	0/1 (0%)	1/1 (100%): –1/1: thymoma
Additional antibody	3/10 (30%): –1/3: GAD –1/3: CV2/CRMP5 –1/3: SOX1, VGCC	0/1 (0%)	n.a.	0/1 (0%)	7/22 (31.8%): –2/22 CRMP5 –1/22 amphiphysin –1/22 SOX1 –2/22 NMDAR –1/22 SOX1, GABABR	0/3 (0%)	0/1 (0%)	0/1 (0%)
Immune therapy[†]	9/10 (90%)	1/1 (100%)	4/4 (100%)	1/1 (100%)	20/21 (95.2%)	3/3 (100%)	1/1 (100%)	1/1 (100%)
First-line	9/10 (90%)	1/1 (100%)	4/4 (100%)	1/1 (100%)	20/21 (95.2%)	3/3 (100%)	1/1 (100%)	1/1 (100%)
Steroids	9/10 (90%)	0/1 (0%)	4/4 (100%)	0/1 (0%)	17/21 (80.9%)	3/3 (100%)	0/1 (0%)	1/1 (100%)
Intravenous immunoglobulin	5/10 (50%)	1/1 (100%)	0/4 (0%)	1/1 (100%)	12/21 (57.1%)	2/3 (66.7%)	1/1 (100%)	0/1 (0%)
PE	2/10 (20%)	0/1 (0%)	0/4 (0%)	0/1 (0%)	6/21 (28.6%)	2/3 (66.7%)	0/1 (0%)	0/1 (0%)
Second-line	1/10 (10%)	1/1 (100%)	0/4 (0%)	1/1 (100%)	5/21 (23.8%)	0/3 (0%)	0/1 (0%)	0/1 (0%)
Rituximab	0/10 (0%)	0/1 (0%)	0/4 (0%)	1/1 (100%)	5/21 (23.8%)	0/3 (0%)	0/1 (0%)	0/1 (0%)
Cyclophosphamide	1/10 (10%)	1/1 (100%)	0/4 (0%)	0/1 (0%)	1/21 (4.8%)	0/3 (0%)	0/1 (0%)	0/1 (0%)

(*continued*)

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Table 4. Summary of the literature review on the treatment of anti-AMPAR encephalitis (all available cohorts were included).[8,63–69] (continued).

	Lai [8]	Bataller [64]	Graus [65]	Wei [66]	Höftberger [63]	Dogan Onugoren [67]	Elamin [68]	Li [69]
Other	0/10 (0%)	0/1 (0%)	0/4 (0%)	1/1 (100%) AZA	0/21 (0%)	0/3 (0%)	0/1 (0%)	0/1 (0%)
Median length of follow-up (range)	15.5 months (0.5–120)	12 months	n.a.	119 days	72 weeks (5–266) (data available in 21/22 patients)	6 months (5–14)	n.a.	10 months
No. of patients who relapsed	5/10 (50%)	0/1 (0%)	0/4 (0%)	0/1 (0%)	1/21 (4.8%)	3/3 (100%)	1/1 (100%)	0/1 (0%)
Outcome	Returned to baseline: 2/10 (20%) Residual deficits: 5/10 (50%) Death: 3/10 (30%)	Residual deficits: 1/1 (100%)	mRS 0–5: 4/4 (100%)	Residual deficits: 1/1 (100%)	mRS 0: 1/21 (4.8%) mRS 1: 4/21 (19%) mRS 2: 5/21 (23.8%) mRS 3: 4/21(19%) mRS 4: 1/21 (4.8%) mRS 5: 1/21 (4.8%) mRS 6: 5/21 (23.8%)	Full recovery: 1/3 (33.3%) Partial recovery: 1/3 (33.3%) Limited recovery: 1/3 (33.3%)	n.a.	Partial recovery: 1/1 (100%)
Memory deficits	4/10 (40%)	1/1 (100%)	n.a.	1/1 (100%)	n.a.	1/3		1/1 (100%)
Psychiatric problems	3/10 (30%) (behavior mood)	0/1 (0%)	n.a.	1/1 (100%) (behavior mood)		3/3 (psychiatric, mood)		0/1 (0%)
Speech problems	1/10 (10%)	0/1 (0%)	n.a.	1/1 (100%)		0/3		1/1 (100%)
Other	1/10 (10%) (muscle spasms and rigidity)	0/1 (0%)	n.a.	0/1 (0%)		0/3		0/1 (0%)

[†]At first episode.
[‡]Data on treatment ad outcome available in 21/22 patients [63].
AZA: Azathioprine; F: Females; LE: Limbic encephalitis; mRS: Modified Rankin scale; n.a.: Not available; PE: Plasma exchange; SCLC: Small cell lung cancer; SOX1; Sry-like high mobility group box 1; CRMP5: Collapsin response-mediator protein 5; VGCC: Voltage-gated calcium channels; NMDAR: *N*-methyl-D-aspartate receptor; GABABR: γ-aminobutyric acid-B receptor.

23.8% (10/42). Second-line immune therapies were administered in 19% (8/42) of patients: rituximab in 14.3% (5/42), cyclophosphamide in 7.1% (3/42) and azathioprine in 2.4% (1/42).

Immune therapy versus no immune therapy

Only two patients in the total cohort did not receive immune therapy. These were two women with tumor and onconeuronal or tumor-related antibodies, and both died (one due to limbic encephalitis, one due to cancer) [8,63].

Timing of immune therapy

Data on the timing of immune therapy are insufficient to establish a relationship with outcome. In the largest series of 22 patients [63], the median time from symptom onset until diagnosis was relatively long (6.5 weeks, interquartile range 4–18.3 weeks), possibly due to the fact that the disease is still incompletely characterized and recognized.[70]

Second-line immune therapy

The eight patients with anti-AMPAR encephalitis who received second-line treatments during the first episode had lower rates of relapses and death (0/8, 0% and 0/8, 0%, respectively) than the 34 patients who did not receive second-line immune therapies (10/34, 29.4% and 8/33, 24.2%, respectively).

Outcome

Length of follow-up ranged between 0.5 and 120 months. 10.8% of patients had a full recovery (mRS 0) (4/37), whereas most cases recovered partially (25/37, 67.6%). Most frequent sequelae were memory deficits (8/16, 50%), psychiatric issues (behavior/mood) (7/16, 43.7%), speech problems (3/16, 18.7%) or muscle spasms and rigidity (1/16, 6.2%). Relapses occurred in 23.8% of patients (10/42), and death in 21.6% (8/37) (related to cancer in five, to cardiorespiratory arrest in one, to myocardial infarction in one and to status epilepticus after a relapse of limbic encephalitis in one).

Anti-GABAAR antibodies

Autoantibodies targeting the GABAAR, the primary ligand-gated fast-acting inhibitory brain receptor,[71] were first identified in 2014 in 18 patients.[12] While six of these had high-titer CSF and serum anti-GABAAR antibodies and a relatively homogeneous presentation with encephalitis and refractory seizures, the remaining 12 patients, with low-titer antibodies present only in the serum, had variable symptomatology including stiff-person syndrome and opsoclonus myoclonus ataxia syndrome. The clinical heterogeneity was further confirmed in a later series, in which clinical syndromes in the 15 cases with available information included isolated seizures, isolated psychiatric disturbances, isolated cognitive impairment, limbic encephalitis and other symptoms.[72] The diversity of these clinical presentations raises questions about the pathogenic role of these antibodies,[73] particularly at lower titers. The detection of tumors is rare, ranging between 11.1% and 21.4%.[12,72] Other autoantibodies have been identified in up to 66.7% of cases, most frequently anti-GAD, anti-thyroid peroxidase, anti-GABABR, anti-ANA, anti-VGKC, anti-NMDAR and others,[12,72] once again raising questions of antibody-specific pathogenicity.

Only 66 cases have been identified so far, 45 of which are described in one recent series (clinical and treatment data only available in 15/45 of these) (Table 5).[12,72,74,75] Age at onset ranged between 2 and 74 years (16/66, 24.2% <20 years), and genders were similarly represented (31/66, 47% females).

Only 54.5% (18/33) of patients with adequate information received immune therapy. This treatment rate was particularly low in the recent retrospective series by Pettingill et al. (4/15, 26.7%), possibly due to the heterogeneity of the clinical phenotypes, which was only rarely suggestive of autoimmune encephalitis to the treating clinician.[72] First-line immune therapies were administered in 54.5% (18/33): steroids in 42.4% (14/33), IVIG in 27.3% (9/33) and PE in 18.2% (6/33). Second-line therapies were used in 18.2% (6/33) of cases: rituximab in 12.1% (4/33), cyclophosphamide in 6.1% (2/33), and azathioprine and cyclosporine in 3% (1/33) each.

The patients receiving immune therapy had better outcomes than those who did not receive immune therapy (mRS 0: 2/18, 11.1% vs. 0/12, 0%), though there was a higher rate of relapse (3/18, 16.7% vs. 1/12, 8.3%). The patients receiving immune therapy were more likely to die (4/18, 22.2% vs. 1/12, 8.3%), possibly related to severity bias. The patients treated with second-line therapy had lower relapse rates than those who did not receive second-line therapy (0/6, 0% vs. 4/24, 16.7%), and better outcomes (mRS 0: 1/6, 16.7% vs. 1/24, 4.2%), despite similar death rates (1/6, 16.7% vs. 4/24, 16.7%).

In the total cohort, relapses occurred in 13.3% (4/30) of patients. At last follow-up, ranging between 1 and 192 months, only 6.7% (2/30) patients had a full recovery, and 10% (3/30) died.

Anti-GABABR antibodies

Epidemiology and clinical features

In 2010, GABABR was identified as the target antigen in a subset of patients with limbic encephalitis [11]. In a subsequent series, anti-GABABR antibodies were detected in 14.3% of patients with limbic encephalitis (10/70).[76] Cerebellar ataxia and other clinical syndromes (including PERM, opsoclonus myoclonus ataxia syndrome and epilepsy) have also been described in association with anti-GABABR antibodies, although uncommonly.[11,76–78] GABABRs have an inhibitory function and are widely expressed in the brain and spinal cord with the highest levels in the hippocampus, thalamus and cerebellum.[79] Clinical, MRI and electroencephalographic data suggest that the brain regions most affected are the hippocampi and temporal lobes, explaining the relative similarity of anti-GABABR encephalitis to other types of limbic encephalitis [11]. Tumors have been detected in up to 80% of patients,[76,77,80] typically SCLC. In the majority of cases, other coexisting autoantibodies have been identified, mostly against intracellular antigens.[78]

Six articles published between 2010 and 2015, with ≥5 patients with positive anti-GABABR antibodies, were included

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Table 5. Summary of the literature review on the treatment of anti-GABAAR encephalitis (all available cohorts were included).[12,72,74,75]

	Petit-Pedrol [12]	Ohkawa [74]	Pettingill [72]	Simabukuro [75]
Study design	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	18	2	45[‡]	1
Clinical description (no. of females)	6/18 with high titer (>1:160) cerebrospinal fluid and serum anti-GABAAR antibody: encephalitis and refractory seizures or status epilepticus 12/18 with low-titer serum only (≤1:160) anti-GABAAR antibody: 6 Encephalitis with seizures, 4 stiff-person syndrome (1 with seizures), and 2 opsoclonus myoclonus ataxia syndrome (F: 6/18, 33.3%)	2/2: encephalitis with cognitive impairment and multifocal brain MRI abnormalities (F: 1/2, 50%)	15/15: variable symptomatology (7/15 seizures, 7/15 memory impairment, 4/15 confusion or disorientation, 5/15 psychiatric features, 2/15 hallucinations, 4/15 anxiety) (F: 23/45, 50%)	1/1: LE (F: 1/1, 100%)
Median age at onset (range)	24.5 years (2–74) (7 children)	52.2 years (46–59)	51 years (2–73) (8/45 were <20 years old)	45 years
Tumor	2/18 (11.1%): –1/18: Hodgkin's lymphoma –1/18: Previous history of ovarian cancer	2/2 (100%): 2/2: Invasive thymoma	3/14 (21.4%): –1/14: dysembryoplastic neuroepithelial tumors –1/14: Prostatic cancer –1/14: Non-Hodgkin's lymphoma	1/1 (100%): –1/1: Thymoma
Additional antibody	12/18 (66.7%): –4/18: GAD –1/18: TPO, thyroglobulin –1/18: TPO –1/18: GABABR –1/18: GABABR, GAD, TPO, thyroglobulin –1/18: GAD, TPO, thyroglobulin –1/18: NMDAR –1/18: ANA, anti-endomysial IgA –1/18: ANA	2/2 (100%): –1/2: AchR, VGKC, LGI1, DCC –1/2: VGKC, Caspr2, DCC	3/15 (20%): –2/15: VGKC complex –1/15: NMDAR, Caspr2, VGKC complex	1/1 (100%): –1/1: LGI1
Immune therapy[†]	12/15 (80%)	1/2 (50%)	4/15 (26.7%)	1/1 (100%)
First-line	12/15 (80%)	1/2 (50%)	4/15 (26.7%)	1/1 (100%)
Steroids	10/15 (66.7%)	1/2 (50%)	2/15 (13.3%)	1/1 (100%)
Intravenous immunoglobulin	7/15 (46.7%)	1/2 (50%)	1/15 (6.7%)	0/1 (0%)
Plasma exchange	3/15 (20%)	0/2 (0%)	2/15 (13.3%)	1/1 (100%)
Second-line	5/15 (33.3%)	0/2 (0%)	1/15 (6.7%)	0/1 (0%)
Rituximab	4/15 (26.7%)	0/2 (0%)	0/15 (0%)	0/1 (0%)
Cyclosporine	2/15 (13.3%)	0/2 (0%)	0/15 (0%)	0/1 (0%)
Other:	1/15 (6.7%) cyclosporine	0/2 (0%)	1/15 (6.7%) azathioprine	0/1 (0%)
Median length of follow-up (range)	24 months (1–192) (d.a. in 9/18)	8 months (d.a. in 1/2 patients)	18 months (2–20) (d.a. in 9/45)	Not available
No. of patients who relapsed	1/15 (6.7%)	1/2 (50%)	1/12 (8.3%)	1/1 (100%)

(*continued*)

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Table 5. Summary of the literature review on the treatment of anti-GABAAR encephalitis (all available cohorts were included).[12,72,74,75] (continued).

	Petit-Pedrol [12]	Ohkawa [74]	Pettingill [72]	Simabukuro [75]
Outcome	Full recovery: 2/15 (13.3%) Substantial/marked improvement: 4/15 (26.7%) Neurological sequelae: 6/15 (40%) Death: 3/15 (20%)	Neurological sequelae: 2/2 (100%)	Improvement: 8/12 (66.7%) Steady decline: 1/12 (8.3%) Huntington disease confirmed: 1/12 (8.3%) Death: 2/12 (16.7%)	Close to baseline: 1/1 (100%)

†At first episode.
‡Clinical and treatment data available only in 15/45 [72].
d.a.: Data available; F: Females; GABAAR: γ-aminobutyric acid-A receptor; GAD: Glutamic acid decarboxylase; TPO: Thyroid peroxidase; VGKC: Voltage-gated potassium channels; NMDAR: *N*-methyl-D-aspartate receptor; ANA: Antinuclear antibodies; AchR: Acetilcholine receptor; LGI1: Leucine-rich, glioma-inactivated protein 1; Caspr2: Contactin-associated protein-2; MRI: Magnetic resonance imaging.

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in this review (Table 6).[11,67,76–78,80] All are retrospective noncontrolled studies, reporting a total of 79 patients (35/79, 44.3% females), with age at onset between 16 and 85 years (3/79, 3.8% ≤18 years).

Treatment

Most of the patients received immune therapy (53/67, 79.1%). First-line treatments were administered in 79.1% (53/67): steroids in 64.2% (43/67), IVIG in 43.3% (29/67) and PE in 19.4% (13/67). Only a minority of patients received second-line immune therapies (9/67, 13.4%): rituximab was used in 6% (4/67), cyclophosphamide in 4.5% (3/67), mycophenolate mofetil in 3% (2/67) and azathioprine in 1.5% (1/67).

Immune therapy versus no immune therapy

In the first series by Lancaster et al. [11], most of the patients who received immune therapy had full or substantial improvement (10/13, 76.9%) as opposed to none of the patients who did not receive immune therapy (0/3, 0%) (p = 0.005); moreover, 23.1% (3/13) of those who received immune therapy eventually died as opposed to all of those who were not treated (3/3, 100%). In the cohort reported by Boronat et al. [76], after excluding one nonassessable patient, 90% (9/10) of patients who received immune therapy and cancer treatment (when appropriate) showed neurological improvement as opposed to none of the four patients who did not receive immune therapy or whose tumor treatment was not completed (p = 0.005). In the combined cohorts, patients who received immune therapy at the first episode had better outcomes than those who did not (mRS 0–1: 23/51, 45.1% vs. 1/13, 7.7%), and lower rates of death (12/51, 23.5% vs. 8/11, 76.9%), despite higher rates of relapses (2/36, 5.5% vs. 0/9, 0%).

Second-line immune therapy

In the series by Kim et al., where the majority of patients recovered only partially (mRS 2 in 3/5, 60%) [80], the authors comment that the relatively partial response to treatment in anti-GABABR encephalitis might be attributed to insufficient immune therapy, including second-line treatments. In concordance with this, in the combined cohorts in this review, the patients who received second-line treatments had a marginally more favorable outcome than those who did not have second-line treatment (mRS 0–1: 3/9, 33.3% vs. 17/55, 30.9%). In addition, patients who received second-line treatment had lower rates of relapses (0/5, 0% vs. 2/41, 4.9%) and of death (1/9, 11.1% vs. 21/55, 38.2%).

Outcome

Relapses occurred in a very limited proportion of patients (2/53, 3.8%). At last follow-up (range 0–72 months), 25.3% (18/71) of patients had a complete recovery and 33.8% (24/71) had died.

Anti-GlyR antibodies

First described in 2008 [7], anti-GlyR antibodies have been reported in a broad range of clinical syndromes, including PERM,[7,81,82] stiff-person syndrome,[83–85] epilepsy,[86,87] limbic encephalitis,[82,88] cerebellar ataxia,[89,90] transverse myelitis,[91] optic neuritis,[92] neuromyelitis optica [93] and multiple sclerosis [84,92]. The association with tumor (thymoma, lymphoma, lung tumor) is rare (0–9%) and has been reported mostly with PERM and stiff-person syndrome,[82,83] in which coexisting anti-GAD antibodies have also been frequently described [82–84] and, more rarely, anti-NMDAR antibodies.[94] Additional antibodies detected in the other clinical phenotypes include anti-VGKC (epilepsy) [82,86] and antibodies against myelin oligodendrocyte glycoprotein and aquaporin-4 (optic neuritis).[92]

Seven articles published between 2013 and 2015 with ≥5 patients, all retrospective, were included in this review (Table 7).[82–84,86,87,90,92] The papers report a total of 112 patients with anti-GlyR antibodies (47/95, 49.5% females), 55 of which derive from two separate cohorts described in one large series.[82] Age at onset ranged between 3 and 75 years (13/89, 14.6% children).

77.3% (58/75) of patients in the combined cohort received immune therapy. First-line agents were administered in 79.4% (54/68) of patients with available data: steroids in 66.2% (45/

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Table 6. Summary of the literature review on the treatment of anti-GABABR encephalitis (only cohorts ≥5 patients included).[11,67,76–78,80]

	Lancaster [11]	Boronat‡ [76]	Jeffery [77]	Höftberger [78]	Kim [80]	Dogan Onugoren [67]
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	17	10	17	20	5	10
Clinical description (no. of females)	15/17: LE 2/17: controls (1: progressive cerebellar ataxia; 1: progressive encephalomyelitis with rigidity and myoclonus) (F: 9/17, 52.9%)	9/10: LE (6: SCLC without onconeural ab; 1: SCLC with Hu-ab; 2: no tumor, no onconeural ab) 1/10: cerebellar ataxia (F: 2/10, 20%)	10/17: LE 1/17: rapidly progressive encephalomyelopathy 1/17: cerebellar ataxia 5/17: other syndromes (3: CSN; 2: PNS) (F: 11/17, 64.7%)	17/20: LE 1/20: ataxia 1/20: status epilepticus 1/20: opsoclonus myoclonus ataxia syndrome (F: 8/20, 40%)	5/5: LE (F: 3/5, 60%)	10/10: LE (F: 2/10, 20%)
Median age at onset (range)	62 years (24–75)	59 years (47–70)	63 years (16–85) (2 children, age 16 and 18 years)	61.5 years (16–77) (1 child, age 16 years)	63 years (58–71)	69.5 years (51–75)
Tumor	7/17 (41.2%): –5/17: SCLC –1/17: neuroendocrine lung tumor -1/17: mediastinal adenopathy	8/10 (80%): –7/10: SCLC –1/10: carcinoid of thymus	13/17 (76.5%): –9/17: SCLC –1/17: SCLC and breast –1/17: lung mass –1/17: multiple myeloma –1/17: rectal carcinoma	10/20 (50%): –10/20: SCLC	4/5 (80%): –4/5: SCLC	5/10 (50%): –4/10: SCLC –1/10: lung cancer
Additional antibody	9/17 (52.9%): –3/17: VGCC –2/17: GAD –1/17: TPO, GAD –1/17: TPO, thyroglobulin –1/17: GAD, TPO, SOX1 –1/17: GAD, TPO, thyroglobulin	6/10 (60%): –2/10: GAD –1/10: SOX1, VGKC –1/10: GAD, SOX1 –1/10: Hu –1/10: BRSK2	16/16 (100%): –10/16: VGCC –1/16: AGNA /SOX1, VGCC, VGKC –1/16: VGCC, VGKC, CRMP5 –1/16: Hu –1/16: Hu, ANNA3 –1/16: ANNA3, GAD –1/16: CRMP5	7/20 (35%): –3/20: SOX1 –1/20: Ri –1/20: Amphiphysin –1/20: GAD –1/20: NMDAR	2/5 (40%): –2/5: Hu	4/10 (40%): –3/10: SOX1 –1/10: Hu
Immune therapy†	13/17 (76.5%)	8/10 (80%)	5/6 (83.3%)	15/19 (78.9%)	4/5 (80%)	8/10 (80%)
First-line	13/17 (76.5%)	8/10 (80%)	5/6 (83.3%)	15/19 (78.9%)	4/5 (80%)	8/10 (80%)
Steroids	11/17 (64.7%)	7/10 (70%)	2/6 (33.3%)	14/19 (73.7%)	3/5 (60%)	6/10 (60%)
Intravenous immunoglobulin	6/17 (35.3%)	7/10 (70%)	1/6 (16.7%)	7/19 (36.8%)	4/5 (80%)	4/10 (50%)
Plasma exchange	2/17 (11.8%)	0/10 (0%)	4/6 (66.7%)	5/19 (26.3%)	0/5 (0%)	2/10 (20%)
Second-line	1/17 (5.9%)	0/10 (0%)	1/6 (16.7%)	4/19 (21%)	0/5 (0%)	3/10 (30%)
Rituximab	0/17 (0%)	0/10 (0%)	0/6 (0%)	2/19 (10.5%)	0/5 (0%)	2/10 (20%)

(*continued*)

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Table 6. Summary of the literature review on the treatment of anti-GABABR encephalitis (only cohorts ≥5 patients included).[11,67,76–78,80] (continued).

	Lancaster [11]	Boronat‡ [76]	Jeffery [77]	Höftberger [78]	Kim [80]	Dogan Onugoren [67]
Cyclophosphamide	0/17 (0%)	0/10 (0%)	1/6 (16.7%)	1/19 (5.3%)	0/5 (0%)	1/10 (10%)
Other:	1/17 (5.9%) mycophenolate mofetil	0/10 (0%)	0/6 (0%)	1/19 (5.3%) mycophenolate mofetil	0/5 (0%)	1/10 (10%) AZA
Median length of follow-up (range)	9 months (0–72)	n.a.	1 months (0–34)	7 months (0.75–45)	3 months (1–12)	3 months (1–12)
No. of patients who relapsed	1/17 (5.9%)	1/10 (10%)	0/12 (0%)	n.a.	0/5 (0%)	0/9 (0%)
Outcome	Full recovery: 4/16 (25%) Substantial improvement: 4/16 (25%) Partial improvement: 2/16 (12.5%) Death: 6/16 (37.5%)	Complete recovery: 3/9 (33.3%) Partial improvement: 1/9 (11.1%) No response: 1/9 (11.1%) Death: 4/9 (44.4%)	Complete resolution: 2/12 (16.7%) Neurological sequelae of varying severity: 7/12 (58.3%) Death: 3/12 (25%)	Complete response: 6/20 (30%) Partial response: 6/20 (30%) Death: 8/20 (40%)	mRS 1: 2/5 (40%) mRS 2: 3/5 (60%)	Complete remission: 1/9 (11.1%) Partial improvement: 3/9 (33.3%) No improvement: 2/9 (22.2%) Death: 3/9 (33.3%)

†At first episode.
‡One patient of this series was excluded as it was included in the initial series by Lancaster et al. [11].
ab: Antibody; AGNA: Anti-glial nuclear antibody; GABABR: γ-aminobutyric acid-B receptor; GAD: Glutamic acid decarboxylase; LE: Limbic encephalitis; mRS: Modified Rankin scale; SCLC: Small cell lung cancer; SOX1; Sry-like high mobility group box 1; TPO: Thyroid peroxidase; VGCC: Voltage-gated calcium channels; VGKC: Voltage-gated potassium channel; NMDAR: N-methyl-D-aspartate receptor; CRMP5: Collapsin response-mediator protein 5.

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Table 7. Summary of the literature review on the treatment of anti-GlyR autoimmunity (only cohorts ≥5 patients were included).[82–84,86,87,90,92]

	McKeon [83]	Brenner [86]	Alexopoulos [84]	Ekizoglu [87]	Carvajal-Gonzalez [82]	Carvajal-Gonzalez [82][§]	Gresa-Arribas [90]	Martinez-Hernandez [92]
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	11	12	11	5	45	10	6	12
Clinical description (no. of females)	5/11: variant SPS[‡] 4/11: classic SPS 1/11: PERM 1/11: control with optic atrophy (F: 6/11, 54.5%)	12/12: epilepsy (F: 6/12, 50%)	9/11: SPS with high titer (>20,000 units) of anti-GAD ab 1/11: SPS with low anti-GAD titer (<50 U/ml) 1/11: relapsing-remitting multiple sclerosis, GAD-negative (F: n.a.)	4/5: focal epilepsy of unknown origin 1/5: mesial temporal lobe epilepsy with hippocampal sclerosis (F: 3/5, 60%)	33/45: PERM 5/45: limbic encephalitis or epileptic encephalopathy 2/45: SPS 2/45: brainstem features 2/45: demyelinating optic neuropathies 1/45: unclear diagnosis (F: 21/45, 46.7%)	5/10: PERM 4/10: SPS 1/10: acquired hyperekplexia (F: 6/10, 60%)	4/6: cerebellar ataxia 2/6: epilepsy (F: n.a.)	7/12: isolated ON (final diagnosis: recurrent isolated ON in 4, monophasic isolated ON in 1, neuromyelitis optica in 1, multiple sclerosis in 1) 5/12: multiple sclerosis (F: 5/7, 71.4%)
Median age at onset (range)	43 years (5–69) (2 children)	47 years (27–73)	n.a.	16 years (3–17) (5 children)	50 years (1–75) (4 children)	42 years (19–54) (d.a. in 9/10)	n.a.	27 years (11–38) (2 children) (d.a. in 7/12)
Tumor	1/11 (9.1%): –1/11: Hodgkin's lymphoma	0/12 (0%)	0/11 (0%)	0/5 (0%)	4/45 (8.9%) –3/45: thymoma –1/45: lymphoma 5/45 (11.1%) had previous tumors, treated	1/10 (10%): –1/10: previous breast cancer	0/6 (0%)	0/12 (0%)
Additional antibody	6/11 (54.5%) –6/11: GAD	1/12 (8.3%) –1/12: VGKC	10/11 (90.9%) –10/11: GAD (9 high titer, 1 low titer)	0/5 (0%)	13/28 (46.4%): –4/28: GAD –3/28 VGKC -complex –3/28: NMDAR –6/45: thyroid ab	4/9 (44.4%): –4/9: GAD	6/6 (100%): –6/6: GAD	4/12 (33.3%): –3/12: MOG –1/12: AQP4 (all patients with ON)
Immune therapy[†]	7/10 (70%)	n.a.	n.a.	2/5 (40%)	37/44 (84.1%)	9/9 (100%)	n.a.	3/7 (42.8%)
First-line	7/10 (70%)			1/5 (20%)	37/44 (84.1%)	9/9 (100%)		n.a.
Steroids	5/10 (50%)			1/5 (20%)	31/44 (70.4%)	8/9 (88.9%)		n.a.
Intravenous immunoglobulin	3/10 (30%)			1/5 (20%)	20/44 (45.4%)	5/9 (55.5%)		n.a.

(*continued*)

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Table 7. Summary of the literature review on the treatment of anti-GlyR autoimmunity (only cohorts ≥5 patients were included).[82–84,86,87,90,92] (continued).

	McKeon [83]	Brenner [86]	Alexopoulos [84]	Ekizoglu [87]	Carvajal-Gonzalez [82]	Carvajal-Gonzalez [82][§]	Gresa-Arribas [90]	Martinez-Hernandez [92]
Plasma exchange	1/10 (10%)			0/5 (0%)	17/44 (38.6%)	2/9 (22.2%)		n.a.
Second-line	2/10 (20%)			1/5 (20%)	11/44 (25%)	0/9 (0%)		3/7 (42.8%)
Rituximab	0/10 (0%)			n.a.	2/44 (4.5%)	0/9 (0%)		1/7 (14.3%)
Cyclosporine	0/10 (0%)			n.a.	4/44 (9.1%)	0/9 (0%)		0/7 (0%)
Other	2/10 (20%) AZA			n.a.	4/44 (9.1%) AZA 3/44 (6.8%) mycophenolate mofetil 1/44 (2.3%) Cyclosporine	0/9 (0%)		1/7 (14.3%) AZA 1/7 (14.3%) methotrexate 1/7 (14.3%) Glatiramer ac.
Median length of follow-up (range)	12 months (0–60)	n.a.	n.a.	n.a.	3 years (2–7), since first ab detection	n.a.	n.a.	41 months (24–133) (data available in 7/12)
No. of patients who relapsed	n.a.	n.a.	n.a.	n.a.	6/43 (13.9%)	n.a.	n.a.	6/7 (data available in 7/12)
Outcome	No symptoms/signs: 1/10 (10%) Near normal: 2/10 (20%) Substantial–considerable improvement: 3/10 (30%) Mild–moderate improvement: 2/10 (20%) Worsening after initial improvement: 1/10 (10%) improvement of visual acuity: 1/10 (10%)	n.a.	n.a.	Good response to AED (no IT): 3/5 (60%) Poor response to AED, good response to IT: 1/5 (20%) Poor response to AED, response to IT n.a.: 1/5 (20%)	mRS 0: 7/44 (15.9%) mRS 1: 19/44 (43.2%) mRS 2: 8/44 (18.2%) mRS 3: 4/44 (9.1%) mRS 4: 1/44 (2.3%) mRS 5: 1/44 (2.3%) mRS 6: 4/45 (8.9%)	Good or very good response to IT: 3/8 (37.5%) Partial or moderate response to IT: 2/8 (25%) Poor response to IT: 3/8 (37.5%)	n.a.	EDSS 0: 5/7 (71.4%) EDSS 2: 1/7 (14.3%) EDSS 2.5: 1/7 (14.3%)

[†]At first episode.
[‡]Patients were classified as having classic SPS if lower extremity and lumbar stiffness and spasms were present, and variant SPS if symptoms were restricted to either axial or extremity muscles or upper body muscles. Patients with hyperekplexia had isolated exaggerated startle in response to tactile or auditory stimuli [83]
[§]Refers to the second cohort of patients described in the paper, available in the supplemental material [82].
ab: Antibody; AED: Antiepileptic drugs; AZA: Azathioprine; EDSS: Kurtzke Expanded Disability Status scale; F: Females; GAD: Glutamic acid decarboxylase; IT: Immune therapy; mRS: Modified Rankin scale; n.a.: Not available; ON: Optic neuritis; PERM: Progressive encephalopathy with rigidity and myoclonus; SPS: Stiff-person syndrome; VGKC: Voltage gated potassium channel; NMDAR: *N*-methyl-D-aspartate receptor; MOG: Myelin oligodendrocyte glycoprotein; AQP4: Aquaporin-4.

68), IVIG in 42.6% (29/68) and PE in 29.4% (20/68). In the largest published series,[82] approaches to first-line immune therapy were variable but typically started with intravenous methylprednisolone followed by high-dose prednisolone, and sometimes by PE, IVIG or both. In the combined cohort from the seven articles, second-line immune therapies were used at the first disease event in 22.7% (17/75): rituximab in 4.3% (3/70), cyclophosphamide in 5.7% (4/70), azathioprine in 10% (7/70), mycophenolate mofetil in 4.3% (3/70), methotrexate in 1.4% (1/70), cyclosporine in 1.4% (1/70) and glatiramer acetate in 1.4% (1/70).

According to available data, the patients who received immune therapy had higher rate of good recovery than those who were not treated (mRS 0–1: 25/44, 56.8% vs. 3/10, 30%) and a slightly lower mortality rate (3/44, 6.8% vs. 1/10, 10%). However, in the patients who received second-line treatment as compared to the patients who did not, there were similar rates of good recovery (mRS 0–1: 4/16, 25% vs. 11/45, 24.4%) and of death (1/16, 6.2% vs. 3/45, 6.7%). Data on the timing of immune therapy are insufficient for comparison.

Follow-up ranged between 0 and 133 months, and relapses occurred in 24% of patients (12/50). 5.3% (4/75) patients died, and 21.3% (13/61) had a good outcome (mRS 0).

Anti-DPPX antibodies

Encephalitis associated with antibodies against DPPX, a regulatory subunit of neuronal Kv4.2 potassium channels, was first described in 2013 in four patients [15]. Since then, 27 additional cases with positive anti-DPPX antibodies have been reported, 20 of which are described in one series (Table 8).[95–98] Anti-DPPX encephalitis is typically characterized by prodromal diarrhea and weight loss, followed by encephalopathy (with delirium, psychosis, depression, seizures, brainstem disorders), sleep disturbances, central hyperexcitability (myoclonus, exaggerated startle, diffuse rigidity, hyperreflexia) and dysautonomia (involving the gastrointestinal tract, bladder, cardiac conduction system and thermoregulation).[96] PERM has also been described in three patients with anti-DPPX antibodies.[95] Most cases are non-paraneoplastic, and tumor was detected in only two patients (B-cell neoplasms) in the largest series of 20 cases (10%).[96] In the same cohort, additional antibodies were detected in five patients (25%).

All five available articles reporting cases with positive anti-DPPX antibodies were included in this review (Table 8).[15,95–98] In the 31 patients reported (11/31, 35.5% females), age at onset ranged between 13 and 76 years (1/13, 7.7% children). 64.3% (18/28) of patients received immune therapy during the first episode of disease. First-line treatments were used in 64.3% (18/28): steroids in 64.3% (18/28), IVIG in 28.6% (8/28) and PE in 21.4% (6/28). 35.7% (10/28) of patients received second-line therapies: 21.4% (6/28) received rituximab, 10.7% (3/28) cyclophosphamide, 10.7% (3/28) azathioprine and 3.6% (1/28) mycophenolate mofetil.

According to available data, diagnosis was often delayed, resulting in long time to initiation of immune therapy (median 16 months, range 5–96).[15,95,97]

Patients who did not receive immune therapy at the first episode had worse outcomes than patients who did receive immune therapy (mRS 0–1: 0/9, 0% vs. 7/18, 38.9%) and higher rates of death (2/9, 22.2% vs. 1/18, 5.5%) despite lower rates of relapses (1/10, 10% vs 7/18, 38.9%). Similarly, patients who received second-line treatments at the first episode had better outcomes than patients who did not receive second-line therapies (mRS 0–1: 4/10, 40% vs. 3/17, 17.6%) and lower rates of death (0/10, 0% vs. 3/17, 17.6%) despite similar rates of relapses (3/10, 30% vs. 5/17, 29.4%).

Length of follow-up ranged between 0 and 18 years. Relapses occurred in 28.6% (8/28) of cases, 26.9% (7/26) of patients had complete remission or mild disability (mRS 0–1) and 11.5% (3/26) died.

Anti-IgLON5 antibodies

In 2014, an atypical sleep disorder with abnormal sleep movements and behavior, and obstructive sleep apnea, was described in eight patients, whose serum or CSF showed an identical pattern of reactivity to the neuropil of rat brain.[16] Immunohistochemical studies identified an antibody against an unknown neuronal cell surface protein, and antigen characterization allowed the identification of IgLON5, a neuronal cell adhesion molecule. The sleep disorder in these patients was characterized by obstructive sleep apnea, stridor and abnormal sleep architecture. The sleep disorder was the initial and main complaint in four patients, who also had bulbar involvement and dysautonomia; two of these also developed movement disorders. In two other patients, the sleep disturbance was preceded by gait instability, and followed by dysarthria, dysphagia, ataxia and chorea. The remaining two patients had a rapid evolution with sleep disorder and disequilibrium, dysarthria, dysphagia, vocal cord paresis and central hypoventilation. Neuropathology in two patients showed neuronal loss and extensive deposits of hyperphosphorylated tau mainly involving the tegmentum of the brainstem and hypothalamus. In the same series, anti-IgLON5 antibodies were also found in a control with progressive supranuclear palsy [16]. Subsequently, two additional patients have been reported.[99,100] All the patients tested carried the HLA-DRB1*1001 and HLA-DQB1*0501 alleles, whereas none had tumor or coexisting antibodies.

All anti-IgLON5 patients were adults (range 52–76 years) (7/10, 70% females).[16,99,100] The majority of patients received immune therapy (9/10, 90%), even though most presented late.[16] First-line treatments were used in 90% (9/10) (steroids in 7/10, 70%; IVIG in 4/10, 40%) and second-line therapies in 70% (7/10) (rituximab in 3/10, 30%; cyclophosphamide in 4/10, 40%). In the series by Sabater, only one patient showed some improvement after immune therapy, but died suddenly thereafter.[16] Relapses were rare (1/10, 10%). Despite the extensive use of immune therapy, at last follow-up (range 0.8–

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Table 8. Summary of the literature review on the treatment of anti-DPPX encephalitis (all available cohorts were included).[15,95–98]

	Boronat [15]	Balint [95]	Tobin [96]	Piepgras [97]	Stoeck [98]
Study design	Retrospective	Retrospective	Retrospective-prospective	Retrospective	Retrospective
No. of patients	4	3	20	3	1
Clinical description (no, of females)	4/4: encephalitis (rapidly progressive encephalopathy with agitation, delusions, hallucinations, myoclonic jerks and diarrhea) (F: 2/4, 50%)	3/3: progressive encephalopathy with rigidity and myoclonus (F: 0/3, 0%)	20/20: encephalopathy (with cortical, cerebellar or brainstem manifestations), myelopathy, weight loss, autonomic dysfunction (F: 8/20, 40%)	3/3: encephalitis (initial diarrhea followed by neuropsychiatric symptoms) (F: 0/3, 0%)	1/1: eEncephalitis (night sweats, diarrhea, ataxia, tremor, memory deficits, and panic attacks) (F: 1/1, 100%)
Median age at onset (range)	59.5 years (45–76)	26 years (15–27) (1 child)	53 years (13–75) (N° of children not available)	68 years (50–68)	40 years
Tumor	0/4 (0%)	0/3 (0%)	2/20 (10%): 1/20: gastrointestinal follicular lymphoma 1/20: chronic lymphocytic leukemia	0/1 (0%)	0/1 (0%)
Additional antibody	0/4 (0%)	0/3 (0%)	5/20 (25%): –1/20: GAD 1/20: GAD, ANA 1/20: dsDNA, APL -IgM, ANA 1/20: Gastric parietal cell 1/20: Thyroglobulin	0/1 (0%)	0/1 (0%)
Immune therapy[†]	3/3 (100%)	2/3 (66.7%)	11/20 (55%)	1/1 (100%)	1/1 (100%)
First-line	3/3 (100%)	2/3 (66.7%)	11/20 (55%)	1/1 (100%)	1/1 (100%)
Steroids	3/3 (100%)	2/3 (66.7%)	11/20 (55%)	1/1 (100%)	1/1 (100%)
Intravenous immunoglobulin	1/3 (33.3%)	1/3 (33.3%)	5/20 (25)	1/1 (100%)	0/1 (0%)
Plasma exchange	0/3 (0%)	1/3 (33.3%)	5/20 (25%)	0/1 (0%)	0/1 (0%)
Second-line	1/3 (33.3%)	0/3 (0%)	8/20 (40%)	0/1 (0%)	1/1 (100%)
Rituximab	1/3 (33.3%)	0/3 (0%)	5/20 (25%)	0/1 (0%)	0/1 (0%)
Cyclophosphamide	0/3 (0%)	0/3 (0%)	3/20 (15%)	0/1 (0%)	0/1 (0%)
Other	0/3 (0%)	0/3 (0%)	2/20 (10%) AZA 1/20 (5%) mycophenolate mofetil	0/1 (0%)	1/1 (100%) AZA
Median length of follow-up (range)	49 months (21–68) (data available in 3/4)	8 years (5–18)	6 months (0–68)	27 months (data available in 1/3)	3 years
No. of patients who relapsed	3/3 (100%)	3/3 (100%)	2/20 (10%)	0/1 (0%)	0/1 (0%)
Outcome	mRS 1: 1/3 (33.3%) mRS 2: 1/3 (33.3%) mRS 3: 1/3 (33.3%)	mRS 3: 2/3 (66.7%) mRS 6: 1/3 (33.3%)	Complete remission or mild disability: 4/18 (22.2%) Partial response to immune therapy: 5/18 (27.8%) Unchanged: 6/18 (33.3%) Progressive worsening: 1/18 (5.6%) Death: 2/18 (11.1%)	Almost complete return to premorbid level of functioning: 1/1 (100%)	Marked improvement: 1/1 (100%)

[†]At first episode.
AZA: Azathioprine; ANA: Antinuclear antibodies; APL: Antiphospholipid; GAD: Glutamic acid decarboxylase.

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13 years), 70% of patients died (7/10) and the remaining 30% (3/10) had unchanged clinical picture.

Anti-D2R antibodies

Basal ganglia encephalitis is dominated by movement and psychiatric disorders, and is similar to encephalitis lethargica, described in epidemic form in the early 20th century.[101–103] In 2012, antibodies to D2R were identified in 12 of 17 patients with basal ganglia encephalitis with negative anti-NMDAR antibodies.[14] In this cohort, the clinical syndrome was dominated by movement disorders (dystonia, parkinsonism, chorea, oculogyric crises), psychiatric disturbances (agitation, emotional lability, anxiety, psychotic symptoms), sleep disturbances, lethargy, drowsiness, brainstem dysfunction, seizures and ataxia.[14] Anti-D2R antibodies were subsequently detected in two patients who relapsed with encephalopathy and chorea after herpes simplex encephalitis.[104] None of the patients reported so far had tumor, and additional antibodies have been detected rarely (anti-NMDAR antibodies, 1/14, 7.1%).[104] In non-encephalopathic patients, anti-D2R antibodies have been identified in Sydenham's chorea, and occasional patients with Tourette syndrome [14] and isolated psychosis.[105]

A total of 14 patients with anti-D2R antibodies-positive basal ganglia encephalitis have been described (8/14, 57.1% females),[14,104] all in pediatric age (range 10 months to 15 years). First-line immune therapies were administered in 57.1% (8/14) of patients (steroids in 8/14, 57.1%; IVIG in 3/14, 21.4%) and second-line treatments in none. In the original series by Dale et al., although the cohort was treated empirically, the most recent patients were treated aggressively and early with immune therapy and made a complete recovery.[14] However, two of the five patients that were not treated had a full recovery, suggesting that the autoimmune process can be spontaneously reversible. In the combined cohorts, relapses occurred in 21.4% (3/14) of patients. At last follow-up (range 1–14 years), 35.7% (5/14) of patients had a full recovery, and the rest were left with neurological sequelae (movement disorder, cognitive impairment, behavioral or psychiatric disturbances).

Anti-mGluR5 antibodies

In 1982, Carr described a neuropsychiatric disorder with memory loss, depression, personality changes and hallucinations in his daughter, who was subsequently diagnosed with Hodgkin's lymphoma.[106] He called this Ophelia syndrome and described resolution of the neurological symptoms with tumor treatment. Subsequently, further cases of Ophelia syndrome were reported (Hodgkin's lymphoma and limbic encephalitis),[107–109] and in 2011 anti-mGluR5 antibodies were detected in two patients.[13] mGluR5 is expressed primarily in the hippocampus and amygdala and plays a role in behavioral learning and memory,[110] which could explain the neurological symptoms in these patients.[111] While a subsequent report confirmed the association of anti-mGluR5 antibodies and Ophelia syndrome,[111] another paper expanded the phenotype with identification of these antibodies in a patient with limbic encephalitis and prosopagnosia, without tumor.[112] Hodgkin's lymphoma has been identified in 75% (3/4) of the anti-mGluR5 patients described.[13,111,112] No additional antibodies have been detected.

The age at onset in the four anti-mGluR5 patients reported ranged between 15 and 46 years (median 32.5) (2/4, 50% females).[13,111,112] Seventy-five percent (3/4) of patients received immune therapy. First-line treatments were administered in 75% (3/4) (steroids in 3/4, 75%, PE in 1/4, 25%) and second-line therapies in 25% (1/4) (rituximab). Both the patients reported by Lancaster et al. [13] had prompt and successful tumor treatment and, although only one received immune therapy, both had a full recovery. Similarly, Carr's daughter had a full recovery in the absence of immune therapy.[106] However, poor outcome with death in Ophelia syndrome has been reported in other cases, with [113] or without [109] immune therapy (antibody status unknown). In a recent case report, the profound improvement of neuropsychiatric abnormalities, prosopagnosia and anterograde amnesia with steroids, PE and rituximab suggested a beneficial role of immune therapy.[112] In the combined cohorts of anti-mGluR5-positive patients, there were no relapses and, at last follow-up (range 17 months to 4 years), 75% (3/4) of patients recovered fully and 25% (1/4) had only partially recovered.

Summary

In the last decade, the progressive identification of a growing number of antibodies to neuronal surface antigens has defined encephalitic syndromes whose etiology was previously unknown. The relatively good response to immune therapy in these patients has led to a paradigm shift in their clinical management.[114] In the absence of randomized controlled trials on the treatment of autoimmune encephalitis with antibodies to neuronal surface antigens, the authors conducted a literature review to define and summarize the available evidence of immune therapy in these disorders. The main results of this review show that immune therapy, especially first-line therapy, is used in most cases, and the available data have demonstrated the following trends (Table 9):

1) The use of immune therapy rather than no therapy is more commonly associated with a better outcome [10,11,14,25,28,29,39,54,59,76,78,95,96,112] and a lower rate of relapses.[29,39]
2) Early commencement of immune therapy is more commonly associated with a better outcome.[14,24,25,28,29,35,39,46,95,96]
3) The use of second-line immune therapies is more commonly associated with a better outcome [29,95,96,112] and a lower rate of relapses,[29,46] although this is particularly influenced by severity bias, as sicker patients are more likely to receive second-line therapy.

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Table 9. Summary of the literature review on the evidence on the efficacy of immune therapy in autoimmune encephalitis, as reported in the original papers (immune therapy vs. no immune therapy, early vs. late commencement of immune therapy and second-line immune therapy vs. no second-line immune therapy).

		N-Methyl-D-aspartate receptor	Leucine-rich, glioma-inactivated protein-1	Contactin-associated protein-2	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor	γ-Aminobutyric acid-A receptor	γ-Aminobutyric acid-B receptor	Glycine receptor	Dipeptidyl-peptidase-like protein-6	IgLON5	Dopamine-2 receptor	Metabotropic glutamate receptor 5
Beneficial use of IT vs. no IT	On outcome	Irani† [28] Titulaer [29] Hacohen [25]	Irani †‡ [10] Irani † [39]	Irani, † [10] Lancaster, [59] Sunwoo, [54]	–	–	Lancaster † [11] Boronat † [76] Höftberger [78]	–	Balint [95] Tobin [96]	–	Dale [14]	Prüss [112]
	On relapses	Titulaer † [29]	Irani [39]	–	–	–	–	–	–	–	–	–
Beneficial effect of early vs. late commencement of IT	On outcome	Irani † [28] Titulaer † [29] Hacohen [25] Dale † [24] Byrne † [35]	Irani †§ [39] Shin [46]	–	–	–	–	–	Balint [95] Tobin [96]	–	Dale [14]	–
	On relapses	–	–	–	–	–	–	–	–	–	–	–
Beneficial use of second-line IT vs. no second-line IT	On outcome	Titulaer † [29]	–	–	–	–	–	–	Balint [95] Tobin [96]	–	–	Prüss [112]
	On relapses	Titulaer† [29]	Shin [46]	–	–	–	–	–	–	–	–	–

Results in one study in anti-leucine-rich, glioma-inactivated protein-1 encephalitis [48] and in anti-*N*-methyl-D-aspartate receptor encephalitis [27] suggested no beneficial effect of early commencement of immune therapy and of use of second-line therapy, respectively.
†With statistical significance.
‡Faciobrachial dystonic seizures were controlled more effectively with IT than antiepileptic drugs ($p = 0.006$) [39].
§Time to return to a modified Rankin scale 1 was significantly correlated with time to immune therapy administration [39].
IT: Immune therapy.

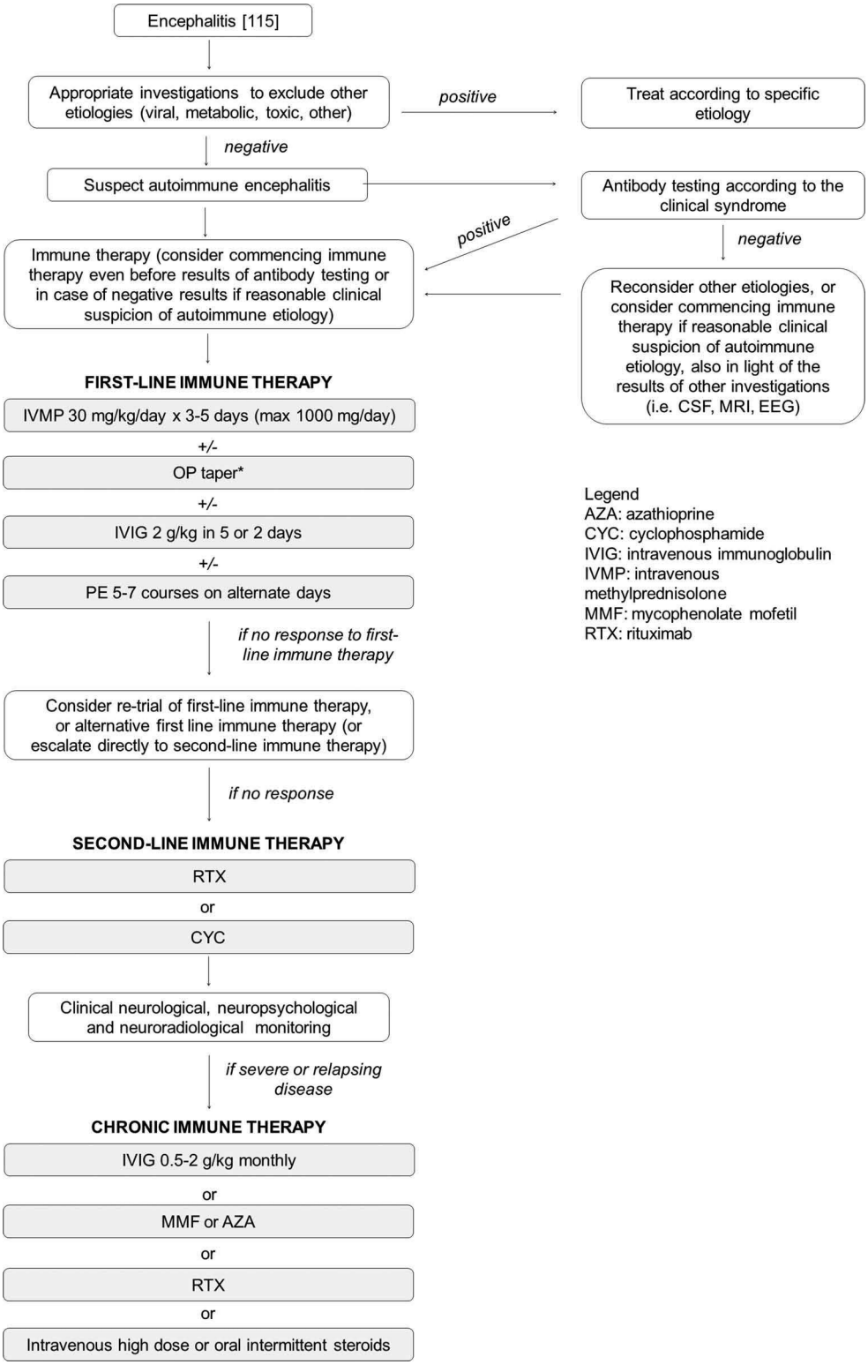

Figure 1. Proposed management and treatment algorithm in autoimmune encephalitis. Oncological searches and tumor treatment, when appropriate, should be done in all patients.

* Oral steroid taper duration should be variable according to severity of clinical syndrome, speed of recovery, risk of relapse and need for second-line therapy.AZA: Azathioprine; CSF: Cerebrospinal fluid; CYC: Cyclophosphamide; EEG: Electroencephalography; IVIG: Intravenous immunoglobulin; IVMP: Intravenous methylprednisolone; MMF: Mycophenolate mofetil; RTX: Rituximab.

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In our literature review, the rate of treatment varied considerably between different disorders. Use of immune therapy was over 92% in anti-NMDAR, anti-LGI1, anti-Caspr2, anti-AMPAR and anti-IgLON5 encephalitis, whereas it dropped down to 53.1% and 57.1% in anti-GABAAR and anti-D2R encephalitis, respectively. This variability in the frequency of treatment is likely influenced by a number of clinical variables. Some of these entities are now well known by treating clinicians (i.e., anti-NMDAR encephalitis), and testing is commonly requested, whereas some of the rarer entities are not commonly recognized, or the presentation is often nonspecific or has a broad differential diagnosis. Especially in the syndromes that have been more extensively described, immune therapy is often started based on clinical suspicion whilst awaiting confirmation of autoantibody status. Figure 1 shows the proposed management and treatment algorithm for autoimmune encephalitis.[115] Despite extensive testing, a significant proportion of encephalitis remains antibody-negative and, while this may be in some cases ascribed to the limitations of the test, future challenges include identification of novel antibodies in patients who are apparently seronegative.[116] A negative test should also raise the possibility of another (non-autoimmune) diagnosis.

Although the majority of encephalitis with neuronal surface antibodies are treatment-responsive, anti-IgLON5 encephalitis appears to be different from the other autoimmune encephalitides, with poor response to immune therapy and high mortality rate.[16]

The main limitations intrinsic to the data reported to date (and therefore this review) are the limited number of patients, and the retrospective and nonstandardized nature of data and outcome measures. Severity and reporting bias are likely to be present in the reported literature. It is also possible that some patients are re-described in different publications. Given the rarity of these disorders, only multicenter collaboratives could conduct randomized controlled trials in autoimmune encephalitis. There is already enough evidence to render a randomized controlled trial of immune therapy against control (null treatment) to be unethical; however, a randomized controlled trial of first-line therapy versus first- and second-line therapy at onset would be a potentially viable option.

Expert commentary

The recent identification of autoantibodies to neuronal cell surface antigens in encephalitis with previously unknown etiology has led to an increased awareness and treatment of autoimmune encephalitis. There are no randomized controlled trials on the treatment of autoimmune encephalitis; available data are mostly based on retrospective studies and, in some cases, on a restricted number of patients. With these limitations, there are trends suggesting a beneficial role of immune therapy on outcome and relapse rate as compared to symptomatic treatment only or no treatment. Furthermore, patients appear to have a better outcome when treated early in the course of the disease. The addition of second-line immune therapy also appears to yield a better outcome and decrease relapses. These data demonstrate the importance of prompt disease recognition, followed by early and aggressive immune treatment to improve outcomes.

Five-year view

While some autoimmune encephalitis syndromes with antibodies to neuronal cell surface antigens are relatively well known (i.e., anti-NMDAR encephalitis), in other cases the recent identification and the rarity of these disorders result in an incomplete clinical characterization of the syndromes and late or missed diagnoses—this represents an obstacle to a prompt diagnosis and early commencement of appropriate therapy, which has been shown to favor a better outcome. The same limitations have resulted in the lack of quality data on treatment to date. In this context, large prospective multicenter cohorts may play a pivotal role in expanding our knowledge of the phenotype of some of these entities, and allowing for quicker disease recognition and reduction in treatment delay. Despite obvious ethical limitations in treatment trials, multicenter collaboratives may also allow for the creation of randomized controlled trials of immune therapy, which would provide important data to guide the management of these disorders. Finally, a proportion of encephalitis with suspected autoimmune etiology remains antibody-negative to date, and future challenges include identification of novel antibodies in these cases. Patients with suspected autoimmune encephalitis who are antibody-negative can be given an empiric therapeutic trial, whilst maintaining vigilance for an alternate diagnosis.

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Key issues

- Antibodies against neuronal cell surface antigens have been recently identified in encephalitis with previously unknown etiology.
- The antigens targeted by these autoantibodies include *N*-methyl-D-aspartate receptor, leucine-rich, glioma-inactivated protein-1, contactin-associated protein-2, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, γ-aminobutyric acid-A receptor, γ-aminobutyric acid-B receptor, glycine receptor, dipeptidyl-peptidase-like protein-6, IgLON5, dopamine-2 receptor and metabotropic glutamate receptor 5.
- The most frequent autoimmune encephalitis with antibodies to neuronal cell surface antigens are anti-*N*-methyl-D-aspartate receptor encephalitis and limbic encephalitis, which can be associated with a diversity of antibodies.
- Compared to classic paraneoplastic disorders with antibodies to intracellular antigens, in autoimmune encephalitis with antibodies to neuronal cell surface antigens, the association with tumor is variable and sometimes absent, the antibodies are considered pathogenic and generally there is good response to immune therapy.
- In view of the rarity of autoimmune encephalitis with antibodies to neuronal cell surface antigens and their recent description, there are no randomized controlled trials on treatment, and data are mostly based on retrospective studies.
- According to available data, there are common therapeutic themes emerging: patients given immune therapy do better and relapse less than patients given no treatment; patients given early treatment do better; and lastly, second-line therapy improves outcomes and reduces relapses.
- When other diagnoses have been excluded and there is a reasonable clinical suspicion of autoimmune encephalitis, immune therapy is often started whilst waiting for results of antibody testing.
- In view of the possible high morbidity in the acute phase, management of autoimmune encephalitis with antibodies to neuronal cell surface antigens is challenging. Symptomatic treatment may be beneficial in addition to immune therapy, especially to address sleep disturbances, agitation, psychiatric issues and seizures.
- Despite the inconsistent association with tumor in autoimmune encephalitis with antibodies to neuronal cell surface antigens, oncological investigations should be performed in all cases as treatment of associated malignancies in these cases is shown to be beneficial.

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References

Papers of special note have been highlighted as:

•• of considerable interest

1. Dalmau J, Furneaux HM, Rosenblum MK, et al. Detection of the anti-Hu antibody in specific regions of the nervous system and tumor from patients with paraneoplastic encephalomyelitis/sensory neuronopathy. Neurology. 1991;41:1757–1764.
2. Voltz R, Dalmau J, Posner JB, et al. T-cell receptor analysis in anti-Hu associated paraneoplastic encephalomyelitis. Neurology. 1998;51:1146–1150.
3. Sillevis Smitt PA, Manley GT, Posner JB. Immunization with the paraneoplastic encephalomyelitis antigen HuD does not cause neurologic disease in mice. Neurology. 1995;45:1873–1878.
4. Lancaster E, Dalmau J. Neuronal autoantigens–pathogenesis, associated disorders and antibody testing. Nat Rev Neurol. 2012;8:380–390.
5. Irani SR, Gelfand JM, Al-Diwani A, et al. Cell-surface central nervous system autoantibodies: clinical relevance and emerging paradigms. Ann Neurol. 2014;76:168–184.
6. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61:25–36.

•• **The first description of anti-*N*-methyl-d-aspartate receptor antibodies.**

7. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008;71:1291–1292.
8. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009;65:424–434.
9. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010;9:776–785.
10. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010;133:2734–2748.
11. Lancaster E, Lai M, Peng X, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol. 2010;9:67–76.

•• **Results of this study show a statistically significant association between good outcome and use of immune therapy.**

12. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol. 2014;13:276–286.
13. Lancaster E, Martinez-Hernandez E, Titulaer MJ, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. Neurology. 2011;77:1698–1701.
14. Dale RC, Merheb V, Pillai S, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and

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psychiatric disorders. Brain. 2012;135:3453–3468.

15. Boronat A, Gelfand JM, Gresa-Arribas N, et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. Ann Neurol. 2013;73:120–128.
16. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol. 2014;13:575–586.
17. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. Ann N Y Acad Sci. 2015;1338:94–114.
18. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7:1091–1098.
19. Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci. 2010;30:5866–5875.
20. Zuliani L, Graus F, Giometto B, et al. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. J Neurol Neurosurg Psychiatry. 2012;83:638–645.
21. Vincent A, Bien CG, Irani SR, et al. Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol. 2011;10:759–772.
22. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology. 2011;77:179–189.
23. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–607.
24. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 2014;83:142–150.

•• **Results of this study show a statistically significant association between good outcome and early commencement of rituximab.**

25. Hacohen Y, Absoud M, Hemingway C, et al. NMDA receptor antibodies associated with distinct white matter syndromes. Neurol Neuroimmunol Neuroinflamm. 2014;1:e2.
26. Wright S, Hacohen Y, Jacobson L, et al. N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. Arch Dis Child. 2015;100:521–526.
27. Zekeridou A, Karantoni E, Viaccoz A, et al. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. J Neurol. 2015;262:1859–1866.
28. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain. 2010;133:1655–1667.

•• **Results of this study show a statistically significant association between good outcome and use of immune therapy, especially when started early in the course of the disease.**

29. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12:157–165.

•• **The largest case series of patients with anti-*N*-methyl-d-aspartate receptor encephalitis, providing important data on treatment. Results of this study show that good outcome was significantly associated with early commencement of immune therapy and use second-line immune therapy. Relapse rate was significantly decreased in patients treated with immune therapy compared to those not treated and in patients who received second-line therapies.**

30. Gable MS, Sheriff H, Dalmau J, et al. The frequency of autoimmune N-Methyl-D-Aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California encephalitis project. Clin Infect Dis. 2012;54:899–904.
31. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10:63–74.
32. Evoli A, Spinelli P, Frisullo G, et al. Spontaneous recovery from anti-NMDAR encephalitis. J Neurol. 2012;259:1964–1966.
33. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009;66:11–18.
34. Mohammad SS, Jones H, Hong M, et al. Symptomatic treatment of children with anti-NMDAR encephalitis. Dev Med Child Neurol. 2015 Aug 28. DOI:10.1111/dmcn.12882. [Epub ahead of print].
35. Byrne S, Walsh C, Hacohen Y, et al. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. Neurol Neuroimmunol Neuroinflamm. 2015;2:e130.

•• **Results of this study show a statistically significant association between good outcome and early commencement of immune therapy.**

36. Tatencloux S, Chretien P, Rogemond V, et al. Intrathecal treatment of anti-N-Methyl-D-aspartate receptor encephalitis in children. Dev Med Child Neurol. 2015;57:95–99.
37. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain. 2004;127:701–712.
38. Quek AM, Britton JW, McKeon A, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol. 2012;69:582–593.
39. Irani SR, Stagg CJ, Schott JM, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain. 2013;136:3151–3162.

•• **Results of this prospective study show a statistically significant association between good outcome (seizure reduction and good cognitive outcome) and use of immune therapy, and between time to recover and time to commencement of immune therapy.**

40. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol. 2011;69:892–900.
41. Shugaiv E, Leite MI, Şehitoğlu E, et al. Progressive encephalomyelitis with rigidity and myoclonus: a syndrome with diverse clinical features and antibody responses. Eur Neurol. 2013;69:257–262.
42. Ramdhani RA, Frucht SJ. Isolated chorea associated with LGI1 antibody. Tremor Other Hyperkinet Mov (N Y). 2014;4:1–2.
43. Gong J, Zhang Y, Wang F, et al. Frequent hemianesthesia as initial symptom of limbic encephalitis associated with LGI1 antibodies. Neurol Sci. 2015;36:1953–1955.

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44. Naasan G, Irani SR, Bettcher BM, et al. Episodic bradycardia as neurocardiac prodrome to voltage-gated potassium channel complex/leucine-rich, glioma inactivated 1 antibody encephalitis. JAMA Neurol. 2014;71:1300–1304.

45. Nilsson AC, Blaabjerg M. More evidence of a neurocardiac prodrome in anti-LGI1 encephalitis. J Neurol Sci. 2015;357:310–311.

46. Shin YW, Lee ST, Shin JW, et al. VGKC-complex/LGI1-antibody encephalitis: clinical manifestations and response to immunotherapy. J Neuroimmunol. 2013;265:75–81.

47. Malter MP, Frisch C, Schoene-Bake JC, et al. Outcome of limbic encephalitis with VGKC-complex antibodies: relation to antigenic specificity. J Neurol. 2014;261:1695–1705.

48. Irani SR, Gelfand JM, Bettcher BM, et al. Effect of rituximab in patients with leucine-rich, glioma-inactivated 1 antibody-associated encephalopathy. JAMA Neurol. 2014;71:896–900.

49. Wegner F, Wilke F, Raab P, et al. Anti-leucine rich glioma inactivated 1 protein and anti-N-methyl-D-aspartate receptor encephalitis show distinct patterns of brain glucose metabolism in 18F-fluoro-2-deoxy-d-glucose positron emission tomography. BMC Neurol. 2014;14:136.

50. Brown JW, Martin PJ, Thorpe JW, et al. Long-term remission with rituximab in refractory leucine-rich glioma inactivated 1 antibody encephalitis. J Neuroimmunol. 2014;271:66–68.

51. Szots M, Marton A, Kover F, et al. Natural course of LGI1 encephalitis: 3-5 years of follow-up without immunotherapy. J Neurol Sci. 2014;343:198–202.

52. Suleiman J, Wright S, Gill D, et al. Autoantibodies to neuronal antigens in children with new-onset seizures classified according to the revised ILAE organization of seizures and epilepsies. Epilepsia. 2013;54:2091–2100.

53. Pinatel D, Hivert B, Boucraut J, et al. Inhibitory axons are targeted in hippocampal cell culture by anti-Caspr2 autoantibodies associated with limbic encephalitis. Front Cell Neurosci. 2015;9:265.

54. Sunwoo JS, Lee ST, Byun JI, et al. Clinical manifestations of patients with CASPR2 antibodies. J Neuroimmunol. 2015;281:17–22.

55. Becker EB, Zuliani L, Pettingill R, et al. Contactin-associated protein-2 antibodies in non-paraneoplastic cerebellar ataxia. J Neurol Neurosurg Psychiatry. 2012;83:437–440.

56. Huda S, Wong SH, Pettingill P, et al. An 11-year retrospective experience of antibodies against the voltage-gated potassium channel (VGKC) complex from a tertiary neurological centre. J Neurol. 2015;262:418–424.

57. Irani SR, Pettingill P, Kleopa KA, et al. Morvan syndrome: clinical and serological observations in 29 cases. Ann Neurol. 2012;72:241–255.

58. Ong E, Viaccoz A, Ducray F, et al. Dramatic improvement after rituximab in a patient with paraneoplastic treatment-refractory Morvan syndrome associated with anti-CASPR2 antibodies. Eur J Neurol. 2013;20:e96–7.

59. Lancaster E, Huijbers MG, Bar V, et al. Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol. 2011;69:303–311.

60. Vincent A, Irani SR. Caspr2 antibodies in patients with thymomas. J Thorac Oncol. 2010;5:S277–S280.

61. Krogias C, Hoepner R, Müller A, et al. Successful treatment of anti-Caspr2 syndrome by interleukin 6 receptor blockade through tocilizumab. JAMA Neurol. 2013;70:1056–1059.

62. Bassani S, Valnegri P, Beretta F, et al. The GLUR2 subunit of AMPA receptors: synaptic role. Neuroscience. 2009;158:55–61.

63. Höftberger R, Van Sonderen A, Leypoldt F, et al. Encephalitis and AMPA receptor antibodies: novel findings in a case series of 22 patients. Neurology. 2015;84:2403–2412.

64. Bataller L, Galiano R, García-Escrig M, et al. Reversible paraneoplastic limbic encephalitis associated with antibodies to the AMPA receptor. Neurology. 2010;74:265–267.

65. Graus F, Boronat A, Xifró X, et al. The expanding clinical profile of anti-AMPA receptor encephalitis. Neurology. 2010;74:857–859.

66. Wei YC, Liu CH, Lin JJ, et al. Rapid progression and brain atrophy in anti-AMPA receptor encephalitis. J Neuroimmunol. 2013;261:129–133.

67. Dogan Onugoren M, Deuretzbacher D, Haensch CA, et al. Limbic encephalitis due to GABAB and AMPA receptor antibodies: a case series. J Neurol Neurosurg Psychiatry. 2015;86:965–972.

68. Elamin M, Lonergan R, Killeen RP, et al. Posterior cortical and white matter changes on MRI in anti-AMPA receptor antibody encephalitis. Neurol Neuroimmunol Neuroinflamm. 2015;2:e118.

69. Li X, Mao YT, Wu JJ, et al. Anti-AMPA receptor encephalitis associated with thymomatous myasthenia gravis. J Neuroimmunol. 2015;281:35–37.

70. Panzer JA, Dale RC. Anti-AMPA receptor encephalitis: the family of glutamatergic autoencephalitides further expands. Neurology. 2015;84:2390–2391.

71. Tretter V, Moss SJ. GABA(A) receptor dynamics and constructing GABAergic synapses. Front Mol Neurosci. 2008;1:1–13.

72. Pettingill P, Kramer HB, Coebergh JA, et al. Antibodies to GABAA receptor α1 and γ2 subunits: clinical and serologic characterization. Neurology. 2015;84:1233–1241.

73. Steiner I, Rüegg S. Neurology. Another autoimmune encephalitis? Not yet. Neurology. 2015;84:1192–1193.

74. Ohkawa T, Satake S, Yokoi N, et al. Identification and characterization of GABA(A) receptor autoantibodies in autoimmune encephalitis. J Neurosci. 2014;34:8151–8163.

75. Simabukuro MM, Petit-Pedrol M, Castro LH, et al. GABAA receptor and LGI1 antibody encephalitis in a patient with thymoma. Neurol Neuroimmunol Neuroinflamm. 2015;2:e73.

76. Boronat A, Sabater L, Saiz A, et al. GABA (B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. Neurology. 2011;76:795–800.

•• **Results of this study show a statistically significant association between good outcome and use of immune therapy.**

77. Jeffery OJ, Lennon VA, Pittock SJ, et al. GABAB receptor autoantibody frequency in service serologic evaluation. Neurology. 2013;81:882–887.

78. Höftberger R, Titulaer MJ, Sabater L, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology. 2013;81:1500–1506.

79. Bettler B, Kaupmann K, Mosbacher J, et al. Molecular structure and physiological functions of GABA(B) receptors. Physiol Rev. 2004;84:835–867.

80. Kim TJ, Lee ST, Shin JW, et al. Clinical manifestations and outcomes of the treatment of patients with GABAB

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encephalitis. J Neuroimmunol. 2014;270:45–50.

81. Bourke D, Roxburgh R, Vincent A, et al. Hypoventilation in glycine-receptor antibody related progressive encephalomyelitis, rigidity and myoclonus. J Clin Neurosci. 2014;21:876–878.

82. Carvajal-González A, Leite MI, Waters P, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. Brain. 2014;137:2178–2192.

83. McKeon A, Martinez-Hernandez E, Lancaster E, et al. Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol. 2013;70:44–50.

84. Alexopoulos H, Akrivou S, Dalakas MC. Glycine receptor antibodies in stiff-person syndrome and other GAD-positive CNS disorders. Neurology. 2013;81:1962–1964.

85. Clardy SL, Lennon VA, Dalmau J, et al. Childhood onset of stiff-man syndrome. JAMA Neurol. 2013;70:1531–1536.

86. Brenner T, Sills GJ, Hart Y, et al. Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. Epilepsia. 2013;54:1028–1035.

87. Ekizoglu E, Tuzun E, Woodhall M, et al. Investigation of neuronal autoantibodies in two different focal epilepsy syndromes. Epilepsia. 2014;55:414–422.

88. Zuliani L, Ferlazzo E, Andrigo C, et al. Glycine receptor antibodies in 2 cases of new, adult-onset epilepsy. Neurol Neuroimmunol Neuroinflamm. 2014;1:e16.

89. Ariño H, Gresa-Arribas N, Blanco Y, et al. Cerebellar ataxia and glutamic acid decarboxylase antibodies: immunologic profile and long-term effect of immunotherapy. JAMA Neurol. 2014;71:1009–1016.

90. Gresa-Arribas N, Ariño H, Martínez-Hernández E, et al. Antibodies to inhibitory synaptic proteins in neurological syndromes associated with glutamic acid decarboxylase autoimmunity. PLoS One. 2015;10:e0121364.

91. Hacohen Y, Absoud M, Woodhall M, et al. Autoantibody biomarkers in childhood-acquired demyelinating syndromes: results from a national surveillance cohort. J Neurol Neurosurg Psychiatry. 2014;85:456–461.

92. Martinez-Hernandez E, Sepulveda M, Rostásy K, et al. Antibodies to aquaporin 4, myelin-oligodendrocyte glycoprotein, and the glycine receptor α1 subunit in patients with isolated optic neuritis. JAMA Neurol. 2015;72:187–193.

93. Woodhall M, Çoban A, Waters P, et al. Glycine receptor and myelin oligodendrocyte glycoprotein antibodies in Turkish patients with neuromyelitis optica. J Neurol Sci. 2013;335:221–223.

94. Turner MR, Irani SR, Leite MI, et al. Progressive encephalomyelitis with rigidity and myoclonus: glycine and NMDA receptor antibodies. Neurology. 2011;77:439–443.

95. Balint B, Jarius S, Nagel S, et al. Progressive encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. Neurology. 2014;82:1521–1528.

96. Tobin WO, Lennon VA, Komorowski L, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014;83:1797–1803.

97. Stoeck K, Carstens PO, Jarius S, et al. Prednisolone and azathioprine are effective in DPPX antibody-positive autoimmune encephalitis. Neurol Neuroimmunol Neuroinflamm. 2015;2:e86.

98. Piepgras J, Höltje M, Michel K, et al. Anti-DPPX encephalitis: pathogenic effects of antibodies on gut and brain neurons. Neurology. 2015;85:890–897.

99. Högl B, Heidbreder A, Santamaria J, et al. IgLON5 autoimmunity and abnormal behaviours during sleep. Lancet. 2015;385:1590.

100. Simabukuro MM, Sabater L, Adoni T, et al. Sleep disorder, chorea, and dementia associated with IgLON5 antibodies. Neurol Neuroimmunol Neuroinflamm. 2015;2:e136.

101. Von Economo C. Encephalitis lethargica. Its sequelae and treatment. Newman KO, Translator. London: Oxford University Press; 1931.

102. Dale RC, Church AJ, Surtees RA, et al. Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity. Brain. 2004;127:21–33.

103. Dale RC, Brilot F. Autoimmune basal ganglia disorders. J Child Neurol. 2012;27:1470–1481.

104. Mohammad SS, Sinclair K, Pillai S, et al. Herpes simplex encephalitis relapse with chorea is associated with autoantibodies to N-Methyl-D-aspartate receptor or dopamine-2 receptor. Mov Disord. 2014;29:117–122.

105. Pathmanandavel K, Starling J, Merheb V, et al. Antibodies to surface dopamine-2 receptor and N-methyl-D-aspartate receptor in the first episode of acute psychosis in children. Biol Psychiatry. 2015;77:537–547.

106. Carr I. The Ophelia syndrome: memory loss in Hodgkin's disease. Lancet. 1982;1:844–845.

107. Pfliegler G, Pósán E, Glaub D, et al. Hodgkin's disease and memory loss: another case of the Ophelia syndrome. Br J Haematol. 1990;74:232.

108. Shinohara T, Kojima H, Nakamura N, et al. Pathology of pure hippocampal sclerosis in a patient with dementia and Hodgkin's disease: the Ophelia syndrome. Neuropathology. 2005;25:353–360.

109. Olmos D, Rueda A, Jurado JM, et al. Presentation of Hodgkin's lymphoma with Ophelia syndrome. J Clin Oncol. 2007;25:1802–1803.

110. Lu YM, Jia Z, Janus C, et al. Mice lacking metabotropic glutamate receptor 5 show impaired learning and reduced CA1 long-term potentiation (LTP) but normal CA3 LTP. J Neurosci. 1997;17:5196–5205.

111. Mat A, Adler H, Merwick A, et al. Ophelia syndrome with metabotropic glutamate receptor 5 antibodies in CSF. Neurology. 2013;80:1349–1350.

112. Prüss H, Rothkirch M, Kopp U, et al. Limbic encephalitis with mGluR5 antibodies and immunotherapy-responsive prosopagnosia. Neurology. 2014;83:1384–1386.

113. Juneja M, Kaur S, Mishra D, et al. Ophelia syndrome: hodgkin lymphoma with limbic encephalitis. Indian Pediatr. 2015;52:335–336.

114. Lim M, Hacohen Y, Vincent A. Autoimmune encephalopathies. Pediatr Clin North Am. 2015 Jun;62(3):667–685. DOI:10.1016/j.pcl.2015.03.011. Epub 2015 Apr 7. Review.

115. Granerod J, Cunningham R, Zuckerman M, et al. Causality in acute encephalitis: defining aetiologies. Epidemiol Infect. 2010;138:783–800.

116. Paul NL, Kleinig TJ. Therapy of paraneoplastic disorders of the CNS. Expert Rev Neurother. 2015;15:187–193.

3.2.2 Clinical and therapeutic aspects of the Italian cohort of paediatric anti-NMDAR encephalitis

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Original article

Paediatric anti-N-methyl-D-aspartate receptor encephalitis: The first Italian multicenter case series

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Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; n.a., not available; OT, ovarian teratoma; PICU, paediatric intensive care unit.

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ABSTRACT

Background: Given the rarity of this condition, especially in children, there is a paucity of large reported paediatric case series of anti-N-methyl-d-aspartate receptor encephalitis.
Methods: To contribute to define the features of this condition, we describe retrospectively a new nationwide case series of 20 children (50% females), referred by 13 Italian centres.
Results: Mean age at onset was 8 years (range 3–17). Prodromal symptoms were reported in 31.6%; onset was with neurological symptoms in 70%, and with behavioural/psychiatric disturbances in 30%. Most patients developed a severe clinical picture (90%), and 41% experienced medical complications; children 12–18 years old seemed to be more severe and symptomatic than younger patients. All children received first-line immune therapy; second-line treatment was administered to 45%. Relapses occurred in 15%. At last follow-up (mean 23.9 months, range 5–82), 85% patients had mRS 0–1; this rate was higher among older patients, and in those receiving first immune therapy within 1 month.
Conclusions: Our case series confirms a symptomatologic core of paediatric anti-N-methyl-d-aspartate receptor encephalitis, even though displaying some distinctive features that may be explained by a specific genetic background or by the limited number of patients. The growing incidence of this condition, the relative age-dependent variability of its manifestations, the availability of immunotherapy and the possible better outcome with early treatment impose a high index of clinical suspicion be maintained. In the absence of data suggesting other specific etiologies, paediatricians should consider this diagnosis for children presenting with neurological and/or behavioural or psychiatric disturbances, regardless of age and gender.
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1. Introduction

Since its description as a paraneoplastic syndrome in women with ovarian teratoma,[1] anti-N-methyl-D-aspartate receptor encephalitis has been increasingly recognized also in children with or without associated tumours. However, despite numerous case reports in the literature, only few large case series are available in paediatric age.[2–8]

In order to contribute to a further definition of the peculiar features of this condition in children and therefore to improve awareness and early diagnosis among paediatricians, we add a new paediatric nationwide case series to the literature. The description and the comparison of such case series may represent the basis for the future development of specific therapeutic recommendations in paediatric age.

2. Methods

In February 2014 the paediatric neurologic units in Italy were contacted and invited to participate to a national working group on paediatric anti-N-methyl-D-aspartate receptor encephalitis (Italian Working Group on Paediatric Anti-N-methyl-D-aspartate Receptor Encephalitis) and to search retrospectively for paediatric cases. The first working meeting was held in Padua, Italy, on 10th March 2014; on such occasion the inclusion and exclusion criteria and the questionnaire for data collection were discussed and shared.

2.1. Inclusion and exclusion criteria

Patients with anti-N-methyl-D-aspartate receptor encephalitis in paediatric age (≤18 years) referred by any of the centres participating to the Italian Working Group on Paediatric Anti-N-methyl-D-aspartate Receptor Encephalitis until July 2014, with diagnosis confirmed by positive anti-N-methyl-D-aspartate receptor antibodies on serum and/or cerebrospinal fluid (CSF). Exclusion criteria were age >18 years, negative anti-N-methyl-D-aspartate receptor antibodies, or antibodies not tested.

2.2. Patient recruitment and data collection

Upon identification of eligible cases, a comprehensive set of clinical and investigative data, organized in a structured questionnaire, was collected for each patient. Data collection was carried out in one of the three following ways: at the meeting held in Padua, Italy, on 10th March 2014; through a telephonic interview to the treating physician conducted by the main investigators (MN, SS, AS); or through a questionnaire filled out by the treating physicians. Data were reviewed by the principal investigators (SS, AS, MN) and the treating physicians were subsequently contacted for clarification and/or completion of missing data.

2.3. Operational definitions

We defined as acute phase of disease the nadir of severity of the illness. Based on the disease manifestations reported in

the literature, we categorized symptoms into eight major groups: behavioural and/or psychiatric disturbances; psychomotor agitation; movement disorder; speech disturbances; seizures; changes in vigilance, hyporeactivity and/or catatonia; autonomic instability; sleep–wake cycle disturbances.[3–5]

Concerning disease severity, we defined "severe" the patients who were bedridden in the acute phase of disease, had at least 7 of the major symptoms described above and at least 1 among need for paediatric intensive care unit and/or length of hospitalization 3 weeks or longer. Conversely, we defined "mild" the cases who did not meet the preceding criteria.

We defined encephalopathy as in the recent consensus definition for ADEM[9] as an alteration in consciousness (e.g. stupor, lethargy) or behavioural change unexplained by fever, systemic illness or postictal symptoms. First-line immune therapy was defined as the employ of corticosteroids, intravenous immunoglobulin (IVIG) and/or plasma exchange; second-line immunotherapy included cyclophosphamide and/or rituximab.

The modified Rankin Scale (mRS) was used to assess outcome at the last follow-up based on the treating physicians' and the principal investigators' judgement (nearly coincident, despite the limitations imposed by the retrospective assessment).

Similarly to other paediatric case series in the literature,[3,5] and taking into account the possible difference between children and adolescents suggested by other authors,[3] we subdivided children by age groups (<12 years and 12–18 years), in order to allow comparison between disease features in these subsets of patients (Table 1). We also analysed data with respect to the youngest group of patients (<5 years of age).

3. Results

3.1. Demographics

Twenty paediatric patients with anti-N-methyl-D-aspartate receptor encephalitis were enrolled in the present study; data are shown in Table 1. Patients were referred by 13 different centres in Italy, and they resided in 14 different Italian provinces. Onset was between May 2007 and November 2013. Mean age at onset was 8 years (age range 3 years and 1 month–17 years and 9 months); most patients were <12 years old (75%, 15/20), while only a fourth were 12–17 years (25%, 5/20). Genders were equally represented in our population (50%, 10/20 males), with a slight preponderance of female gender in the younger age group as compared to the older patients. Most patients were Caucasian (60%, 12/20), 15% (3/20) were Asiatic, 10% (2/20) African, 5% (1/20) Hispanic and 10% (2/20) were of mixed ethnic origin.

3.2. Family and personal history

Family history for autoimmune and immune-mediated diseases was reported in 18.7% (3/16); personal history was unremarkable in 76.5% (13/17), while in 2 cases (11.8%, 2/17) dysgraphia and dyslexia were reported respectively.

3.3. Initial symptoms

Prodromal flu-like symptoms were reported in 31.6% (6/19) patients. In most patients disease onset was characterized by a neurologic manifestation (seizures, movement disorder, changes in vigilance, autonomic or sleep–wake cycle disturbances) (70%, 14/20) (in 2 of these 14 cases with neurological onset, psychiatric disturbances associated shortly thereafter), whereas in 30% (6/20) the first symptom was behavioural or psychiatric disturbance (in addition to psychiatric symptoms, 4 of these 6 patients had neurological symptoms shortly thereafter) (Fig. 1). With the limitations imposed by the restricted number of patients, the rate of neurological presentation was higher among older patients as compared to the younger ones (80% versus 66.7%). Among patients with neurological onset, seizures were the most common manifestation (Table 1), followed by movement disorder and changes in vigilance. Among patients with seizures as the first symptom of disease, genders were similarly distributed, with a slight preponderance of females (66.7%, 4/6).

3.4. Symptoms in the acute phase of disease

In the acute phase of disease, all of the patients were encephalopathic and 90% (18/20) developed a severe clinical picture. A milder phenotype was observed in two of our children: in particular, they were not bedridden, had no autonomic instability and did not require admission to the paediatric intensive care unit. Both these two patients belonged to the youngest age group (<5 years).

The mean number of major symptoms was 7.3 (range 4–8). During the course of their illness, all patients developed behavioural changes and/or psychiatric disturbances, speech disturbances, and movement disorder (100%, 20/20 each). Psychomotor agitation and changes in consciousness and vigilance were reported in 95% (19/20) each, autonomic instability in 90% (18/20), seizures in 85% (17/20), and sleep–wake cycle disturbances in 82.3% (14/17). Movement disorders included mostly limb dyskinesias, dystonias, choreoathetosis, oro-facial dyskinesias, and freezing; most common dysautonomias were hyperthermia, cardiac rhythm disturbances, hypo/hyperventilation, blood pressure dysregulation. During the acute phase of their illness, 47.4% (9/19) patients were admitted to the intensive care unit, 36.8% (7/19) underwent intubation, and 41.2% (7/17) experienced medical complications; all these rates were higher in the older age group, especially when compared to the patients < 5 years (Table 1). Medical complications included weight loss, muscular abscess, pyelonephritis, rhabdomyolysis, paralytic ileus, colelitiasis, normocytic anaemia, macrocytic anaemia, pneumonia, malignant hyperthermia, syndrome of inappropriate antidiuretic hormone secretion, fracture of radial bone, deep venous thrombosis, and vaginal candidiasis.

3.5. Tumour

Oncologic searches were negative in all patients at first episode (20/20), but ovarian teratoma was detected in 1 girl belonging to the older age group at disease relapse, about 18 months from onset; in this patient, oncologic markers,

Table 1 – Clinical features, diagnostic tests, treatment and outcome of the 20 children with anti-N-methyl-D-aspartate encephalitis. Legend: EEG: electroencephalography; IVIG: intravenous immunoglobulin; MRI: magnetic resonance imaging; n.a.: not available; OT: ovarian teratoma; PICU: paediatric intensive care unit; ≈: about.

Age	<5 years	<12 years	12–18 years	All patients
Number of patients	9/20 (45%)	15/20 (75%)	5/20 (25%)	20
Proportion of females	4/9 (44.4%)	8/15 (53.3%)	2/5 (40%)	10/20 (50%)
Mean age at onset (range)	4 years (3.1–4.9)	6.1 years (3.1–11.9)	13.7 years (12–17.7)	8 years (3.1–17.7)
Ethnic origin				
Caucasic	4/9 (44.4%)	9/15 (60%)	3/5 (60%)	12/20 (60%)
Asiatic	1/9 (11.1%)	2/15 (13.3%)	1/5 (20%)	3/20 (15%)
African	1/9 (11.1%)	1/15 (6.7%)	1/5 (20%)	2/20 (10%)
Hispanic	1/9 (11.1%)	1/15 (6.7%)	0/5 (0%)	1/20 (5%)
Mixed	2/9 (22.2%)	2/15 (13.3%)	0/5 (0%)	2/20 (10%)
Referring center				
Northern Italy	5/9 (55.6%)	11/15 (73.3%)	3/5 (60%)	14/20 (70%)
Central Italy	1/9 (11.1%)	1/15 (6.7%)	1/5 (20%)	2/20 (10%)
Southern Italy	3/9 (33.3%)	3/15 (20%)	1/5 (20%)	4/20 (20%)
Positive family history for autoimmune and immune-mediated conditions	1/7 (14.3%)	2/12 (16.7%)	1/4 (25%)	3/16 (18.7%) (1/2 Hashimoto's thyroiditis; 1/2 multiple sclerosis; 1/2 n.a.)
Positive personal medical history	0/8 (0%)	0/13 (0%)	2/4 (50%)	2/17 (11.8%) (1/2 dysgraphia; 1/2 dyslexia)
Prodromal symptoms	3/9 (33.3%)	5/15 (33.3%)	1/4 (25%)	6/19 (31.6%)
Type of onset				
Neurologic	7/9 (77.8%)	10/15 (66.7%)	4/5 (80%)	14/20 (70%)
Seizures	- 3/9 (33.3%)	–4/10 (40%)	–2/4 (50%)	–6/14 (42.8%)
Movement disorder	–2/9 (22/2%)	–4/10 (40%)	–0/4 (0%)	–4/14 (28.6%)
Changes in vigilance	–1/9 (11.1%)	–1/10 (10%)	–1/4 (25%)	–2/14 (14.3%)
Autonomic instability	–0/9 (0%)	–0/10 (0%)	–1/4 (25%)	–1/14 (7.1%)
Sleep-wake cycle disturbances	–1/9 (11.1%)	–1/10 (10%)	–0/4 (0%)	–1/14 (7.1%)
Behavioural/Psychiatric (unusual behaviour, aggressiveness, irritability, confusion, hallucinations)	2/9 (22.2%)	5/15 (33.3%)	1/5 (20%)	6/20 (30%)
Severity of phenotype in the acute phase				
Severe	7/9 (77.8%)	13/15 (86.7%)	5/5 (100%)	18/20 (90%)
Mild	2/9 (22.2%)	2/15 (13.3%)	0/5 (0%)	2/20 (10%)
Symptoms in the acute phase				
Mean number of major symptoms (range)	7 (4–8)	7.3 (4–8)	7.6 (7–8)	7.3 (4–8)
Movement disorder	9/9 (100%)	15/15 (100%)	5/5 (100%)	20/20 (100%)
Behavioural/Psychiatric disturbances	9/9 (100%)	15/15 (100%)	5/5 (100%)	20/20 (100%)
Speech disturbances	9/9 (100%)	15/15 (100%)	5/5 (100%)	20/20 (100%)
Psychomotor agitation	8/9 (88.9%)	14/15 (93.3%)	5/5 (100%)	19/20 (95%)

Changes in vigilance, hyporeactivity	8/9 (88.9%)	14/15 (93.3%)	5/5 (100%)	19/20 (95%)
Autonomic instability	7/9 (77.8%)	13/15 (86.7%)	5/5 (100%)	18/20 (90%)
Seizures	7/9 (77.8%)	12/15 (80%)	5/5 (100%)	17/20 (85%)
Sleep-wake cycle disturbances	6/9 (66.7%)	12/15 (80%)	3/3 (100%)	15/18 (83.3%)
Associated tumour	0/9 (0%)	0/15 (0%)	1/5 (20%)	1/20 (5%) (OT)
PICU	2/8 (25%)	6/14 (42.8%)	3/5 (60%)	9/19 (47.4%)
Orotracheal intubation	2/8 (25%)	4/14 (28.6%)	3/5 (60%)	7/19 (36.8%)
Medical complications	1/8 (12.5%)	4/12 (33.3%)	3/5 (60%)	7/17 (41.2%)
Abnormal MRI	6/9 (66.7%)	7/15 (46.7%)	3/5 (40%)	9/20 (45%)
Abnormal EEG	8/8 (100%)	14/14 (100%)	5/5 (100%)	19/19 (100%). Recorded seizures in 6/19 (31.6%)
Cerebrospinal fluid				
Pleocytosis	2/7 (28.6%)	6/13 (46.1%)	3/3 (100%)	9/16 (56.2%)
Oligoclonal bands	5/7 (71.4%)	8/13 (61.5%)	3/4 (75%)	11/17 (64.7%)
Time from onset to first immune therapy				
<30 days	5/7 (71.4%)	9/13 (69.2%)	2/3 (66.7%)	11/16 (68.7%)
≥30 days	2/7 (28.6%)	4/13 (30.8%)	1/3 (33.3%)	5/16 (31.2%)
Immune therapy		15/15 (100%)	5/5 (100%)	20/120 (100%)
1 treatment	0/9 (0%)	−1/15 (6.7%)	−1/5 (20%)	−2/20 (10%) (IVIG)
≥2treatments	9/9 (100%)	−14/15 (93.3%)	−4/5 (80%)	−18/20 (90%)
First-line immune therapy	9/9 (100%)	13/13 (100%)	5/5 (100%)	18/18 (100%)
Corticosteroids	−9/9 (100%)	−14/15 (93.3%)	−4/5 (80%)	−18/20 (90%)
IVIG	−9/9 (100%)	−13/15 (86.7%)	−4/5 (80%)	−17/20 (85%)
Plasma exchange	−2/9 (22.2%)	−5/15 (33.3%)	−2/5 (40%)	−7/20 (35%)
Second-line immune therapy	4/9 (44.4%)	7/15 (46.7%)	2/5 (40%)	9/20 (45%)
Cyclophosphamide	−3/9 (33.3%)	−6/15 (40%)	−1/5 (20%)	−7/20 (35%)
Rituximab	−2/9 (22/2%)	−2/15 (13.3%)	−1/5 (20%)	−3/20 (15%)
Other treatments				
Antiepileptic drugs	8/9 (88.9%)	14/15 (93.3%)	5/5 (100%)	19/20 (95%)
Antipsychotic drugs	3/6 (50%)	7/10 (70%)	3/3 (100%)	10/13 (76.9%)
Mean length of hospitalization (range) (data available in 18/20)	7.9 weeks (1−20	11.4 weeks (1−32)	8.6 weeks (3−13)	10.7 weeks (1−32)
Length of hospitalization < 4 weeks	4/8 (50%)	4/14 (28.6%)	1/4 (25%)	5/18 (27.8%)
Destination at discharge				
Home	8/9 (88.9%)	12/14 (85.7%)	3/4 (75%)	15/18 (27.8%)
Rehabilitation	1/9 (11.1%)	2/14 (14.3%)	1/4 (25%)	3/18 (16.7%)
Relapses	1/9 (11.1%)	2/15 (13.3%)	1/5 (20%)	3/20 (15%)
Time from disease onset to relapse	3 years	3 years and 4 years	1.5 years	2.8 years (range 1.5−4 years)
Presenting symptom at relapse	Movement disorder	1/2 Movement disorder 1/2 Headache, seizures, behavioural disturbances	1/1 Behavioral disturbances	1/3 Movement disorder 1/3 Headache, seizures, behavioural disturbances 1/3 Behavioral disturbances

(*continued on next page*)

Table 1 – (continued)

Age	<5 years	<12 years	12–18 years	All patients
Mean length of follow-up (range) (data available in 19/20)	18 months (5–57)	23.5 months (5–82)	16.5 month (6–24)	23.9 months (5–82)
EEG normalization at last follow-up	4/8 (50%)	7/13 (50%)	3/5 (60%)	10/18 (55.5%)
Ongoing epilepsy at last follow-up	0/9 (0%)	0/14 (0%)	1/4 (25%)	1/18 (5.5%)
Ongoing antiepileptic treatment at last follow-up	5/7 (71.4%)	5/12 (41.7%)	1/3 (33.3%)	6/15 (40%)
Neurological outcome at last follow-up				
mRS 0-1	7/9 (77.8%)	12/15 (80%)	5/5 (100%)	17/20 (85%) (mean length of follow-up available in 15/16: 21.9 months; range 5–71 months)
mRS 2–3	1/9 (11.1%)	2/15 (13.3%)	0/5 (0%)	2/20 (10%) (mean length of follow-up: 44 months; range 6–82 months)
mRS 4–6	1/9 (11.1%)	1/15 (6.7%)	0/5 (0%)	1/20 (5%) (length of follow-up: 17 months)

abdominal ultrasounds and magnetic resonance were initially negative, but pelvic ultrasound detected teratoma at follow-up.

3.6. *Investigations*

Anti-N-methyl-D-aspartate receptor antibodies were tested on CSF in 13/20 cases (positive in 100% 13/13); in the remaining 7 cases, they were tested on serum (positive in 100%, 7/7). Brain magnetic resonance imaging was normal in 55.5% (11/20) cases. Electroencephalographic (EEG) tracing was abnormal in all patients (19/19), but epileptic seizures were captured only in a minority of cases (31.6%, 6/19). In all the cases with available information, slowing of EEG was reported (11/11), whereas epileptic spikes were detected in half (7/14). CSF pleocytosis was reported in 56.2% (9/16); intrathecal oligoclonal bands were present in 64.7% (11/17).

3.7. *Treatment*

All of our patients received an immune treatment. First immune therapy was administered within 29 days of symptom onset in 68.7% (11/16), while in the remaining 31.2% (5/16) it was administered after the 30th day. Mean time from disease onset to first immune treatment was 23.7 days (range 5–60; data available in 16/20 patients).

Treatment strategies varied greatly; 90% of patients (18/20) received at least two treatments, while in 10% cases (2/20) patients were only treated with IVIG. In 45% of cases (9/20), after first-line immune therapy patients received a second-line immune therapy. Treatment involved corticosteroids in 90% (18/20) (intravenous methylprednisolone in most cases), IVIG in 85% (17/20), plasma exchange in 35% (7/20), cyclophosphamide in 35% (7/20), rituximab in 15% (3/20). In 15% (3/20) mycophenolate mofetil was also administered. Antiepileptic treatment was administered to 95% (19/20) patients, treatment for psychiatric disturbances or psychomotor agitation to 76.9% (10/13).

3.8. *Outcome*

None of the patients died. Mean length of hospitalization was 10.7 weeks (range 1–32 weeks) (data available in 18/20); length of hospitalization was slightly shorter in the older age group. Most patients were discharged home (83.3%, 15/18), while 16.7% (3/18) were transferred to a rehabilitation unit. Mean duration of follow-up was 23.9 months (range 5–82 months) (data available in 19/20).

3.9. *Relapses*

Relapse of disease occurred in 3 cases (15%), at about 1.5, 3 and 4 years from disease onset respectively. Two of these cases were younger than 12 years (1 male, 1 female), 1 was older (1 female). All 3 cases had a severe disease course during the first episode, and had a substantial recovery before the following episode. During the first episode none of these patients received second-line treatments: 2 were treated with corticosteroids and IVIG, 1 only with IVIG. In 2 of the 3 cases, the clinical picture at relapse was milder than at presentation.

3.10. *Neurological outcome at last follow-up*

At last follow-up, mean mRS score was 0.9 (median 1, range 0–5). Of the 3 patients who had a multiphasic disease course with relapses, 2 had an mRS score of 1 and 1 had an mRS score of 0. Rate of good recovery (mRS 0–1) was higher among older patients (12–18 years), especially when compared to the very young age group (<5 years).

Rate of mRS 0 or 1 at last follow-up was higher among the 11 patients in whom first immune therapy was administered within 29 days from disease onset (90.9%, 10/11) than in the 5 cases in whom it was administered after 29 days from disease onset (60%, 3/5) (Table 2). At last follow-up, ongoing epilepsy was reported in 5.5% (1/15) patients, and ongoing antiepileptic treatment in 40% (6/15). Electroencephalographic normalization occurred in 55.5% (9/18).

4. Discussion

We described the first Italian case series of paediatric anti-N-methyl-D-aspartate receptor encephalitis. Large case series of children with anti-N-methyl-D-aspartate receptor encephalitis are rare in the literature (Table 3). Among these, are those described by Florance in 2009 (n = 32)[3], by Titulaer in 2013 (n = 212)[5], by Dale in 2014 (n = 39)[6], and by Armangue in 2013 (n = 20)[4]; the latter is particularly comparable to ours as regards the number and the ethnic origin of the subjects. Among smaller case series are those reported in 2009 by Dale (n = 10)[2] and later by Hacohen (n = 13).[7,8]

Our case series is mostly confirmatory of data previously reported in the literature, though some differences can be observed. The significance of these latter is possibly strengthened by the overall concordance of our findings with previously published cohorts, supporting the general reliability of our data. With regards to demographic features, the prevalence of female gender described in paediatric and adult literature[4–6,10] is not observed in our population; this finding may possibly be incidental, considered the limited sample size. Of note, family history for autoimmune and immune-mediated diseases was reported in nearly 19% of cases. Positive family history is reported in other autoimmune diseases and, while in the case of anti-N-methyl-D-aspartate receptor encephalitis available data are not yet sufficient to confirm this finding, this remains an area of interest requiring further work.

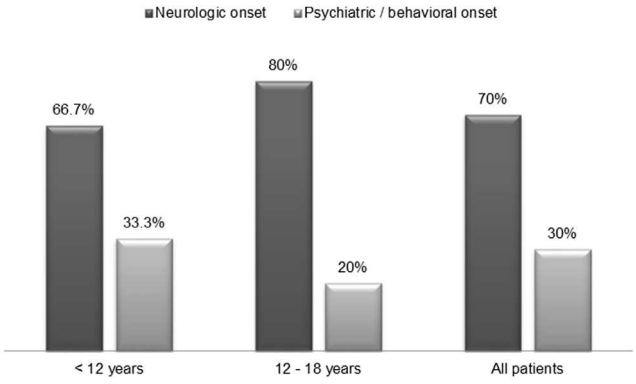

Fig. 1 – Disease onset divided by neurological symptoms (seizures, movement disorder, changes in vigilance, autonomic or sleep–wake cycle disturbances) or psychiatric symptoms (psychiatric or behavioral changes) in the patients < 12 years, in the patients 12–18 years and in all patients.

Prodromal symptoms are reported in over 85% of adult cases,[1] and in 48%–100% of children[3,4,11] in the literature. The lower rate of prodromal symptoms in our population (less than one third of cases) is possibly due to underreporting, in consideration of the retrospective nature of our work. As regards disease onset, the first symptoms were psychiatric or behavioural in one third of cases, and neurologic in over two thirds, most frequently seizures and movement disorder, followed by changes in vigilance, autonomic instability and sleep–wake cycle disturbances. The rate of neurological presentation is similar to that reported by Armangue and coworkers,[4] whereas in the ten cases described by Dale and colleagues[2] neurologic and psychiatric presentation were equally distributed, and "pure" neurological presentation dropped to 12.5% in the cases reported by Florance.[3] Data in the literature suggest an increase of the rate of psychiatric presentation with age,[3,4] peaking to 77% in adult series,[1] but our population does not reflect this trend. In contrast to recent data in the literature,[12] we did not observe male prevalence among our cases presenting with seizures. It is noteworthy that the seizures reported at disease presentation occurred before the first access to the hospital and were witnessed by non-medical personnel; therefore, considered the variety of movement disorders and of paroxysmal non epileptic manifestations in these patients, the epileptic nature of the events reported as "seizures" by care-givers should not be taken for granted.[13] Similarly, during the course of the disease only in a subset of patients EEG tracing allowed to capture an epileptic seizure. In accordance to our findings, electroencephalographic detection of unequivocal ictal activity is relatively rare in the literature.[12,14–21]

Similarly to the cases described by Armangue,[4] most of our patients developed a severe clinical picture in the acute phase of disease, being bedridden and displaying a variable combination of other severe symptoms. As an additional indicator of the potential severity of anti-N-methyl-D-aspartate receptor encephalitis, medical complications and the use of symptomatic therapies were common in our cohort. Medical complications are a relevant aspect of anti-N-methyl-D-aspartate receptor encephalitis, since they can severely affect the overall recovery process and the length of hospitalization. Therefore, future guidelines for the management of this disease should include the optimal management of medical complications.

During disease course, movement disorder, behavioural or psychiatric disturbances and speech problems were observed in all our cases; besides, over 90% had psychomotor agitation, changes in vigilance, hyporeactivity, catatonia and autonomic instability, and over 80% had seizures and sleep–wake cycle disturbances. In the older age group (12–18 years) all patients had all the symptoms and none had the mild form of the disease according to our categorization, possibly suggesting a more severe and symptomatic phenotype in older patients as

Table 2 – Neurological outcome at last follow-up in relation to the timing of initiation of first immune therapy from disease onset.

Neurological outcome at last follow-up in relation to the timing of initiation of first immune therapy from disease onset	
	In the 11/16 in whom first immune therapy was started < 30 days from disease onset (mean length of follow-up, available in 10/11: 24.8 months; range 5–71)
mRS 0–1	10/11 (90.9%) (mean length of follow-up available in 9/10: 25.7 months; range: 5–71 months)
mRS 2-3	0/11 (0%)
mRS 4–6	1/11 (9.1%) (length of follow-up: 17 months)
	In the 5/16 in whom first immune therapy was started ≥ 30 days from disease onset (mean length of follow-up: 27.2 months; range 6–82)
mRS 0–1	3/5 (60%) (mean length of follow-up: 16 months; range: 15–18 months)
mRS 2–3	2/5 (40%) (mean length of follow-up: 44 months; range: 6–82 months)
mRS 4–6	0/5 (0%)

compared to younger children, and in particular to the youngest group (<5 years). Accordingly, more patients in the older age group as compared to younger patients, and especially to patients <5 years, had medical complications, were admitted to the paediatric intensive care unit and underwent orotracheal intubation. In possible accordance with our findings, in the case series by Titulaer and colleagues more patients in the older age group had autonomic instability and central hypoventilations as compared to cases younger than 12 years,[5] and a lower severity of autonomic manifestations and central hypoventilation in children as compared to adults is reported also by Florance and colleagues.[3] Though, definite conclusions on the different severity of disease in the two age groups can't be drawn due to the limited number of cases in our population.

Tumour (ovarian teratoma) was found in one girl belonging to the older age group (5% of all patients), only after the patient presented a clinical relapse; similar rates of tumour detection are reported by Dale et al. (7.7%)[6] and by Titulaer et al., even though in this latter case in patients younger than 12 years (6%)[5]; our rate of tumour detection is considerably lower than those reported by Armangue (18%) and Florance (25%),[3,4] despite a longer follow-up.

All of our patients received immune therapy. Mean time from disease onset to first immune therapy was about 23 days, similarly to data reported by Titulaer and colleagues (21 days).[5] First immune therapy was administered within the 29th day from disease onset in about two thirds of cases, and in a higher proportion of patients as compared to what reported in the case series by Armangue and coworkers[4]; this may be possibly ascribed to the ever-growing knowledge of this condition, likely responsible for its earlier detection than in the past. In the case series reported by Armangue,[4] a higher rate of early treatment (<30 days) in children < 12 years is reported as compared to children aged 12–18 years (66.67% versus 45.45%); this difference is only minimal in our population. Relapses occurred in 15% of our children; of note, the three patients that relapsed received only first-line immune therapy. In the case series described by Titulaer and coworkers,[5] a relapse-decreasing effect of second-line immunotherapy was observed in patients without tumour and in patients who had already relapsed. Accordingly, a higher relapse rate occurred in cohorts in which a lower rate of second-line immune therapy was used.[2,3,8] All the three cases that relapsed in our cohort had completely normalized before relapsing. Therefore, these data suggest that clinical normalization does not guarantee an absolutely reduced risk of relapse, and that possibly the length of treatment should not rely solely on the clinical normalization, even though reliable biological markers of the disease are lacking at the moment.

At last follow-up, 85% of patients had a good recovery (mRS 0–1), similarly to the rate of full recovery and mild disability in the case series by Armangue and colleagues (85%),[4] with similar length of follow-up; all the 3 patients who had relapses had a substantial recovery at last follow-up. Of utmost importance among our findings, rate of low mRS (0–1) at follow-up was higher among patients in whom the first immune therapy was started within 1 month from disease onset (Table 2). Supporting our results, early immune therapy has been reported to yield better outcomes in other case series in the literature.[5,6,22] These data suggest the importance of an early recognition of this disorder in order to allow for early immune therapy and therefore possibly for a better outcome.

4.1. *Limitations*

The restricted number of patients is among the main limitations of our study, hampering statistical analysis, especially among subgroups of cases. The multicenter nature of our work, although allowing for the collection of a larger number of cases than if limited to a single centre, is responsible for the incompleteness or heterogeneity of information in some subsets of data.

4.2. *Conclusions*

The characteristics of the Italian population of children with anti-N-methyl-D-aspartate receptor encephalitis are mostly confirmatory of data in the literature, though some distinctive

Table 3 – Major findings from some of the main pediatric case series in the literature of patients with anti-N-methyl-D-aspartate receptor encephalitis (case series with ≥10 patients were included). Legend: AZA: azathioprine; CS: corticosteroids; CSF: cerebrospinal fluid; CYC: cyclophosphamide; EEG: electroencephalography; IVIG: intravenous immunoglobulines; MMF: mycophenolate mofetil; MRI: magnetic resonance imaging; N°: number; Neurol.: neurological; n.a.: not available; OCB: oligoclonal bands; PE: plasma exchange; PICU: pediatric intensive care unit; prodr.: prodromal; RTX: rituximab.

Articles (notes)	Florance et al., 2009[3]	Dale et al., 2009[2]	Armangue et al., 2013[4]	Titulaer et al., 2013[5] (data in adults + children, unless otherwise specified)	Dale et al., 2014[20]	Hacohen et al., 2014[8] (NMDAR ab positive patients, different clinical syndromes)
N° of cases (<18 years)	32	10	20	211 (+367 adults)	39	46
Females	26/32 (81%)	8/10 (80%)	14/20 (70%)	468/577 (81%)	29/39 (74%)	32/46 (69%)
Age at onset	Median 14 years (range 1.9–18)	Median 7 years (range 1.3–13)	Median 13 years (range 0.7–18)	Median 21 years (range 1–85)	Median 8.7 years (range 1.6–17 years)	Median 10.5 years (range 1–18)
Prodr. symptoms	15/31 (48%)	n.a.	11/20 (55%)	n.a.	n.a.	n.a.
Onset type						
Neurol.	4/32 (12.5%)	5/10 (50%)	12/20 (60%)	Neurol. in most children <12 years;	n.a.	43/46 (93%)
Psychiatric	28/32 (87.5%)	5/10 (50%)	8/20 (40%)	behavioral in most adults.	n.a.	3/46 (7%)
Disease severity	n.a.	n.a.	PCPC maximum: median 4 (range 4–6)	- 495/570 (87%): maximum mRS 5 - 498/571 (87%) patients developed ≥4 of the 8 categories of symptoms - 435/567 (77%) ICU	Median worst mRS: 5	n.a.
Tumour	8/32 (27%)	0/10 (0%)	2/20 (10%)	220/577 (38%)	3/39 (8%)	1/46 (2%)
Abnormal EEG	25/25 (100%)	n.a.	18/20 (90%)	432/482 (90%)	n.a.	
Abnormal MRI	10/32 (31%)	3/10 (30%)	9/20 (45%)	180/540 (33%)	n.a.	19/46 (41%)
CSF						
Pleocytosis	27/31 (87%)	4/10 (40%)	14/20 (70%)	Abnormal CSF in 418/532 (79%)	n.a.	n.a.
OCB	5/6 (83%)	9/9 (100%)	n.a.		n.a.	OCB: 14/32 (44%)
Time from onset to first immune therapy	n.a.	n.a.	n.a.	Median 21 days (range 2–730)	Disease duration before RTX: median 0.1 years (range 0.05–5.1)	n.a.
Immune therapy	1st-line: 30/32 (97%) 2nd-line: 7/32 (22%)	n.a.	1st-line: 20/20 (100%) 2nd-line: 7/20 (35%)	1st-line: 462/501 (92%) 2nd-line: 134/501 (27%)	2nd-line: 39/39 9100%)	1st-line: 41/46 (89%) 2nd-line: 12/46 (26%)
	CYC: 5/32 (16%) RTX: 6/32 (19%)		CS: 20/20 (100%) IVIG: 15/20 (75%) PE: 1/20 (5%) CYC: 3/20 (15%) RTX: 7/20 (35%)	CS: 421/501 (84%) IVIG: 346/501 (69%) PE: 163/501 (33%) CYC: 81/501 (16%) RTX: 101/501 (20%)	CS: 37/39 (95%) IVIG: 34/39 (87%) PE: 11/39 (28%) CYC: 8/39 (20%) RTX: 39/39 (100%) MMF/AZA: 4/39 (10%)	CS: 36/46 (78%) IVIG: 25/46 (54%) PE: 14/46 (30%) CYC: 2/46 (4%) RTX: 5/46 (11%) MMF: 7/46 (15%) AZA: 1/46 (2%)
Length of admission	n.a.	Mean 13.6 weeks (range 6–35)	Mean 56 days (range 13–336)	n.a.	n.a.	n.a.

(continued on next page)

Table 3 – (continued)

Articles (notes)	Florance et al., 2009[3]	Dale et al., 2009[2]	Armangue et al., 2013[4]	Titulaer et al., 2013[5] (data in adults + children, unless otherwise specified)	Dale et al., 2014[20]	Hacohen et al., 2014[8] (NMDAR ab positive patients, different clinical syndromes)
Length of follow-up	Median 4.5 months (range 2–14.5)	Mean 27 months (range 6–84)	Median 17.5 months (range 4–149)	24 months	Median follow-up post-RTX 1.3 years (range 0.4–4.5)	n.a.
Relapses	8/32 (25%)	2/10 (20%)	3/20 (15%)	45/577 (8%)	n.a.	17/46 (37%)
Neurol. outcome	- Complete/substantial recovery: 23/31 (74%) - Limited recovery: 8/31 (26%)	- Complete recovery: 4/10 (40%) - Significant motor, cognitive or psychiatric impairments: 6/10 (60%)	- Substantial improvement: 17/20 (85%) - Moderate/severe disability: 2/20 (10%) - Death: 1/20 (5%)	- Good outcome: 394/501 (79%) (mRS 0–2) - Death: 30/501 (6%).	Median mRS 1 - Ongoing disability: 32/39 (82%) - Death: 2/39 (5%)	- Full recovery: 17/46 (37%)

features can be observed. The limited number of patients may be implicated in these differences, especially in the older age group; a different genetic background in the population can't be ruled out, either. The growing incidence of this condition, the availability of therapeutic interventions, the possibility of a better outcome with early treatment and with second-line immune therapies, and the relative age-dependent variability of clinical manifestations impose a high clinical suspicion towards this disease be maintained. In the absence of clinical-anamnestic data or physical and neuroradiologic findings suggesting other specific etiologies, paediatricians should always consider this diagnosis when a child of any age and gender presents with a combination of one or more neurological deficits (especially dyskinetic movement disorder, paroxysmal episodes of uncertain aetiology and classification, speech disturbances) and one or more behavioural or psychiatric disturbances (including subtle behavioural changes, apathy, withdrawal, disinhibition, agitation).

Compliance with ethical standards

The present study was conducted according to Helsinki declaration. The retrospective review of medical files of the patients reported in this paper is conform to the indications provided by our Institutional Review Board.

Conflict of interest

The authors declare that they have no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejpn.2015.02.006.

REFERENCES

1. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;**61**:25–36.
2. Dale RC, Irani SR, Brilot F, et al. N-methyl-D-aspartate receptor antibodies in pediatric dyskinetic encephalitis lethargica. *Ann Neurol* 2009;**66**:704–9. http://dx.doi.org/10.1002/ana.21807.
3. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009;**66**:11–8. http://dx.doi.org/10.1002/ana.21756.

4. Armangue T, Titulaer MJ, Málaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013;**162**:850–6. http://dx.doi.org/10.1016/j.jpeds.2012.10.011. e2.
5. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013;**12**:157–65. http://dx.doi.org/10.1016/S1474-4422(12)70310-1.
6. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology* 2014;**83**:142–50. http://dx.doi.org/10.1212/WNL.0000000000000570.
7. Hacohen Y, Wright S, Waters P, et al. Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. *J Neurol Neurosurg Psychiatry* 2013 Jul;**84**(7):748–55. http://dx.doi.org/10.1136/jnnp-2012-303807. Epub 2012 Nov 22.
8. Hacohen Y, Absoud M, Hemingway C, et al. NMDA receptor antibodies associated with distinct white matter syndromes. *Neurol Neuroimmunol Neuroinflamm* 2014 Apr 24;**1**(1):e2. http://dx.doi.org/10.1212/NXI.0000000000000002.
9. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, Ghezzi A, Hintzen R, Kornberg A, Pohl D, Rostasy K, Tenembaum S, Wassmer E, International Pediatric Multiple Sclerosis Study Group. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler* 2013;**19**:1261–7. http://dx.doi.org/10.1177/1352458513484547.
10. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;**7**:1091–8. http://dx.doi.org/10.1016/S1474-4422(08)70224-2.
11. Poloni C, Korff CM, Ricotti V, et al. Severe childhood encephalopathy with dyskinesia and prolonged cognitive disturbances: evidence for anti-N-methyl-D-aspartate receptor encephalitis. *Dev Med Child Neurol* 2010;**52**:e78–82. http://dx.doi.org/10.1111/j.1469-8749.2009.03542.x.
12. Titulaer MJ, Dalmau J. Seizures as first symptom of anti-NMDA receptor encephalitis are more common in men. *Neurology* 2014;**82**:550–1. http://dx.doi.org/10.1212/WNL.0000000000000131.
13. Nosadini M, Boniver C, Zuliani L, et al. Longitudinal Electroencephalographic (EEG) findings in pediatric Anti-N-Methyl-d-Aspartate (Anti-NMDA) receptor encephalitis: the Padua Experience. *J Child Neurol* 2015;**30**:238–45. http://dx.doi.org/10.1177/0883073813515947.
14. Bayreuther C, Bourg V, Dellamonica J, et al. Complex partial status epilepticus revealing anti-NMDA receptor encephalitis. *Epileptic Disord* 2009;**11**:261–5. http://dx.doi.org/10.1684/epd.2009.0266.
15. Gataullina S, Plouin P, Vincent A, et al. Paroxysmal EEG pattern in a child with N-methyl-D-aspartate receptor antibody encephalitis. *Dev Med Child Neurol* 2011;**53**:764–7. http://dx.doi.org/10.1111/j.1469-8749.2011.03956.x.
16. Goldberg EM, Taub KS, Kessler SK, Abend NS. Anti-NMDA receptor encephalitis presenting with focal non-convulsive status epilepticus in a child. *Neuropediatrics* 2011;**42**:188–90. http://dx.doi.org/10.1055/s-0031-1295408.
17. Johnson N, Henry C, Fessler AJ, Dalmau J. Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. *Neurology* 2010;**75**:1480–2. http://dx.doi.org/10.1212/WNL.0b013e3181f8831a.
18. Kirkpatrick MP, Clarke CD, Sonmezturk HH, Abou-Khalil B. Rhythmic delta activity represents a form of nonconvulsive status epilepticus in anti-NMDA receptorantibody encephalitis. *Epilepsy Behav* 2011;**20**:392–4. http://dx.doi.org/10.1016/j.yebeh.2010.11.020.
19. Kleinig TJ, Thompson PD, Matar W, et al. The distinctive movement disorder of ovarian teratoma-associated encephalitis. *Mov Disord* 2008;**23**:1256–61. http://dx.doi.org/10.1002/mds.22073.
20. Millichap JJ, Goldstein JL, Laux LC, et al. Ictal asystole and anti-N-methyl-D-aspartate receptor antibody encephalitis. *Pediatrics* 2011;**127**:e781–786. http://dx.doi.org/10.1542/peds.2010-2080.
21. Motoyama R, Shiraishi K, Tanaka K, Kinoshita M, Tanaka M. Anti-NMDA receptor antibody encephalitis with recurrent optic neuritis and epilepsy. *Rinsho Shinkeigaku* 2010;**50**:585–8 [Article in Japanese].
22. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, Friese MA, Galea I, Kullmann DM, Beeson D, Lang B, Bien CG, Vincent A. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010;**133**:1655–67. http://dx.doi.org/10.1093/brain/awq113.

3.2.3 Herpes simplex virus-induced anti-NMDAR encephalitis

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Herpes simplex virus-induced anti-*N*-methyl-D-aspartate receptor encephalitis: a systematic literature review with analysis of 43 cases

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ABBREVIATIONS

HSE	Herpes simplex encephalitis
HSV	Herpes simplex virus
mRS	Modified Rankin Scale
NMDAR	*N*-methyl-D-aspartate receptor
PCR	Polymerase chain reaction

AIM To conduct a systematic literature review on patients with biphasic disease with herpes simplex virus (HSV) encephalitis followed by anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.

METHOD We conducted a case report and systematic literature review (up to 10 December 2016), focused on differences between herpes simplex encephalitis (HSE) and anti-NMDAR encephalitis phases, age-related characteristics of HSV-induced anti-NMDAR encephalitis, and therapy. For statistical analyses, McNemar's test, Fisher's test, and Wilcoxon rank sum test were used (two-tailed significance level set at 5%).

RESULTS Forty-three patients with biphasic disease were identified (31 children). Latency between HSE and anti-NMDAR encephalitis was significantly shorter in children than adults (median 24 vs 40.5d; p=0.006). Compared with HSE, anti-NMDAR encephalitis was characterized by significantly higher frequency of movement disorder (2.5% vs 75% respectively; p<0.001), and significantly lower rate of seizures (70% vs 30% respectively; p=0.001). Compared with adults, during anti-NMDAR encephalitis children had significantly more movement disorders (86.7% children vs 40% adults; p=0.006), fewer psychiatric symptoms (41.9% children vs 90.0% adults; p=0.025), and a slightly higher median modified Rankin Scale score (5 in children vs 4 in adults; p=0.015). During anti-NMDAR encephalitis, 84.6 per cent of patients received aciclovir (for ≤7d in 22.7%; long-term antivirals in 18.0% only), and 92.7 per cent immune therapy, but none had recurrence of HSE clinically or using cerebrospinal fluid HSV polymerase chain reaction (median follow-up 7mo).

INTERPRETATION Our review suggests that movement disorder may help differentiate clinically an episode of HSV-induced anti-NMDAR encephalitis from HSE relapse. Compared with adults, children have shorter latency between HSE and anti-NMDAR encephalitis and, during anti-NMDAR encephalitis, more movement disorder, fewer psychiatric symptoms, and slightly more severe disease. According to our results, immune therapy given for HSV-induced anti-NMDAR encephalitis does not predispose patients to HSE recurrence.

Herpes simplex encephalitis (HSE) is one of the most common causes of severe sporadic encephalitis. Herpes simplex virus (HSV) 1 is usually the responsible pathogen in adults and children, whereas HSV2 is mostly detected in neonates.[1] Symptoms in the early stages in adults and children include fever, headache, fatigue, vomiting, seizures, confusion, somnolence, decreased consciousness, and focal neurological signs.[2–4] HSE is characterized by unfavourable outcome with severe neurological sequelae or death in about 35% of patients.[5] While HSE is usually a monophasic disease, relapses have been reported in 7.1% to 12.5% of adult patients,[3] and in 14.3% to 26.7% of children.[2,6,7] In some cases, the association of relapses with a low initial dose of aciclovir,[6] the good response to a second course of aciclovir,[2] or the detection of positive HSV-polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) have suggested incomplete viral inactivation or new viral replication.[4] However, in other cases, the negativity of HSV PCR in CSF at relapse, the absence of new necrotic haemorrhagic lesions on brain magnetic resonance imaging (MRI), the poor response to aciclovir, and the efficacy of immune therapy have

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suggested that an immune-mediated mechanism may be responsible.[8]

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a condition characterized by multistage progression with psychiatric and behavioural symptoms, movement disorder, seizures, speech disturbances, decreased consciousness, and dysautonomias. After its description, it has been suggested that anti-NMDAR antibodies may be implicated in the immune-mediated relapses after HSE,[9] and cases of anti-NMDAR encephalitis after HSE have been subsequently described both in adult and paediatric age.

We report the case of a 7-year-old female who recently presented to our hospital with anti-NMDAR encephalitis following an episode of HSE. As correct and early recognition of this condition is crucial for the commencement of appropriate therapy, this case prompted us to perform a systematic review of the literature on patients with biphasic disease with HSE followed by anti-NMDAR encephalitis (HSV-induced anti-NMDAR encephalitis) and on the relationship between central nervous system (CNS) HSV infection and anti-NMDAR antibodies.

What this paper adds

- Movement disorder is characteristic of anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis but not of herpes simplex virus (HSV) encephalitis.
- Despite immune therapy for HSV-induced anti-NMDAR encephalitis, none of the patients had recurrence of HSV encephalitis.

METHOD

Case report and literature review

We illustrate a new case of biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis, and we present the results of a systematic literature review on the relationship between CNS HSV infection and the development of anti-NMDAR antibodies. A literature search was first done by one of the researchers (FC), and then carried out again by another researcher (MN), independently, in order to ensure inclusion of all relevant papers. The literature review was carried out in PubMed only (up to 10 December 2016), using the following search terms: 'NMDAR' OR 'anti-NMDAR' OR 'anti-NMDAR encephalitis' OR 'NMDA receptor encephalitis' OR 'N-Methyl-D-Aspartate' OR 'Anti-N-Methyl-D-Aspartate Receptor' OR 'Anti-N-Methyl-D-Aspartate Receptor encephalitis'. The available results were searched manually for 'herpes', 'HSV', and 'herpetic'.

Inclusion criteria

Patients with biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis were included in the literature review. We also included, separately, patients with HSE with detection of anti-NMDAR antibodies (in the absence of a clinical episode of anti-NMDAR encephalitis), and patients with anti-NMDAR encephalitis with concomitant positive HSV markers (in the absence of a preceding clinical or radiological episode of HSE). Both full-text and abstract-only articles were included.

Data extraction and collection

In the selected articles, a comprehensive data set was collected via a form designed for the present study. The form was created by one of the authors (MN) after reading the relevant literature, to capture core features and relevant data on published patients with biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis. The form consisted of an Excel spreadsheet (Microsoft, Redmond, WA, USA), where each column captured a different piece of information and data relative to each patient was recorded in a different line. When data were inadequate or insufficient for a definite piece of information, we recorded it as 'not available'. Data of the individual patients were then pooled and analysed via the spreadsheet. A Microsoft Word document transposition of the form is provided as Appendix S1 (online supporting information).

Data extraction was first done by one of the researchers (FC), and then verified by another researcher (MN), who checked for accuracy and completeness of collected data. Other authors were involved in data analysis, interpretation, and supervision of the project. Data collection focused on symptoms during HSE and anti-NMDAR encephalitis, CSF data, evidence of CNS HSV infection, antibody status, antiviral and immune therapy, and outcome. Similar to other major published case series of anti-NMDAR encephalitis,[10,11] we categorized the main symptoms of disease as encephalopathy (defined as altered level of consciousness persisting for >24h and including lethargy, irritability, or a change in personality and behaviour);[12] psychiatric/behavioural changes or agitation; movement disorder; speech disturbances; cognitive deterioration; seizures; autonomic disturbances; and sleep–wake cycle disturbances. We defined first-line immune therapy as corticosteroids, intravenous immunoglobulin and plasmapheresis, and second-line immune therapy as rituximab, cyclophosphamide, mycophenolate mofetil, azathioprine, and others. With regard to severity of disease and outcome, based on the clinical description available in the case reports, modified Rankin Scale (mRS) score was retrospectively assigned in different phases:[13] at nadir of the episode of HSE; at recovery (before onset of anti-NMDAR encephalitis); at nadir of the episode of anti-NMDAR encephalitis; and at last available follow-up. mRS scores were assigned independently by two of the main investigators (MN and FC) and then compared. Discordant ratings were resolved by consensus. For paediatric patients, the Pediatric Cerebral Performance Category scale, as done by Armangue et al.,[14] was also applied (MN) in addition to the mRS scoring. Comparison of percentages and median values were used in most cases as main summary measures. The literature review was subject to publication bias and selective reporting within studies.

Statistical methods

Comparison of symptoms between the HSE and the anti-NMDAR encephalitis phases was done with McNemar's

test (the analysis was carried out only for symptoms comparable between HSE and anti-NMDAR encephalitis). The frequency of symptoms at anti-NMDAR encephalitis was compared with Fisher's exact test between adults and children. The Wilcoxon rank sum test was used for the comparison between children and adults with regard to median mRS score and median time between onset of HSE and of anti-NMDAR encephalitis. The significance level was set at 5% (two-tailed). Data were entered into an Excel spreadsheet and analysed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) for Windows.

RESULTS

Case report

A previously well 7-year-old female presented to the paediatric emergency department at the University Hospital of Padua (Italy) with a prolonged febrile generalized convulsive seizure followed by vomiting. The patient was lethargic, irritable, confused, and disoriented in space and time, and had a 3-day history of headache and fever. An electroencephalography showed significant bilateral slowing, more marked on the right side, with bilateral temporo-occipital epileptic discharges and subclinical focal temporal seizures (Fig. S1a, b; online supporting information). Brain MRI demonstrated diffusion restriction in temporal, mesial, and insular areas, prevalent on the right hemisphere (Fig. 1a–c), and a lumbar puncture showed 152/μL white cells (mostly mononuclear), no red cells, glucose 2.7mmol/L, normal lactate and proteins, and negative anti-NMDAR antibodies. mRS score in the acute phase was 5. Antiepileptic drugs and empirical intravenous aciclovir (60mg/kg/day) were started, and continued after confirmation of positive HSV PCR in CSF. At discharge after 21 days of antiviral treatment, the patient had regained normal consciousness and had no motor deficits, although she was not independent in activities of daily living and had residual cognitive deficits with slowed cognition, movements, and speech; inability to read; and prosopagnosia (mRS score 3).

Eight days after discharge (31d after onset of HSE), the patient returned to the emergency department with a 2-day history of lethargy, irritability, confusion, echolalia, nonsense talk, obsessions, sleep–wake cycle disturbances, drooling, dyskinesias, and stereotypies. Treatment with intravenous aciclovir was resumed. Electroencephalography showed poor organization of background activity, especially on the right hemisphere, bilateral frontotemporal slow waves, and epileptiform discharges (Fig. S1c). Brain MRI showed evolution of the previous lesions, in the absence of new areas of cytotoxic oedema (Fig. 1d, e), and the lumbar puncture disclosed negative HSV PCR and positive anti-NMDAR antibodies. mRS score in the acute phase of the relapse was 5. The patient received five plasma exchanges (started 9d after onset of anti-NMDAR encephalitis) and high-dose intravenous methylprednisolone (30mg/kg/day for 5d, started 22d after onset of anti-NMDAR encephalitis) followed by oral prednisolone (1mg/kg/day for 2mo, tapered in 1mo, total 3mo), with significant improvement. She was discharged on oral prednisone, carbamazepine, and olanzapine after 34 days of the relapse admission. At the 16-month follow-up from the onset of HSE, the patient had mild residual persistent prosopagnosia, mild mood disorder, and obsessive–compulsive behaviours (mRS score 2). She was back in mainstream school (with support), and she had normal sleep–wake cycle, no motor deficits, no seizures, and remained on carbamazepine.

Literature review

Biphasic illness: HSE followed by HSV-induced anti-NMDAR encephalitis

Our literature search led to the identification of 20 articles, published between 2013 and 2016, reporting a total of 42 patients who experienced biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis.[14–33] The full text of all articles was available. With the addition of our case, a total of 43 patients with biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis were identified (31 children). Data on these patients are detailed in Table SI (online supporting information), and the main results are highlighted in the following sections.

Main clinical differences between the HSE and the anti-NMDAR encephalitis phases

Compared with the HSE phase, the anti-NMDAR encephalitis phase was characterized by a significantly lower rate of seizures (n=28/40 [70%] in HSE vs n=12/40 [30%] in anti-NMDAR encephalitis; p=0.001), and by a significantly higher frequency of movement disorder (n=1/40 [3%] in HSE vs n=30/40 [75%] in anti-NMDAR encephalitis; p<0.001). During anti-NMDAR encephalitis, the most frequent type of movement disorder (according to the terminology reported in the original papers) was choreoathetosis (n=22/30; 73%), followed by dyskinesias (n=16/30; 53%), ballismus or hemiballismus (n=7/30; 23%), dystonia (n=5/30; 17%), athetosis (n=3/30; 10%), and stereotypies, posturing, intentional tremor, and myoclonus (n=1/30; 3% each). Movement disorder was generalized in 48% (n=12/25), and the orofacial region was involved in 69% (18/26).

Main differences between children and adults during the anti-NMDAR encephalitis phase

The median time between onset of HSE and onset of anti-NMDAR encephalitis was significantly shorter in children (median 24d) than in adults (median 40.5d) (p=0.006). During anti-NMDAR encephalitis, movement disorder occurred significantly more often in children than in adults (n=26/30 [87%] in children vs n=4/10 [40%] in adults; p=0.006), whereas psychiatric symptoms were reported more frequently in adults than in children (n=9/10 [90%] in adults vs n=13/31 [42%] in children; p=0.025). No statistically significant differences between children and adults were detected as regards cognitive

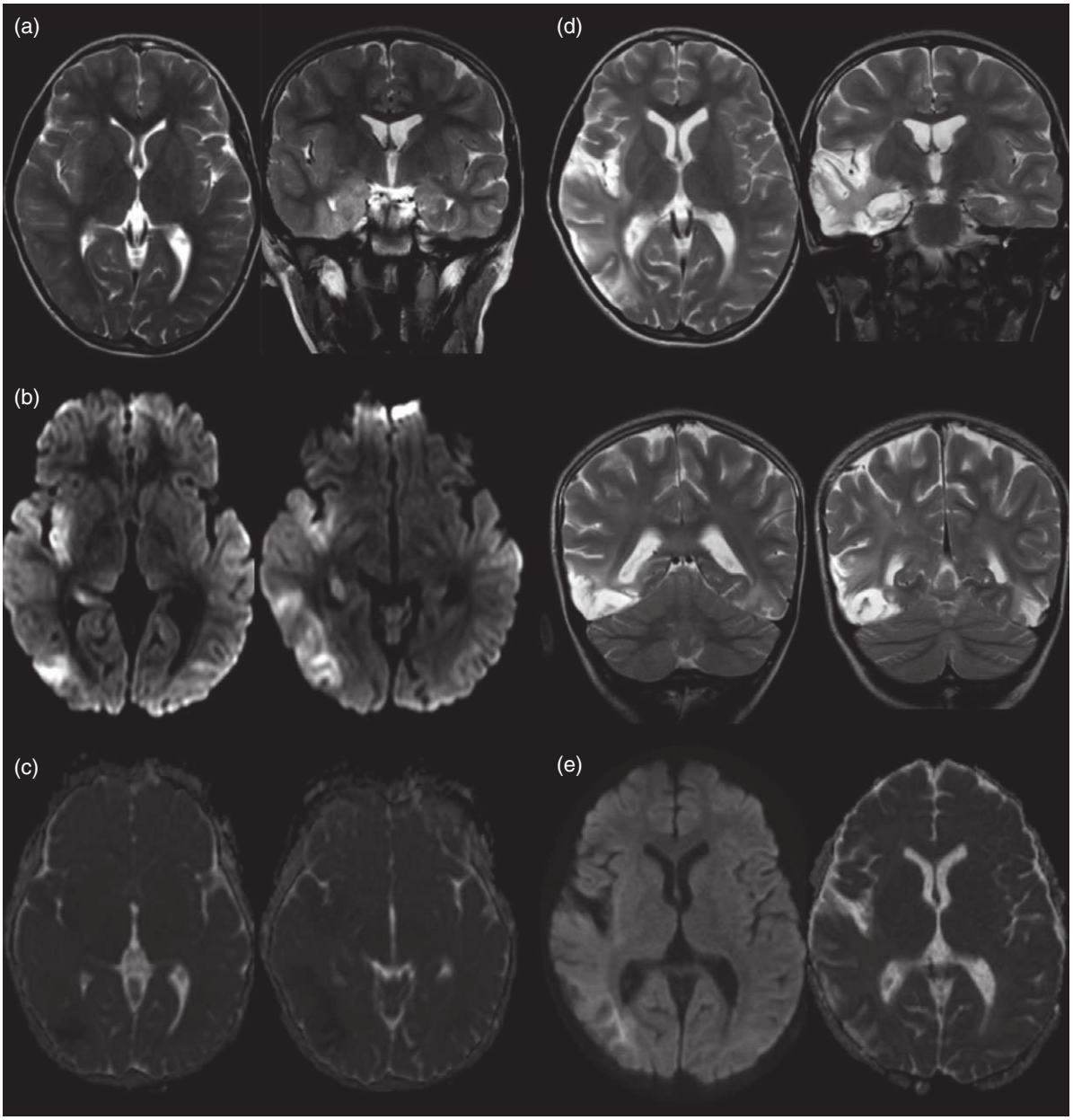

Figure 1: Brain magnetic resonance imaging (MRI) in our paediatric patient with biphasic disease with herpes simplex encephalitis (HSE) followed by herpes simplex virus (HSV)-induced anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis. (a–c) Brain MRI 4 days after onset of HSE. (a) T2-weighted axial and coronal images; (b) diffusion-weighted images, axial; (c) apparent diffusion coefficient images, axial. The brain MRI at day 4 from onset of HSE demonstrated diffusion restriction in cortical–subcortical regions in the right temporal lobe, in the right insula, and the right parieto-occipital region. T2-weighted images also showed cortical thickening of the right temporomesial lobe with increased intensity of right parieto-occipital areas. A smaller area of increased intensity was shown in left temporoparietal cortex. (d, e) Brain MRI 4 days after onset of anti-NMDAR encephalitis (33 days from onset of HSE). (d) T2-weighted axial and coronal images; (e) diffusion-weighted images and apparent diffusion coefficient axial images. The brain MRI at day 4 from onset of anti-NMDAR encephalitis showed high signal in right temporal subcortical white matter, atrophic evolution of the known right parietal–insular–temporal lesion, ex vacuo dilatation of the temporal horn of the right ventricle, and small atrophic–degenerative cortical–subcortical areas in the left inferior and mesial temporal gyri. No cytotoxic oedema and no enhancement after gadolinium were observed.

deterioration, seizures, sleep–wake cycle disturbances, dysautonomias, and speech problems. The severity of disease measured with mRS score was slightly higher in children than in adults at nadir of anti-NMDAR encephalitis (median 5 vs 4; p=0.015) (no statistically significant difference between children and adults was observed between median mRS at nadir of HSE, at recovery after HSE, or at last follow-up).

Treatment during HSE and anti-NMDAR encephalitis phases, and disease recurrences

In total, 98% (n=40/41) of the patients with available information received aciclovir during the episode of HSE, and only 5% received additional intravenous immunoglobulin and/or corticosteroids (n=2/43).[22,33]

At the onset of anti-NMDAR encephalitis, 85% (33/39) of the patients were still on aciclovir from the previous episode of HSE or were started on a new empirical course. In these patients, duration of antiviral treatment from anti-NMDAR encephalitis was less than or equal to 7 days in 23% (n=5/22) and greater than or equal to 14 days in the remaining 77% (n=17/22) (data available for n=22/33); only four patients (n=4/22; 18%) received a prolonged course with oral valaciclovir/aciclovir (for 122d, 152d, 153d, and 243d respectively).[20,24,31] During the episode of anti-NMDAR encephalitis, first- and second-line immune therapies were administered in 93% (n=38/41) and 53% (n=21/40) of patients respectively.

None of the patients who received immune therapy for HSV-induced anti-NMDAR encephalitis were reported to have new viral replication with recurrence of HSE at a median follow-up of 7 months (mean 15.9, range 1.2–160; data available for 39 patients).

Patients with HSE and detection of anti-NMDAR antibodies, and patients with anti-NMDAR encephalitis with concomitant positive HSV markers

HSE with detection of anti-NMDAR antibodies (in the absence of a clinical episode of anti-NMDAR encephalitis). The detection of anti-NMDAR antibodies during or after an episode of HSE, in the absence of a clinical episode of anti-NMDAR encephalitis, was reported in 25 adult patients described in one retrospective and one prospective series (both had available full text; top part of Table SII, online supporting information).[9,34] All these patients had HSE confirmed by positive CSF HSV PCR, and positive anti-NMDAR antibodies in CSF and/or serum (n=25/25; 100%). In the prospective series by Westman et al.,[34] antibodies were detectable only after 3 months in 10 of 12 positive cases. The rate of detection of anti-NMDAR antibodies (IgG type) in patients with HSE was 9% and 25% respectively, in the two studies.[9,34] In the prospective series by Westman et al.,[34] the development of anti-NMDAR autoantibodies was associated with significantly impaired recovery of neurocognitive performance. On the contrary, Prüss et al.[9] were unable to detect significant clinical differences between the antibody-positive and antibody-negative patient groups.

Anti-NMDAR encephalitis with concomitant positive HSV markers (in the absence of clinical or radiological evidence of HSE). The detection of positive HSV PCR in CSF during an episode of anti-NMDAR encephalitis was reported in six patients, described in five articles (all had full text available).[35–39] Data on these patients are limited (bottom part of Table SII). These patients had clinical anti-NMDAR encephalitis (confirmed by anti-NMDAR antibodies in serum and/or CSF in six of six patients [100%]), with detection of positive CSF HSV PCR (n=6/6; 100%) concomitantly or before detection of autoantibodies (in the absence of clinical or radiological evidence of HSE). In two of these patients the initial positive CSF HSV PCR was negative on subsequent testing, prompting the authors to consider it a spurious result.[35,37] Interestingly, in one patient with anti-NMDAR encephalitis confirmed by positive anti-NMDAR antibodies in CSF, the detection of HSV in CSF by PCR discouraged the use of immune therapy, and the patient received only antiviral treatment with improvement in psychiatric symptoms but persistence of mild memory impairment.[39]

DISCUSSION

We present a comprehensive and up-to-date systematic literature review on the relationship between HSV and anti-NMDAR antibodies, and we describe a new illustrative paediatric case with HSE followed by HSV-induced anti-NMDAR encephalitis.

Clinical features of HSV-induced anti-NMDAR encephalitis

We were able to identify 43 patients with biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis. Our review confirms that the appearance of movement disorder is one of the main symptoms differentiating HSV-induced anti-NMDAR encephalitis from the preceding episode of HSE (Table SI).[20] Choreoathetosis and dyskinesias were the most frequent types of movement disorder, and the orofacial region was often involved. In this respect, other case reports and series published before the description of anti-NMDAR encephalitis have pointed to movement disorder, especially choreoathetosis, as a key feature of relapses post-HSE, often reporting negativity of viral testing.[4,40–44] With regard to the overall clinical manifestations during HSV-induced anti-NMDAR encephalitis, our literature review shows that the clinical picture is similar to that of anti-NMDAR encephalitis not preceded by HSE, including the known age-specific features of the disease. Indeed, psychiatric symptoms were more frequent in adults in our literature cohort, whereas neurological manifestations, such as movement disorder, were more represented in children (Table SI), similarly to what was previously reported in patients with anti-NMDAR encephalitis not preceded by HSE.[11,45,46] Although it should be taken into account that under-reporting of psychiatry and cognitive features in young children is possible, we also observed a slightly more severe disease in children than in adults, and a shorter latency between HSE and autoimmune encephalitis in children.

Therapeutic decision-making in relapses after HSE

In case of recurrence of symptoms after HSE, high clinical suspicion should be maintained towards both the possibilities of a viral and an autoimmune relapse, and antiviral therapy should be started promptly. Subsequently, in the

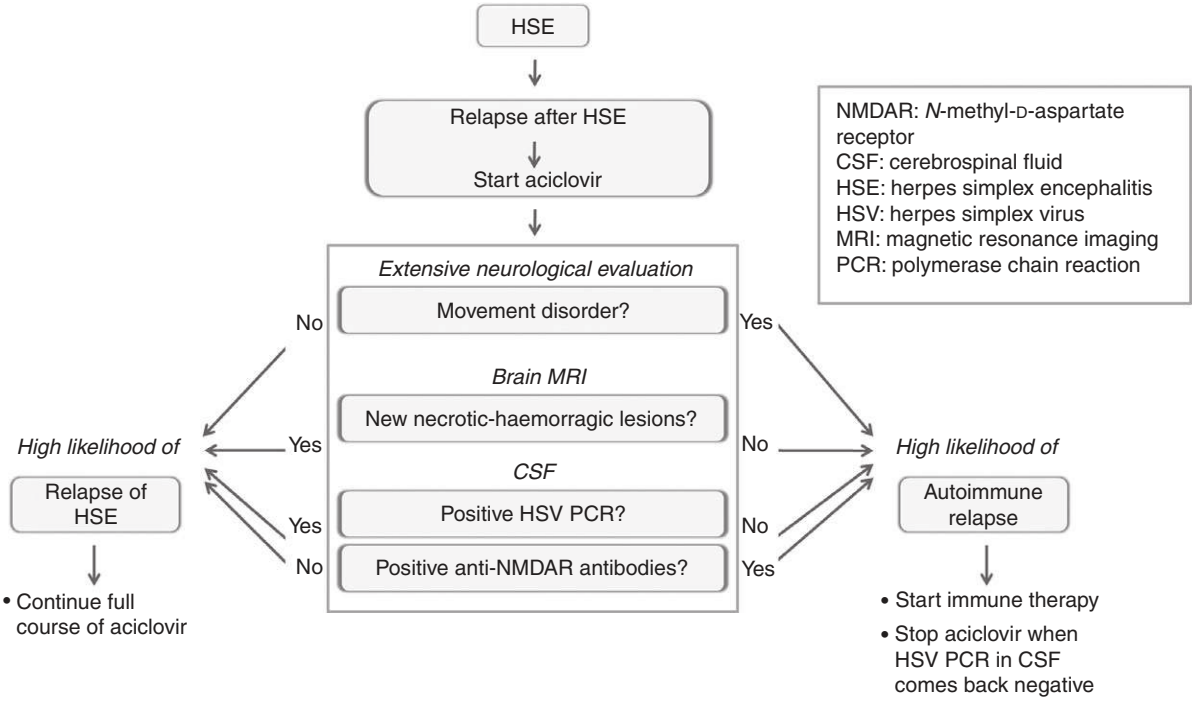

Figure 2: Proposed algorithm for clinical and therapeutic approach in relapses after HSE. In case of recurrence of symptoms after HSE, both a viral and an autoimmune relapse should be suspected, and aciclovir should be promptly started at presentation. The subsequent treatment approach should be guided by a combination of clinical, radiological, and laboratory data. In particular, the presence of movement disorder should raise the suspicion of an autoimmune relapse, as this symptom is very uncommon in HSE, whereas it is characteristic of anti-NMDAR encephalitis. However, the detection of new necrotic–haemorrhagic MRI lesions is more suggestive of an episode of new viral replication, even although extension of previous lesions is possible in autoimmune relapses. While CSF data may be regarded as the most decisive in differentiating between viral and autoimmune relapses after HSE (in particular, CSF HSV PCR and anti-NMDAR antibodies), the availability of these data is generally delayed by a few days after presentation, hence the relevance of identifying other clinical–radiological features differentiating viral and autoimmune relapses. When an autoimmune relapse is suspected based on the abovementioned data, immune therapy should be started, and when viral searches are confirmed as negative aciclovir may be discontinued.

absence of microbiological and neuroradiological findings consistent with a viral reactivation, early commencement of immune therapy should also be considered. Indeed, in view of the known pathogenicity of anti-NMDAR antibodies,[47] immune therapy may be associated with a good response, especially if administered early.[10,11,19,48–51] An algorithm for clinical and therapeutic approach in relapses after HSE is proposed in Figure 2.

Pathogenic hypotheses

The results of our literature review on patients with biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis support the hypothesis that CNS HSV infection may trigger an autoimmune response in the CNS, resulting in the production of anti-NMDAR antibodies and in a fully-fledged autoimmune clinical syndrome.[9] Indeed, an independent co-occurrence of viral and autoimmune encephalitis is unlikely given the relative rarity of both conditions. The mechanisms underlying the synthesis of anti-NMDAR antibodies following HSV infection remain unknown. As hypothesized by other authors, the virus-induced neuronal destruction may expose neuronal antigens to the systemic immunity, initiating a primary autoimmune response.[9] Other possibilities may involve non-specific B-cell activation and/or molecular mimicry due to shared epitopes between HSV and NMDAR, as seen in other neurological diseases such as multiple sclerosis, acute disseminated encephalomyelitis, Guillain–Barré syndrome, and Sydenham chorea.[52–55] The possibility of a common genetic predisposition between the two entities may also contribute.[29]

Different to the biphasic disease described above (HSE followed by HSV-induced anti-NMDAR encephalitis; Table SII, top part), in patients with HSE with concomitant detection of anti-NMDAR antibodies (in the absence of a clinical episode of anti-NMDAR encephalitis) the pathogenic role of antibodies remains unclear.[9,34] In particular, whether some of the clinical manifestations observed in these cases during HSE may be due to an additional effect of anti-NMDAR antibodies is not

known. In this setting, the anti-NMDAR antibodies may be just a 'silent marker' of a postinfective autoimmune response without a specific contributory or causal role. Interestingly, no significant clinical differences were observed between the anti-NMDAR seropositive and seronegative subgroups of HSE patients reported by Prüss et al.,[9] questioning whether the anti-NMDAR antibodies in these patients are therefore contributing to the disease.[9] On the contrary, the development of anti-NMDAR autoantibodies was associated with significantly impaired recovery of neurocognitive performance in another prospective series.[34]

In the group of patients with clinical anti-NMDAR encephalitis and concomitant detection of HSV in the CSF by PCR (in the absence of a clinical or radiological episode of HSE),[35–39] data are very limited (Table SII, bottom part). With regard to the (sometimes transient) detection of positive HSV PCR of CSF, a laboratory error was hypothesized by the authors in one-third of these patients (false positive);[35,37] although definite conclusions cannot be drawn, it cannot be excluded that a previous subclinical CNS HSV infection may have triggered anti-NMDAR encephalitis.

Supporting these findings, an interesting recent work focused on the frequency of coexisting herpes viruses and autoantibodies in patients with encephalitis (herpes or autoimmune) in clinical laboratory service, disclosing that autoantibodies and herpes virus DNA frequently coexist in encephalitic CSF.[56] In this study, as well as in other case reports, other types of herpes viruses beside HSV have been found in association with anti-NMDAR antibodies, including Epstein–Barr virus, human herpesvirus 6 and 7, and varicella zoster virus.[56–60] However, other autoantibodies to neuronal surface antigens, in particular anti-dopamine-2 receptor,[20] anti-γ-aminobutyric acid A receptor antibodies and antibodies against unknown neuronal cell surface proteins,[27] have also been detected in patients with immune-mediated encephalitis (with negative CSF HSV PCR) occurring after HSE,[16,27] suggesting that other antibodies may also be produced in this syndrome. In these cases, similarly to what is suggested for anti-NMDAR antibodies, it may be hypothesized more broadly that autoantibody production is triggered by herpes viruses infection, but further study for novel autoantibodies is required.

Insights into the use of immune therapy in HSE

The hypothesis that CNS HSV infection may trigger an autoimmune response sheds more light on the pathogenesis of HSE itself, supporting the observation that the cerebral insult in HSE results not only from neuronal cell death secondary to direct viral invasion, but also from secondary inflammatory changes and cerebral oedema due to the immune response to the virus. Therefore, in view of their anti-inflammatory action, corticosteroids could have an important role also in the management of the acute phase of HSE.[61] So far, corticosteroid use has been limited by concerns that their immunosuppressive actions could increase viral replication and spread. However, experimental animal models of HSE have shown that the addition of corticosteroids to aciclovir treatment does not increase viral replication and dissemination.[61,62] In this respect, it is noteworthy that in our literature cohort none of the patients treated with immune therapy for HSV-induced anti-NMDAR encephalitis (or for HSE) was reported to have recurrence of HSE, despite only very few receiving long-term antiviral therapy.[20,24,31] Moreover, the beneficial effect of adjunctive steroids in HSE has been anecdotally described both in paediatric and adult age,[63–66] and in an experimental study on a mouse model of HSE, the severity of long-term MRI anti-*N*-methyl-D-aspartate receptor (NMDAR) abnormalities was significantly reduced with add-on corticosteroids during acute HSE.[62] The optimal timing for adjunctive steroid therapy has not yet been established,[65] and while in some cases a beneficial effect has been reported after early simultaneous administration of aciclovir and steroids,[64] in other cases steroid administration was delayed by a few days to weeks, with good results.[65] Delayed but not early glucocorticoid treatment was associated with neuroprotection and survival in a study on experimental HSE in mice.[67] Clinical trials in this field are under way.[68]

Limitations

The small number of patients and the retrospective nature represent the main limitations of our work. Moreover, disease severity scoring was likely subject to significant intrinsic biases, mostly relative to the availability and heterogeneity of information in the original papers, and the fact that the scoring was done retrospectively and by two researchers only. It is possible that the overall outcome may also be influenced by a reporting bias, due to unwillingness to report fatal outcomes. While the study of the outcome according to the administration of adjunctive immune therapy during HSE would be of great clinical interest, this could not be evaluated because only a few of the patients received immune therapy during HSE. Similarly, owing to the small numbers, a comparison between the outcome of patients with a clinical episode of anti-NMDAR encephalitis who did or did not receive immune therapy was not possible. Also, the study of the timing of appearance of anti-NMDAR antibodies after HSE could not be defined, in view of the different timing of antibody testing. The statistical analysis in our work was limited by the small number of patients and by the heterogeneity of data availability in the original papers; individual data for each patient were especially limited in case series compared with reports.[19]

CONCLUSION

The development of HSV-induced anti-NMDAR encephalitis, along with the detection of anti-NMDAR antibodies during HSE and of HSV in CSF with PCR

during anti-NMDAR encephalitis, supports the likelihood that CNS HSV infection may trigger a secondary autoimmune response, resulting in the production of anti-NMDAR antibodies. Moreover, the hypothesis of an autoimmune response triggered by a CNS HSV infection supports the possibility that the pathogenesis and the neuronal damage of HSE involves not only a direct viral insult, but also a secondary autoimmune process, possibly providing arguments in favour of the rationale for the debated use of immune therapy in the acute phase of HSE. Interestingly, our review shows that despite the use of immune therapy for HSV-induced anti-NMDAR encephalitis, none of the patients experienced recurrence of HSE. Finally, while remaining vigilant for the possibility of new viral replication, high clinical suspicion toward an autoimmune aetiology should be maintained in case of relapses of HSE, in view of the different treatment and the good response to immune therapy. The identification of early predictors of autoimmune relapse post-HSE would allow early intervention and, possibly, prevention of secondary autoimmunity, and it remains among future challenges.[69]

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Form used for data collection for the literature review on patients with herpes simplex encephalitis followed by herpes simplex virus-induced anti-*N*-methyl-D-aspartate receptor encephalitis (Word document transposition of the Excel spreadsheet form).

Figure S1: Electroencephalography (EEG) tracings in a paediatric patient with biphasic disease with herpes simplex encephalitis (HSE) followed by herpes simplex virus (HSV)-induced anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis. (a, b) EEG tracing 4 days from onset of HSE, showing significant bilateral slowing, more marked on the right side, with (a) bilateral temporo-occipital periodic epileptiform discharges and (b) subclinical focal temporal right seizures. (c) EEG tracing 4 days after onset of anti-NMDAR encephalitis (33 days from onset of HSE), showing slowed and poorly organized electrical activity, especially in the right hemisphere, with significant slow activity and epileptiform discharges in the frontotemporal areas bilaterally; no delta brush patterns nor seizures were recorded.

Table SI: Main results of our literature review: demographics, clinical data, laboratory investigations, treatment, and outcome of the paediatric and adult patients identified with biphasic disease with herpes simplex encephalitis (HSE) followed by herpes simplex virus (HSV)-induced anti-*N*-methyl-D-aspartate encephalitis, including our paediatric case (total 43 patients)

Table SII: Main results of our literature review on patients with herpes simplex encephalitis (HSE) with detection of anti-*N*-methyl-D-aspartate (anti-NMDAR) antibodies (in the absence of a clinical episode of anti-NMDAR encephalitis), and on patients with anti-NMDAR encephalitis and concomitant detection of positive polymerase chain reaction for herpes simplex virus in cerebrospinal fluid (in the absence of a preceding clinical or radiological episode of HSE)

REFERENCES

1. Whitley RJ, Lakeman F. Herpes simplex virus infections of the central nervous system: therapeutic and diagnostic considerations. *Clin Infect Dis* 1995; **20**: 414–20.
2. Kimura H, Aso K, Kuzushima K, Hanada N, Shibata M, Morishima T. Relapse of herpes simplex encephalitis in children. *Pediatrics* 1992; **89**: 891–94.
3. Sköldenberg B, Aurelius E, Hjalmarsson A, et al. Incidence and pathogenesis of clinical relapse after herpes simplex encephalitis in adults. *J Neurol* 2006; **253**: 163–70.
4. Schleede L, Bueter W, Baumgartner-Sigl S, et al. Pediatric herpes simplex virus encephalitis: a retrospective multicenter experience. *J Child Neurol* 2013; **28**: 321–31.
5. Raschilas F, Wolff M, Delatour F, et al. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. *Clin Infect Dis* 2002; **35**: 254–60.
6. Ito Y, Kimura H, Yabuta Y, et al. Exacerbation of herpes simplex encephalitis after successful treatment with acyclovir. *Clin Infect Dis* 2000; **30**: 185–87.
7. De Tiège X, Rozenberg F, Des Portes V, et al. Herpes simplex encephalitis relapses in children: differentiation of two neurologic entities. *Neurology* 2003; **61**: 241–43.
8. De Tiège X, De Laet C, Mazoin N, et al. Postinfectious immune-mediated encephalitis after pediatric herpes simplex encephalitis. *Brain Dev* 2005; **27**: 304–07.
9. Prüss H, Finke C, Höltje M, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol* 2012; **72**: 902–11.
10. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010; **133**: 1655–67.
11. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013; **12**: 157–65.
12. Granerod J, Cunningham R, Zuckerman M, et al. Causality in acute encephalitis: defining aetiologies. *Epidemiol Infect* 2010; **138**: 783–800.
13. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; **19**: 604–07.
14. Armangue T, Titulaer MJ, Málaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013; **162**: 850–56.e2.
15. Leypoldt F, Titulaer MJ, Aguilar E, et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology* 2013; **81**: 1637–39.
16. Armangue T, Leypoldt F, Málaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol* 2014; **75**: 317–23.
17. Desena A, Graves D, Warnack W, Greenberg BM. Herpes simplex encephalitis as a potential cause of anti-N-methyl-D-aspartate receptor antibody encephalitis: report of 2 cases. *JAMA Neurol* 2014; **71**: 344–46.
18. Hacohen Y, Deiva K, Pettingill P, et al. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. *Mov Disord* 2014; **29**: 90–6.
19. Hacohen Y, Absoud M, Hemingway C, et al. NMDA receptor antibodies associated with distinct white matter syndromes. *Neurol Neuroimmunol Neuroinflamm* 2014; **1**: e2.

20. Mohammad SS, Sinclair K, Pillai S, et al. Herpes simplex encephalitis relapse with chorea is associated with autoantibodies to N-Methyl-D-aspartate receptor or dopamine-2 receptor. *Mov Disord* 2014; **29**: 117–22.

21. Wickström R, Fowler A, Cooray G, Karlsson-Parra A, Grillner P. Viral triggering of anti-NMDA receptor encephalitis in a child - an important cause for disease relapse. *Eur J Paediatr Neurol* 2014; **18**: 543–46.

22. Bektaş Ö, Tanyel T, Kocabaş BA, Fitöz S, Ince E, Deda G. Anti-N-methyl-D-aspartate receptor encephalitis that developed after herpes encephalitis: a case report and literature review. *Neuropediatrics* 2014; **45**: 396–401.

23. Yushvayev-Cavalier Y, Nichter C, Ramirez-Zamora A. Possible autoimmune association between herpes simplex virus infection and subsequent anti-N-methyl-D-aspartate receptor encephalitis: a pediatric patient with abnormal movements. *Pediatr Neurol* 2015; **52**: 454–56.

24. Bamford A, Crowe BH, Hacohen Y, et al. Pediatric herpes simplex virus encephalitis complicated by N-methyl-D-aspartate receptor antibody encephalitis. *J Pediatric Infect Dis Soc* 2015; **4**: e17–21.

25. Ellul MA, Griffiths MJ, Iyer A, et al. Anti-N-methyl-D-aspartate receptor encephalitis in a young child with histological evidence on brain biopsy of co-existent herpes simplex virus type 1 infection. *Pediatr Infect Dis J* 2016; **35**: 347–49.

26. Sutcu M, Akturk H, Somer A, et al. Role of autoantibodies to N-methyl-D-aspartate (NMDA) receptor in relapsing herpes simplex encephalitis: a retrospective, one-center experience. *J Child Neurol* 2016; **31**: 345–50.

27. Armangue T, Moris G, Cantarín-Extremera V, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. *Neurology* 2015; **85**: 1736–43.

28. Pistacchi M, Marsala SZ, Gioulis M, Sanson F, Giometto B. Uncommon relapse after post-herpes simplex encephalitis: an atypical case report. *Acta Neurol Belg* 2015; **115**: 691–95.

29. Morris NA, Kaplan TB, Linnoila J, Cho T. HSV encephalitis-induced anti-NMDAR encephalitis in a 67-year-old woman: report of a case and review of the literature. *J Neurovirol* 2016; **22**: 33–37.

30. García-Moreno J, Igartua Laraudogoitia J, Montes Ros M. *Pneumocystis jirovecii* pneumonia in a patient with anti-N-methyl D-aspartate receptor postherpetic encephalitis. *Pediatr Infect Dis J* 2016; **35**: 816–17.

31. Geoghegan S, Walsh A, King MD, et al. Anti-N-methyl-D-aspartate receptor antibody mediated neurologic relapse post herpes simplex encephalitis: a case series. *Pediatr Infect Dis J* 2016; **35**: e258–61.

32. Casares-Vivas M, Portilla-Cuenca JC, Gallego-Texeira I, Calderón-Pecellín A, Gallego-Curto E, Casado-Naranjo I. Anti-NMDA antibody encephalitis secondary to herpes simplex virus infection. *Med Intensiva* 2016; **40**: 193–95.

33. Schein F, Gagneux-Brunon A, Antoine JC, et al. Anti-N-methyl-D-aspartate receptor encephalitis after herpes simplex virus-associated encephalitis: an emerging disease with diagnosis and therapeutic challenges. *Infection* 2016 Nov 8. doi: 10.1007/s15010-016-0959-y. [E-pub ahead of print].

34. Westman G, Studahl M, Ahlm C, et al. N-methyl-D-aspartate receptor autoimmunity affects cognitive performance in herpes simplex encephalitis. *Clin Microbiol Infect* 2016; **22**: 934–40.

35. Davies G, Irani SR, Coltart C, et al. Anti-N-methyl-D-aspartate receptor antibodies: a potentially treatable cause of encephalitis in the intensive care unit. *Crit Care Med* 2010; **38**: 679–82.

36. Hacohen Y, Wright S, Waters P, et al. Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. *J Neurol Neurosurg Psychiatry* 2013; **84**: 748–55.

37. Safadieh L, Dabbagh O. Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis in a young Lebanese girl. *J Child Neurol* 2013; **28**: 1222–25.

38. Veciana M, Becerra JL, Fossas P, et al. EEG extreme delta brush: an ictal pattern in patients with anti-NMDA receptor encephalitis. *Epilepsy Behav* 2015; **49**: 280–85.

39. Huang X, Fan C, Wu J, et al. Clinical analysis on anti-N-methyl-D-aspartate receptor encephalitis cases: Chinese experience. *Int J Clin Exp Med* 2015; **8**: 18927–35.

40. Pike MG, Kennedy CR, Neville BG, Levin M. Herpes simplex encephalitis with relapse. *Arch Dis Child* 1991; **66**: 1242–44.

41. Gascon GG, al-Jarallah AA, Okamoto E, al Ahdal M, Kessie G, Frayha H. Chorea as a presentation of herpes simplex encephalitis relapse. *Brain Dev* 1993; **15**: 178–81.

42. Wang HS, Kuo MF, Huang SC, Chou ML. Choreoathetosis as an initial sign of relapsing of herpes simplex encephalitis. *Pediatr Neurol* 1994; **11**: 341–45.

43. Barthez-Carpentier MA, Rozenberg F, Dussaix E, et al. Relapse of herpes simplex encephalitis. *J Child Neurol* 1995; **10**: 363–68.

44. Hargrave DR, Webb DW. Movement disorders in association with herpes simplex virus encephalitis in children: a review. *Dev Med Child Neurol* 1998; **40**: 640–42.

45. Huang Q, Wu Y, Qin R, Wei X, Ma M. Clinical characteristics and outcomes between children and adults with anti-N-Methyl-D-Aspartate receptor encephalitis. *J Neurol* 2016; **263**: 2446–55.

46. Duan BC, Weng WC, Lin KL, et al. Variations of movement disorders in anti-N-methyl-D-aspartate receptor encephalitis: a nationwide study in Taiwan. *Medicine (Baltimore)* 2016; **95**: e4365.

47. Kreye J, Wenke NK, Chayka M, et al. Human cerebrospinal fluid monoclonal N-methyl-D-aspartate receptor autoantibodies are sufficient for encephalitis pathogenesis. *Brain* 2016; **139**: 2641–52.

48. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology* 2014; **83**: 142–50.

49. Byrne S, Walsh C, Hacohen Y, et al. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. *Neurol Neuroimmunol Neuroinflamm* 2015; **2**: e130.

50. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. *Expert Rev Neurother* 2015; **15**: 1391–19.

51. Sartori S, Nosadini M, Cesaroni E, et al. Paediatric anti-N-methyl-D-aspartate receptor encephalitis: the first Italian multicenter case series. *Eur J Paediatr Neurol* 2015; **19**: 453–63.

52. Reiber H, Ungefehr S, Jacobi C. The intrathecal, polyspecific and oligoclonal immune response in multiple sclerosis. *Mult Scler* 1998; **4**: 111–17.

53. Smyk DS, Alexander AK, Walker M, Walker M. Acute disseminated encephalomyelitis progressing to multiple sclerosis: are infectious triggers involved? *Immunol Res* 2014; **60**: 16–22.

54. Loshaj-Shala A, Regazzoni L, Daci A, et al. Guillain Barré syndrome (GBS): new insights in the molecular mimicry between *C. jejuni* and human peripheral nerve (HPN) proteins. *J Neuroimmunol* 2015; **289**: 168–76.

55. Cunningham MW. Rheumatic fever, autoimmunity, and molecular mimicry: the streptococcal connection. *Int Rev Immunol* 2014; **33**: 314–29.

56. Linnoila JJ, Binnicker MJ, Majed M, Klein CJ, McKeon A. CSF herpes virus and autoantibody profiles in the evaluation of encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2016; **3**: e245.

57. Casanova-Gracia N, Banzo-Arguis C, Sanz-Asin P, Zapata-Usabel M, Jordana-Vilanova N, Cortina-Lacambra MT. Encephalitis associated to anti-NMDA receptor antibodies: a description of two cases in the child/youth population (In Spanish). *Rev Neurol* 2012; **54**: 475–78.

58. Schäbitz WR, Rogalewski A, Hagemeister C, Bien CG. VZV brainstem encephalitis triggers NMDA receptor immunoreaction. *Neurology* 2014; **83**: 2309–11.

59. Venâncio P, Brito MJ, Pereira G, Vieira JP. Anti-N-methyl-D-aspartate receptor encephalitis with positive serum antithyroid antibodies, IgM antithyroid antibodies, IgM antibodies against mycoplasma pneumoniae and human herpesvirus 7 PCR in the CSF. *Pediatr Infect Dis J* 2014; **33**: 882–83.

60. Solís N, Salazar L, Hasbun R. Anti-NMDA Receptor antibody encephalitis with concomitant detection of Varicella zoster virus. *J Clin Virol* 2016; **83**: 26–28.

61. Thompson KA, Blessing WW, Wesselingh SL. Herpes simplex replication and dissemination is not increased by corticosteroid treatment in a rat model of focal Herpes encephalitis. *J Neurovirol* 2000; **6**: 25–32.

62. Meyding-Lamadé U, Oberlinner C, Rau PR, et al. Experimental herpes simplex virus encephalitis: a combination therapy of acyclovir and glucocorticoids reduces long-term magnetic resonance imaging abnormalities. *J Neurovirol* 2003; **9**: 118–25.

63. Yamamoto K, Chiba HO, Ishitobi M, Nakagawa H, Ogawa T, Ishii K. Acute encephalopathy with bilateral striatal necrosis: favourable response to corticosteroid therapy. *Eur J Paediatr Neurol* 1997; **1**: 41–45.

64. Kamei S, Sekizawa T, Shiota H, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. *J Neurol Neurosurg Psychiatry* 2005; **76**: 1544–49.

65. Musallam B, Matoth I, Wolf DG, Engelhard D, Averbuch D. Steroids for deteriorating herpes simplex virus encephalitis. *Pediatr Neurol* 2007; **37**: 229–32.

66. Maraş Genç H, Uyur Yalçın E, Sayan M, et al. Clinical outcomes in children with herpes simplex encephalitis receiving steroid therapy. *J Clin Virol* 2016; **80**: 87–92.

67. Sergerie Y, Boivin G, Gosselin D, Rivest S. Delayed but not early glucocorticoid treatment protects the host

during experimental herpes simplex virus encephalitis in mice. *J Infect Dis* 2007; **195**: 817–25.

68. Martinez-Torres F, Menon S, Pritsch M, et al. Protocol for German trial of Acyclovir and corticosteroids in Herpes-simplex-virus-encephalitis (GACHE): a multicenter, multinational, randomized, double-blind, placebo-controlled German, Austrian and Dutch trial [ISRCTN45122933]. *BMC Neurol* 2008; **8**: 40.

69. Kothur K, Wienholt L, Mohammad SS, et al. Utility of CSF cytokine/chemokines as markers of active intrathecal inflammation: comparison of demyelinating, anti-NMDAR and enteroviral encephalitis. *PLoS ONE* 2016; **11**: e0161656.

Supplementary material

Supplementary Figure 1

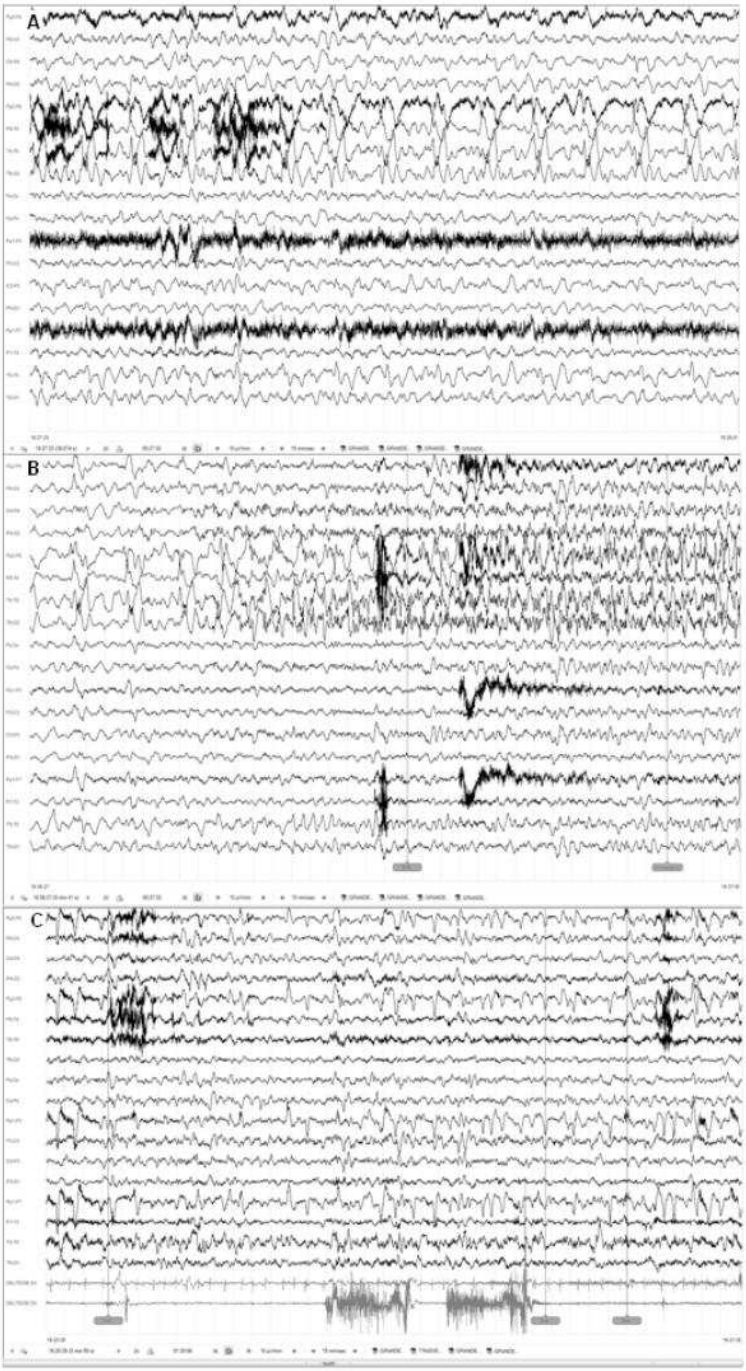

Figure S1: Electroencephalography (EEG) tracings in a paediatric patient with biphasic disease with herpes simplex encephalitis (HSE) followed by herpes simplex virus (HSV)-induced anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. (a, b) EEG tracing 4 days from onset of HSE, showing significant bilateral slowing, more marked on the right side, with (a) bilateral temporo-occipital periodic epileptiform discharges and (b) subclinical focal temporal right seizures. (c) EEG tracing 4 days after onset of anti-NMDAR encephalitis (33 days from onset of HSE), showing slowed and poorly organized electrical activity, especially in the right hemisphere, with significant slow activity and epileptiform discharges in the frontotemporal areas bilaterally; no delta brush patterns nor seizures were recorded.

Supplementary Table 1

Results of the literature review on reported patients with HSE with detection of anti-NMDAR antibodies (in the absence of a clinical episode of anti-NMDAR encephalitis)	
Articles reporting patients with HSE with detection of anti-NMDAR antibodies (in the absence of an episode of anti-NMDAR encephalitis)	2[9,30]
Number of patients	25
Demographics	
Gender	14/25 (56%) females
Median age at HSE	53 y (mean 53, range 24-79) [data in 13/13]
Clinical data during HSE*	
Fever	25/25 (100%)
Seizures	8/25 (32%)
Encephalopathy/Drowsiness/Decreased consciousness	11/13 (84.6%)
Headache	18/25 (72%)
Speech difficulties	2/13 (15.4%)
Irritability or behavioural change	4/13 (30.8%)
Vomiting	6/13 (46.1%)
Memory impairment	8/13 (61.5%)
Feeding difficulties/Oro-motor dysfunction	1/13 (15.4%)
Diarrhoea	0/13 (0%)
Movement disorder	0/13 (0%)
Laboratory investigations during HSE	
CSF pleocytosis (>4 WBC/ml)	25/25 (100%) (median 237, mean 390.3, range 132-1288, data in 13/13)
CSF proteinorrachia (>45 g/L)	13/13 (100%) (median 121, mean 140.5, range 47-346, data in 13/13)
CSF oligoclonal bands	6/12 (50%)
Evidence of HSV infection	25/25 (100%): HSV-PCR in CSF in 25/25
Data on anti-NMDAR antibodies	
Rate of detection of anti-NMDAR antibodies (IgG) in HSE reported in the original articles	4/44 (9%)[9] – 12/49 (24.5%)[30]
Positive anti-NMDAR antibodies in serum and/or CSF	25/25 (100%)
Timing of detection of anti-NMDAR antibodies	≥3 m after HSE in 10/12[30]
Treatment	
Acyclovir	25/25 (100%); 7/25 received valaciclovir follow-up therapy for 3 months
Immune therapy	4/25 (16%) (adjunctive corticosteroids)
Disease severity and outcome	
Median mRS at nadir of HSE	3 (mean 3.3, range 3-6) [data in 12/25]
Median mRS at last follow-up	n.a.
Median length of follow-up from onset of HSE	n.a.
Results of the literature review on reported patients with anti-NMDAR encephalitis and concomitant detection of positive HSV-PCR in CSF (in the absence of a preceding clinical or radiological episode of HSE)	
Articles reporting patients with anti-NMDAR encephalitis with detection of positive HSV-PCR in CSF (in the absence of a preceding episode of HSE)	5[34-38]
Number of patients	6~
Demographics	
Gender	1/3 (33.3%) females
Median age at anti-NMDAR encephalitis	29 y (mean 25.3, range 4-43) [data in 3/6]
Clinical data during anti-NMDAR encephalitis	
Encephalopathy	2/2 (100%)
Movement disorder	2/2 (100%)
Psychiatric symptoms or behavioural changes	2/2 (100%)
Cognitive deterioration	2/2 (100%)
Seizures	1/2 (50%)
Sleep-wake cycle disturbances	1/2 (50%)
Autonomic disturbances	0/2 (0%)
Speech disturbances	1/2 (50%)
Tumour	0/6 (0%)
Laboratory investigations during anti-NMDAR encephalitis	
CSF pleocytosis (>4 WBC/ml)	2/3 (66.7%) (median 12, mean 58, range 4-158)
CSF proteinorrachia (>45 g/L)	1/2 (50%) (median 57.5, mean 57.5, range 17-98)
CSF oligoclonal bands	n.a.
Evidence of HSV infection (CSF and/or serum)	6/6 (100%): HSV-PCR in CSF in 6/6
Positive anti-NMDAR antibodies in serum and/or CSF	6/6 (100%): 4/5 serum, 2/2 CSF
Treatment	
Acyclovir	5/5 (100%)
Immune therapy	4/5 (80%)
First-line immune therapy	4/5 (80%)
Corticosteroids	3/5 (60%)
Intravenous immunoglobulin	3/5 (60%)
Plasma exchange	3/5 (60%)
Second-line immune therapy	0/5 (0%)
Time from first symptoms of anti-NMDAR encephalitis to first immune therapy	7 d [data in 1/6]
Disease severity and outcome	
Median mRS at nadir of anti-NMDAR encephalitis	4.5, (mean 4.5, range 4-5) [data in 2/6]
Median mRS at last follow-up	0 (mean 1.3, range 0-4) [data in 3/6]
Median length of follow-up from onset of anti-NMDAR encephalitis	5 m (mean 5.8, range 2.5-10) [data in 3/6]

Supplementary Table 1. Top part: Demographics and clinical data on the literature review on paediatric and adult patients with HSE with detection of anti-NMDAR antibodies (in the absence of a clinical episode of anti-NMDAR encephalitis). Bottom part: Demographics and clinical data on the literature

review on paediatric and adult patients with anti-NMDAR encephalitis and concomitant detection of positive HSV-PCR in CSF (in the absence of a preceding clinical or radiological episode of HSE).

Legend: anti-NMDAR encephalitis: anti-N-methyl-D-aspartate receptor encephalitis; CSF: cerebrospinal fluid; d: days; HSE: herpes simplex encephalitis; mRS: modified Rankin Scale; HSV: herpes simplex virus; m: months; n.a.: not available; m: months; OCB: oligoclonal bands; WBC: white blood cells; y: years.

*One patient had headache, fever, memory impairment, confusion, somnolence, status epilepticus; he developed hemorrhagic necrosis, massive swelling, herniation, and died.[9]

§Of the 8 patients with positive anti-NMDAR antibodies in serum reported by Prüss and colleagues, 3/8 had positive IgA and/or IgM with negative IgG, and 5/8 had positive IgG inconstantly associated with positive IgA and/or IgM.[9] Of the 11 patients with positive anti-NMDAR antibodies in CSF, 6/11 had positive IgA and/or IgM with negative IgG, and 5/11 had positive IgG inconstantly associated with positive IgA and/or IgM.[9]

~ The two patients described by Hacohen et al, 2013,[35] despite the limited availability of information, were considered to have positivity of HSV-PCR in CSF during anti-NMDAR encephalitis in view of the fact that they became progressively worse despite adequate antiviral therapy, were found to have NMDAR antibodies when reinvestigated, and showed a definite response to intensive immunotherapy with steroids, IVIG and plasma exchange.

Supplementary information: form for data collection

Form used for data collection for the literature review on patients with HSE followed by HSV-induced anti-NMDAR encephalitis (word document transposition of the Excel spreadsheet form)

	Article and patient data			First disease phase: HSE							Second disease phase: anti-NMDARE								Outcome		
#	**Article reference**	**Patient age**	**Sex**	**Clinical manifestations of HSE***	**mRS at nadir of HSE**	**mRS at recovery from HSE** (and before onset of anti-NMDARE)	**CSF data**: WBC, RBC, proteins, OCB, HSV-PCR, anti-NMDAR ab	**Serum data**: HSV-PCR, HSV serology, anti-NMDAR ab (if done)	**Antiviral treatment**: type, dose and duration	**Adjunctive immune therapy**	**Time from onset of HSE to onset of anti-NMDARE**	**Clinical manifestations of anti-NMDARE****	**Tumour**	**mRS at nadir of anti-NMDARE**	**CSF data**: WBC, RBC, proteins, OCB, HSV-PCR, anti-NMDAR ab	**Serum data**: HSV-PCR, HSV serology, anti-NMDAR ab	**Antiviral treatment**: type, dose and duration ^	**Immune therapy** (time from onset of anti-NMDARE to first immune therapy; type of immune therapy)	**Recurrences** (recurrences of HSE? recurrences of anti-NMDARE?)	**mRS at last follow-up**	**Time from onset of HSE to last follow-up**
1																					
2																					
3																					
4																					
5																					
6																					
7																					
etc																					

Legend: ab: antibodies; anti-NMDARE: anti-N-methyl-D-aspartate receptor encephalitis; CSF: cerebrospinal fluid; HSE: herpes simplex encephalitis; HSV: herpes simplex virus; mRS: modified Rankin Scale (mRS was scored by the authors based on the case description); OCB: oligoclonal bands; PCR: polymerase chain reaction; RBC: red blood cells; WBC: white blood cells.

#Patient number

*Clinical manifestations of HSE: in particular: Fever? Seizures? Encephalopathy / Decreased consciousness / Drowsiness? Headache? Speech difficulties? Irritability / Behavioural changes? Vomiting? Memory disturbances? Feeding difficulties / Oro-motor dysfunction? Diarrhoea? Movement disorder? Other?

**Clinical manifestations of anti-NMDAR encephalitis: in particular: Encephalopathy? Movement disorder (and type of movement disorder)? Psychiatric symptoms or behavioural changes / Agitation? Cognitive deterioration? Seizures? Sleep-wake cycle disturbances? Autonomic disturbances? Speech disturbances? Other?

^Antiviral treatment: other information collected was: Was the antiviral treatment still ongoing from the episode of HSE? In case antiviral treatment was no more ongoing, or in case it had not been given for the preceding episode of HSE, was it started empirically at the time of anti-NMDAR encephalitis?

3.3 Modes of use, efficacy and tolerability of individual immune therapeutic agents in different clinical situations in paediatric neurology

3.3.1 Intravenous immunoglobulin in acute Sydenham's chorea

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JOURNAL CLUB

Intravenous immunoglobulin in acute Sydenham's chorea: A systematic review

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Abstract: Sydenham's chorea (SC) is a major manifestation seen in 25% of patients with acute rheumatic fever. SC is the prototypic autoimmune neurological disorder, which has a less appreciated associated risk of psychiatric morbidity. We undertook a systematic review to examine whether the use of intravenous immunoglobulin affects clinical recovery and morbidity.

Key words: behavioural; developmental; general paediatrics; immunology; neurology.

Clinical Scenario

A 13-year-old girl of Polynesian background presented with asymmetric generalised chorea and emotional lability over a 1-week period. She had a high erythrocyte sedimentation rate (ESR) of 45 mm/h, tested negative for antinuclear and anti double-stranded DNA antibodies and had a pan-systolic murmur that was confirmed to be due to mitral regurgitation on echocardiography. A diagnosis of acute rheumatic fever (ARF) with Sydenham's chorea (SC) as a major feature was made, as per the revised Jones criteria.[1] She was given 2 g/kg of intravenous immunoglobulin (IVIg) in the acute phase and monitored with serial Unified SC Rating Scale (USCRS) scores,[2,3] which normalised over a 3-month period (45/108 at onset, 18/108 at 3-week follow-up and 2/108 at 3-month follow-up). The USCRS contains six behaviour items, seven activities of daily living (ADL) items and 14 motor items; the total score ranges from 0 to 108, with 108 indicating maximum severity. This scale was tested on 84 Brazilian patients and validated by strong interrater reliability across most domains except for some behavioural domains.[3] At 6-month follow-up, there was no chorea and her behaviour and functioning were normal.

SC is one of the major criteria for diagnosis of ARF and is seen in ~25% of cases.[4] The incomplete resolution of chorea in some cases,[5] risk of antipsychotic-related parkinsonism[6] and psychiatric morbidity[7,8] associated with SC has long been highlighted by detailed follow-up studies, but is still not widely appreciated.

SC is the prototypic autoimmune movement and neuropsychiatric disorder, triggered after streptococcal infection. The autoimmune basis of SC is supported by the recent finding of antibodies to cell surface dopamine-2 receptors.[9,10]

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The fact that SC predominantly affects young people such as our index case raises the important question whether residual morbidity can be prevented with the use of immune therapies in the acute phase. We undertook a systematic review on the evidence for use of IVIg in acute SC.

Structured Clinical Question

Does the use of IVIg in acute SC

a. Reduce the duration of acute chorea and neurocognitive symptoms?
b. Prevent development of long-term neurological and psychiatric complications?
   (P) Population = children with acute SC
   (I) Intervention = IVIg
   (C) Comparator = supportive therapy or placebo
   (O) Outcome = duration of chorea and/or long-term neurological or psychiatric problems

Search strategy

We searched Medline from 1946 to the third week of December 2014 and Excerpta Medica dataBASE – EMBASE for the key words: ((Sydenham* AND chorea) OR (rheumatic chorea)) AND (IVIg OR immunoglobulin). We also reviewed all references in the relevant search results to ensure that any studies were not missed. We limited the search results to randomised controlled trials (RCTs), uncontrolled trials, cohort studies and case series (>2 patients). We found only two studies (Table 1) that met our search criteria. We did not include comparator or outcome parameters in our search because of the limited number of eligible studies.

Selected studies and critical appraisal

We summarise and appraise both selected RCTs (Table 1) in our discussion using the Critical Appraisal Skills Programme tool

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Table 1 Immune therapy using IVIg in SC – comparison of two randomised controlled trials

Author, year	Study population	Study design and Level of evidence	Intervention	Measures of outcome	Follow-up	Results	Relapses in IVIg-treated patients	Limitations
Garvey *et al*., 2005[11]	18 children with acute SC (4/18 randomised to IVIg, 6/18 to Prednisone, 8/18 to PEX)	RCT Level II (IVIg vs. Steroids vs PEX)	Prednisone 1 mg/kg for 10 days, 10-day taper IVIg 1 g/kg on 2 days PEX five to six courses	1. Severity scale a. Functionality b. Severity of chorea	12 months	Prednisone group (n = 6): 29% reduction in mean chorea score IVIg group (n = 4): 72% reduction in mean chorea score PEX group (n = 8): 50% reduction in mean chorea score	2/4 (50%)	No placebo No blinding on follow-up No behaviour domains in rating scale Small number of cases Smaller and shorter prednisone dose
Walker *et al*., 2012[12]	20 children with acute SC (10/20 randomised to IVIg)	RCT Level II (IVIg vs. symptomatic treatment)	Symptomatic treatment (haloperidol) versus Symptomatic treatment (haloperidol) + IVIg	1. Severity scale a. Behaviour b. Functionality c. Motor function 2. SPECT findings 3. Duration of symptomatic treatment	6 months	In the symptomatic treatment + IVIg group, as compared with the symptomatic treatment only: (i) improved clinical score at 1, 3 and 6 months ($P < 0.05$); and (ii) shorter symptomatic treatment ($P < 0.05$)	1/10 (10%)	No placebo Non-validated rating scale Small number of cases SPECT results not analysed

IVIg, intravenous immunoglobulin; PEX, plasma exchange; RCT, randomised controlled trial; SC, Sydenham's chorea; SPECT, single photon emission CT.

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based on the Journal of the American Medical Association guidelines.[13] A simplified version of the checklist can be accessed at: http://www.casp-uk.net/#!casp-tools-checklists/c18f8.

The first study is an RCT by Garvey and colleagues[11] who examined whether IVIg or plasma exchange (PEX) are superior to prednisone in decreasing the severity of SC. The study did not compare the effect of immune therapy to placebo or symptomatic treatment only. Eighteen patients were included in the study, from a cohort of 38 children with acute SC seen in a tertiary hospital over an 8-year period. The diagnosis of SC was clinical after excluding other causes of chorea. Patients with severe heart failure, previous SC (2/38), mild chorea (15/38), mental retardation and another neurological or psychiatric disorder were excluded. Of the 18 patients included in the study, four were randomised to IVIg (1 g/kg for 2 days), eight to PEX (single-volume PEX cycles, five to six exchanges) and six to prednisone (1 mg/kg/day for 10 days followed by a taper over the next 10 days). The three treatment groups were comparable in age and gender distribution. Prior to immune therapy, 14/18 children were on symptomatic treatment (valproate in 9/18, haloperidol in 8/18, others in 5/18). The symptomatic medications were not altered during immune therapy, except in two patients. In the IVIg group, the mean time from diagnosis to initiation of immune treatment was 10 weeks (median 7.8, range 5.4–19.0). The investigators used a 6-point chorea rating scale, which evaluated chorea severity and functional ability to carry out ADL at 1, 2, 3, 6 and 12 months following treatment. The scale did not include measures of behavioural and emotional symptoms, which are commonly seen in SC and are often the major cause of morbidity.[3] During intervention and follow-up, the investigators were not blinded to the immune therapy. In the IVIg group, the mean severity score decreased from 13.6 (median 13.5, range 11–16.6) at baseline, to 3.75 (median 4, range 2–5) at 1 month and then 1.75 (median 2, range 0–3) at 12 months after immune therapy. Although the IVIg group showed a quicker improvement in chorea, no statistically significant difference was found in the change of severity scores between the groups at 1- or 12-month follow-up. 2/4 patients in the IVIg group relapsed within 1 year, compared with 2/8 in the PEX group, and none in the prednisone group. Serious side effects in the IVIg group occurred in 1/4 (hepatitis C infection). Minor side effects in the IVIg group included mild nausea ($n = 2$) and vomiting and headache during the infusion ($n = 1$).

The more recent South African study by Walker and colleagues[12] compared the outcome of 10 children with SC treated with symptomatic management (haloperidol 0.025–0.05 mg/kg/day) to that of 10 children who received additional IVIg. None of the patients in the study received other immune treatments, and the study did not have a placebo arm. The investigators enrolled 20/23 children with SC seen in a tertiary hospital over a 6-year period. Exclusion criteria included children with mild chorea, heart failure, IgA deficiency, known allergy to IVIg, age >14 years or weight >50 kg. Data on the interval between diagnosis and initiation of immune therapy was not provided. The investigators used a locally derived severity scale at 1, 3 and 6 months, scoring of single photon emission CT (SPECT) scans at baseline and 1 month, and duration of symptomatic therapy with haloperidol as outcome measures. The severity score included domains of behaviour, functional abilities to perform daily tasks and rating of motor function including severity of chorea. In contrast to the first study from Garvey *et al*.[11] the scale included neurological as well as psychiatric symptoms; hence, making it more suited for complete evaluation of SC patients, although this scale has not been formally validated. The baseline chorea rating was not blinded, but follow-up clinical rating and rating of the SPECT scans were done by the principle investigator as well as by a blinded observer with good inter-investigator agreement. At baseline, there was no statistical difference in the clinical severity score between the two treatment groups (IVIg group: mean 11.8, standard deviation (SD) 2.04; symptomatic treatment group: mean 10.6, SD 2.41). At 1-month follow-up, those treated with IVIg had significantly better scores (IVIg group: mean 3.7; symptomatic treatment: mean 7.4; $P = 0.006$). At 3 and 6 months, the clinical scores in the IVIg group were better than the symptomatic group, but the statistical significance was not maintained. The SPECT scan findings could not be analysed due to limited numbers (only 14/20 patients had SPECT scan at baseline, and only 12/14 had 1-month scan). The mean time on haloperidol was 51 days (median 46) in the IVIg group. This was significantly shorter than in the symptomatic treatment only group who received a mean 136.7 days of haloperidol (median 180) ($P = 0.015$). At 6-month follow-up, 1/20 patients in the IVIg group and 2/20 in the symptomatic treatment group had relapsed with chorea. At 6-month follow-up, no patients in the IVIg group had ongoing problems, whereas six patients in the symptomatic group had ongoing problems of learning difficulties, attention-deficit/hyperactivity disorder, behaviour and mood problems, and/or persisting chorea or tics. No side effects of treatment occurred in the IVIg group, whereas in the symptomatic, group five patients had drowsiness, two had slurring of speech, one had headache and one had drooling and dizziness.

How can the research be done better?

SC is a relatively uncommon disorder particularly in resource rich countries. This makes it difficult to conduct an RCT spanning many years. The trial by Garvey *et al*.[11] did not include a placebo arm. This is obviously difficult because of ethical and logistical issues with sham PEX or intravenous infusion. However, sham or placebo could be incorporated for IVIg and for oral steroids in a future study. As many patients with SC currently do not receive any active pharmacological intervention, introduction of a placebo arm should be ethically justifiable, but these would be milder patients. Symptomatic treatment with anticonvulsants like carbamazepine and valproate as well as neuroleptics is known to decrease manifest chorea. A stringent clinical trial could have more control over the type, dose and duration of symptomatic medications used to minimise confounding effects. A further issue is that the dose of steroid used in this study was of lower dose, and of shorter duration than in other autoimmune brain conditions. Likewise, intravenous methylprednisolone is more rapidly effective than oral prednisolone and could have been more effective. These factors could have led to a false impression of the steroid group responding more slowly than the IVIg and PEX groups. The study was also weakened by the lack of blinding on follow-up. The major morbidity from SC, apart from concomitant

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rheumatic heart disease, is long-term neuropsychiatric sequelae. Both of the trials reviewed here did not have long enough follow-up to capture the burden of these sequelae and compare them between the treatment groups. The trials used scoring systems focussed on motor ability. Although the scale used by Walker *et al*.[12] used measures of behaviour, it is not clear whether specific components of the scoring system improved more significantly than others on follow-up. Future trials require longer follow-up using a validated scale such as the USCRS or a similar validated scale with better performance on the psychiatric domains. The time from diagnosis to immune therapy was not standardised in the first study and not detailed in the second. Early immune therapy may work better than later immune therapy as demonstrated by other immune-mediated neurological disorders like anti-N-methyl D-aspartate receptor (NMDAR) encephalitis.[14] A future trial should prospectively define the time frame within which immune therapy could be initiated, and could also compare early versus later immune therapy to examine whether this makes a difference to outcome.

How would I apply the information to patients?

The studies reviewed here demonstrate a short-term benefit in symptomatic improvement from SC with use of IVIg. However, they do not clarify an optimum timing and duration for use of IVIg, and do not provide data on the effect on long-term neurological and psychiatric complications. IVIg is attractive compared with steroids and PEX in view of a better side effect profile and being less invasive than PEX. The experience of IVIg contamination with hepatitis C in the Garvey *et al*. study highlights that IVIg is not risk-free and should be used with consideration.

The recognition of long-term neuropsychiatric morbidity in SC, and the possibility of improving outcome with early immune therapy holds promise. However, the 'partially resolving' nature of SC should preclude the use of more potent and toxic immune suppressing agents such as rituximab. In our opinion use of a single 2 g/kg dose of IVIg in children with moderate-severe SC associated with significant impairment is reasonable in view of the risk of long-term psychiatric morbidity. We would also remind clinicians that SC is a neuropsychiatric disorder and it is important to screen both adults and children for behavioural and psychiatric problems in the acute phase and on follow-up.

References

1 Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. *JAMA* 1992; **268**: 2069–73.

2 Teixeira AL Jr, Maia DP, Cardoso F. [The initial testing and the discrimination property of the UFMG Sydenham's Chorea Rating Scale (USCRS)]. *Arq. Neuropsiquiatr* 2005; **63** (3B): 825–7.

3 Teixeira AL Jr, Maia DP, Cardoso F. UFMG Sydenham's chorea rating scale (USCRS): reliability and consistency. *Mov. Disord.* 2005; **20**: 585–91.

4 Cardoso F, Eduardo C, Silva AP, Mota CC. Chorea in fifty consecutive patients with rheumatic fever. *Mov. Disord.* 1997; **12**: 701–3.

5 Cardoso F, Vargas AP, Oliveira LD, Guerra AA, Amaral SV. Persistent Sydenham's chorea. *Mov. Disord.* 1999; **14**: 805–7.

6 Teixeira AL, Cardoso F, Maia DP, Cunningham MC. Sydenham's chorea may be a risk factor for drug induced parkinsonism. *J. Neurol. Neurosurg. Psychiatry* 2003; **74**: 1350–1.

7 Moreira J, Kummer A, Harsanyi E, Cardoso F, Teixeira AL. Psychiatric disorders in persistent and remitted Sydenham's chorea. *Parkinsonism Relat. Disord.* 2014; **20**: 233–6.

8 Aron AM, Freeman JM, Carter S. The natural history of Sydenham's chorea. Review of the literature and long-term evaluation with emphasis on cardiac sequelae. *Am. J. Med.* 1965; **38**: 83–95.

9 Dale RC, Merheb V, Pillai S *et al*. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. *Brain* 2012; **135** (Pt 11): 3453–68.

10 Cox CJ, Sharma M, Leckman JF *et al*. Brain human monoclonal autoantibody from Sydenham chorea targets dopaminergic neurons in transgenic mice and signals dopamine D2 receptor: implications in human disease. *J. Immunol.* 2013; **191**: 5524–41.

11 Garvey MA, Snider LA, Leitman SF, Werden R, Swedo SE. Treatment of Sydenham's chorea with intravenous immunoglobulin, plasma exchange, or prednisone. *J. Child Neurol.* 2005; **20**: 424–9.

12 Walker K, Brink A, Lawrenson J, Mathiassen W, Wilmshurst JM. Treatment of Sydenham chorea with intravenous Immunoglobulin. *J. Child Neurol.* 2012; **27**: 147–55.

13 Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. *JAMA* 1994; **272**: 1367–71.

14 Dale RC, Brilot F, Duffy LV *et al*. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology* 2014; **83**: 142–50.

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3.3.2 Intravenous immunoglobulin in paediatric neurology

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Intravenous immunoglobulin in paediatric neurology: safety, adherence to guidelines, and long-term outcome.

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Intravenous immunoglobulin in paediatric neurology: safety, adherence to guidelines, and long-term outcome

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***See Appendix for members of IVIG in Neurology Study Group.**

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ABBREVIATIONS

IVIG	Intravenous immunoglobulin
mRS	Modified Rankin Scale
NMDAR	*N*-methyl-D-aspartate receptor
PNS	Peripheral nervous system

AIM Intravenous immunoglobulin (IVIG) is an expensive therapy used in immunodeficiency and autoimmune disorders. Increasing demands and consequent shortages result in a need for usage to conform to guidelines.

METHOD We retrospectively evaluated IVIG use for neuroimmunological indications and adherence to existing guidelines in a major Australian paediatric hospital between 2000 and 2014.

RESULTS One-hundred and ninety-six children (96 male, 100 female; mean age at disease onset 6y 5mo [range 3mo–15y 10mo], mean age at first IVIG dose 7y 2mo [range 3mo–16y 5mo]) received IVIG for neuroimmunological indications during the study period (28.1% had Guillain–Barré syndrome), representing 15.5% of all hospital indications. In total, 1669 IVIG courses were administered (total 57 221g, median 78g/patient, range 12–5748g). The highest median numbers of courses were in chronic inflammatory demyelinating polyneuropathies, opsoclonus-myoclonus ataxia syndrome, suspected immune-mediated epilepsies, and Rasmussen's encephalitis. Adverse reactions occurred in 25.5% of patients, but these were mostly minor. Outcome at follow-up was best in anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, Guillain–Barré syndrome, and myasthenia gravis, and worst in Rasmussen's encephalitis and epilepsies. The total cost of IVIG was US$2 595 907 (median $3538/patient, range $544–260 766). Of patients receiving IVIG, 45.4% to 57.1% were given the therapy for 'weak' indications or indications 'not listed' in international guidelines. Some entities commonly treated with IVIG in current practice, such as anti-NMDAR encephalitis and transverse myelitis, are not listed in most guidelines.

INTERPRETATION Our study demonstrates that IVIG is generally well tolerated but expensive, and discloses discrepancies between guidelines and clinical practice in paediatric neurology, suggesting both the need for greater adherence to current recommendations, and for recommendations to be updated to accommodate emerging indications.

Intravenous immunoglobulin (IVIG) is a fractionated blood product made from pooled human plasma, that has been used in the treatment of immune deficiencies and autoimmune disorders for almost four decades.[1] Supplementation of the immune system with IVIG broadens the spectrum of a recipient's immune response and attenuates autoimmune reactivity,[1] although the precise mechanisms of anti-inflammatory and immunoregulatory action are not completely understood, and are thought to be diverse according to the underlying pathophysiology.[1–3]

The demand for IVIG has increased over the years, resulting in high cost to health providers and IVIG shortages.[2] Guidelines regulating IVIG use according to the evidence base have been created in different countries, to ensure its availability for patients who are most likely to benefit from the therapy.[4–9] However, recommendations vary across different guidelines. In Australia, the use of IVIG is regulated by the National Blood Authority of Australia Criteria. Based on the available evidence, these identify conditions for which the role of IVIG is 'established', 'emerging', 'supported in exceptional circumstances only', or 'not supported'.[9] The United Kingdom guidelines use a similar descriptive classification for the use of IVIG: 'highest priority', 'appropriate', 'limited/little/no evidence', 'not recommended'.[7] In other guidelines, such as those from North America and Europe, recommendations are based on levels of evidence categorized as 'A (established effective)', 'B (probably effective)', 'C (possible effective)', and 'U (inadequate data)'.[4,6,8]

To review the current clinical practice regarding the use of IVIG in paediatric neurology, we carried out a

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retrospective study in a large paediatric neurology centre in Sydney, Australia, focusing on the clinical indications for IVIG administration, adherence to guidelines, cost, tolerability, and long-term outcome.

What this paper adds

- Intravenous immunoglobulin (IVIG) is an expensive but relatively well tolerated treatment commmonly used in paediatric neurology.
- Some indications for IVIG administration seem to respond poorly to treatment.
- Other conditions commonly treated with IVIG are not listed in most guidelines.
- Greater adherence to current recommendations is required, and recommendations need to be updated.

METHOD

Patient identification

The study was conducted at the Children's Hospital at Westmead, New South Wales, Australia, approved as service improvement (activity number: 4695). A list of all patients who received IVIG at the Children's Hospital at Westmead between January 2000 and June 2014 was provided by the hospital pharmacy and the blood bank (independent sources distributing all IVIG at the hospital). A total of 1264 children was treated with IVIG for any paediatric indication in the study period. To identify the patients who received IVIG for neurological indications only, the clinical files of the 1264 total patients were reviewed in the hospital informatic database (PowerChart; Cerner Corporation PTY Ltd., North Sydney, NSW, Australia). Seven patients were excluded because of insufficient clinical information, and 1038 because of IVIG administration for non-neurological indications (Fig. 1). Of the non-neurological indications, the most common were Kawasaki disease (312 of 1264, 24.7%) and acute lymphoblastic leukaemia (128 of 1264, 10.1%). A total of 219 children who received IVIG for neurological indications was identified (219 of 1264, 17.3%). Of these, 23 did not have a neuroimmunological disorder, and were excluded (Fig. 1). Therefore, 196 children received IVIG for neuroimmunological indications at the Children's Hospital at Westmead during the study period, and were included in our study (196 of 1264 of all patients, 15.5%).

Data collection

Data were collected via retrospective chart review of the hospital informatic database. The clinical diagnosis in the discharge letter was verified by correlating with the diagnostic investigations performed, and with the diagnosis at follow-up. The clinical indications for IVIG administration were grouped into central nervous system (CNS) and peripheral nervous system (PNS) indications (Fig. 1). The indications for which IVIG was dispensed were reviewed in light of the most recent available international guidelines on IVIG use.[4–7,9] Data collected on IVIG use included type, dose, number of courses, total quantity administered, and side effects. To calculate the cost of IVIG, we used the mean price of all IVIG products used at the Children's Hospital at Westmead as of July 2015 in Australian dollars (AUD), and then converted this to American dollars (USD) (currency conversion as of December 2015: 1 AUD=0.73 USD). Other immune therapies received besides IVIG were also recorded and categorized as first-line (corticosteroids, plasma exchange) and second-line (mycophenolate mofetil, cyclophosphamide, rituximab, azathioprine, methotrexate, and other).

With regard to the severity of disease, modified Rankin Scale (mRS) score[10] was assigned retrospectively by the main investigators (RCD, MN) based on the clinical data in the acute phase before receiving IVIG. Outcome was assessed retrospectively at the last follow-up available in the informatic database, and scored via mRS and via type of ongoing impairments (subdivided into: none, cognitive/learning, behavioural, motor, visual, epilepsy, and other). Scores of 0 to 2 were interpreted as a good outcome, as in previous studies.[11] For some patients, the available follow-up in the informatics database was ≤12 months from the first IVIG administration (and the patients were lost to follow-up). In these cases, we conducted telephone interviews to the patients (if current age ≥18y) or to their family (if current age <18y), to extend the length of follow-up (total 43 interviews). This was done after approval from the local ethics committee (LNR/15/SCHN/218) and after obtaining informed consent from the family. After extending follow-up, only 23 patients had follow-up ≤12 months (23 of 196, 11.7%).

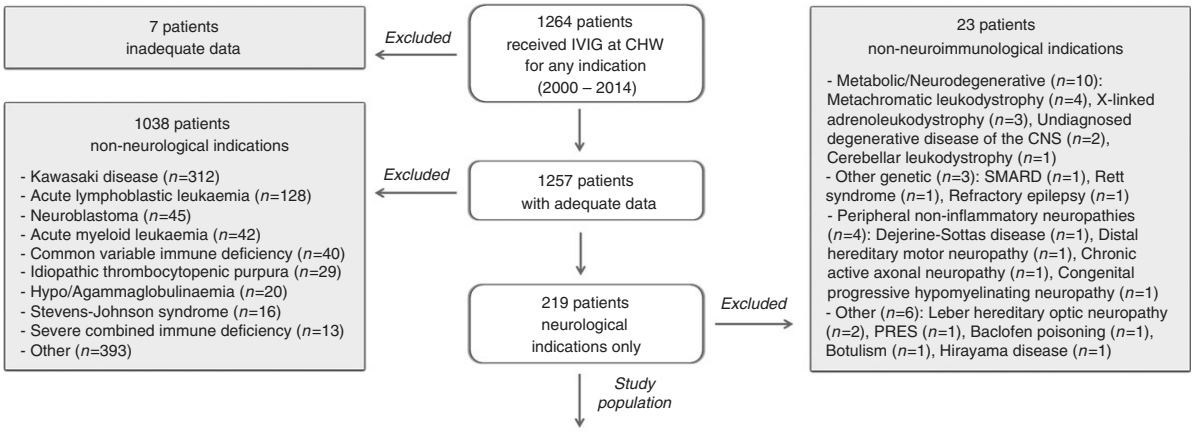
RESULTS

Demographics

There were similar distributions of male (96 of 196, 49%) and female (100 of 196, 51%) patients in our cohort. Mean age at disease onset was 6 years 5 months (median 5y 1mo, range 3mo–15y 10mo). Mean age at first IVIG dose was 7 years 2 months (median 6y 3mo, range 3mo–16y 5mo). An increasing number of patients was started on IVIG for neuroimmunological indications during the study period: 48 between 2000 and 2004, 57 between 2005 and 2009, and 91 between 2010 and 2014 (Fig. 2).

Clinical indications for IVIG administration

The clinical indications for IVIG administration in our cohort are detailed in Figure 1. Central neuroimmunological disorders (113 of 196, 57.7%) were slightly more common than peripheral neuroimmunological disorders (83/196, 42.3%). Over time, there was a relative rise in the proportion of patients who received IVIG for central, as opposed to peripheral, indications (Fig. 2). The most common central indications were encephalitis (47 of 196, 24%), followed by inflammatory demyelinating CNS disorders (29 of 196, 14.8%), and epilepsy (11 of 196, 5.6%). Among peripheral indications, the most common indications were demyelinating neuropathies (64 of 196, 32.6%), followed by disorders of the neuromuscular junction (12 of 196, 6.1%). The most common individual indication was Guillain–Barré syndrome (55 of 196, 28.1% of the whole cohort).



Indication categories	Indication groups: Specifications
CNS INDICATIONS (*n*=113, 57.7%)	
Encephalitis (n=47)[a]	Infectious and infection-associated encephalitis (*n*=11): Enterovirus (*n*=7), Mycoplasma (*n*=1), HSV (*n*=1), Acute necrotizing encephalopathy (*n*=1), Influenza (*n*=1) Anti-NMDAR encephalitis (*n*=8) Acute disseminated encephalomyelitis (*n*=7) Rasmussen's encephalitis (*n*=5) Other autoimmune or immune-mediated encephalitis (*n*=16): Basal ganglia (*n*=4), anti-VGKC (*n*=1), Suspected autoimmune encephalitis (*n*=11)
Inflammatory demyelinating CNS diseases (n=29)	Monophasic inflammatory demyelinating CNS diseases (*n*=22): Transverse myelitis (*n*=21), Optic neuritis (*n*=1) Relapsing inflammatory demyelinating CNS diseases (*n*=7): Multiple sclerosis (*n*=4), Neuromyelitis optica with anti-AQP4 or anti-MOG antibodies (*n*=3)[b]
Epilepsies (n=11)	Epilepsies (*n*=11): FIRES (*n*=3), Lennox-Gastaut (*n*=2), Landau-Kleffner (*n*=1), Other (*n*=5)
Autoimmune CNS syndromes (n=10)	Opsoclonus-myoclonus ataxia syndrome (*n*=9) ROHHAD syndrome (*n*=1)
Postinfectious movement disorders (n=6)	Sydenham chorea (*n*=4) Other (*n*=2): Acute cerebellar ataxia (*n*=1), Complex movement disorder (*n*=1)
Paediatric acute neuropsych. syndromes (n=3)	Paediatric acute neuropsych. syndromes (*n*=3): PANDAS/Tourette syndrome (*n*=2), PANS (*n*=1)
Genetic auto-inflammation (n=2)	Genetic auto-inflammation (*n*=2): Aicardi–Goutières syndrome (*n*=1), Suspected autoinflammatory neurodegenerative brain disorder (*n*=1)
CNS involvement in systemic inflammatory diseases (n=2)	Neuropsych. systemic lupus erythematosus (*n*=2)
Undiagnosed complex autoimmune disorders (n=3)[c]	Undiagnosed complex autoimmune disorders (*n*=3)
PNS INDICATIONS (*n*=83, 42.3%)	
Demyelinating neuropathies (n=64)	Acute demyelinating neuropathies (*n*=55): Guillain-Barré syndrome (*n*=55) Chronic demyelinating neuropathies (*n*=9): Chronic inflammatory demyelinating polyneuropathy (*n*=7), Mononeuritis (*n*=2)
Disorders of the neuromuscular junction (n=12)	Myasthenia gravis (*n*=12)
Inflammatory myopathies (n=7)	Inflammatory myopathies (*n*=7): Dermatomyositis (*n*=6), Orbital myositis (*n*=1)

Figure 1: Cohort selection. From the total 1264 children who received IVIG at the Childrens Hospital at Westmead between January 2000 and June 2014, only the 196 patients who received IVIG for neuroimmunological indications were included in our cohort (study population). The central nervous system (CNS) and peripheral nervous system (PNS) indications for IVIG administration in our cohort are shown. Of these, only the indication groups with at least five patients were used for the major analyses in the text and in Figure 3. [a]Classification of encephalitis adapted from Pillai et al.[37] [b]The diagnosis of neuromyelitis optica was made according to the revised Wingerchuk criteria,[38]and met also the latest criteria for neuromyelitisoptica spectrum disorder.[39] [c]Details on the patients in the group of undiagnosed complex autoimmune disorders are provided in the online supporting information. AQP4, aquaporin-4; CHW, the Childrens Hospital at Westmead, New South Wales, Australia; CNS, central nervous system; FIRES, febrile infection-related epilepsy syndrome; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; MOG, myelin oligodendrocyte glycoprotein; neuropsych, neuropsychiatric; NMDAR, *N*-methyl-D-aspartate receptor; PANDAS, paediatric autoimmune neuropsychiatric disorder associated with group A streptococci; PANS, paediatric acute-onset neuropsychiatric syndrome; PNS, peripheral nervous system; PRES, posterior reversible encephalopathy syndrome; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; SMARD, spinal muscular atrophy with respiratory distress; VGKC, voltage-gated potassium channel.

Severity of disease

In the patients with available information (190 of 196, 96.9%), the mean mRS before receiving IVIG was 3.7 (median 4, range 2–5). The mRS scores before IVIG initiation and on last follow-up according to category of clinical indication are shown in Figure 3. Of the patients in the cohort, 31.2% were admitted to the intensive care unit (60 of 192).

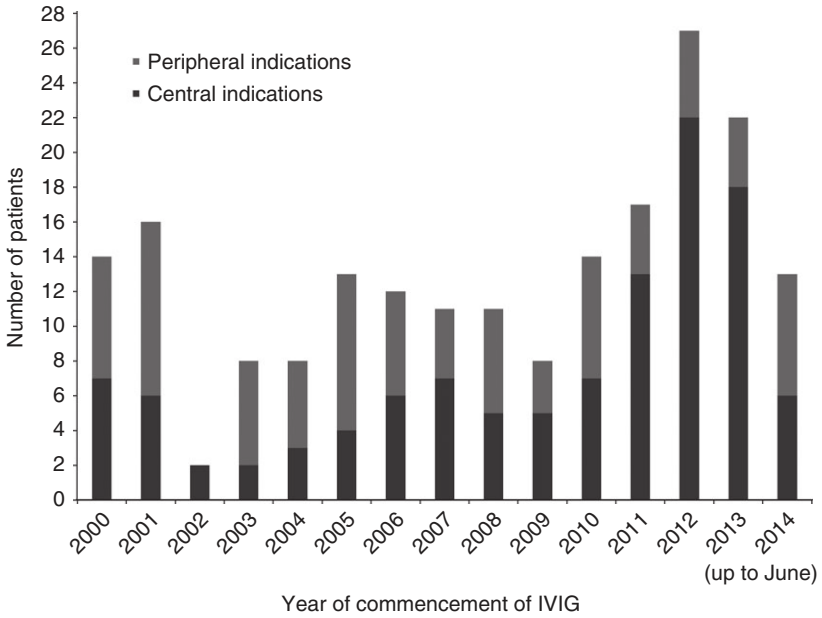


Figure 2: Number of patients started on intravenous immunoglobulin (IVIG), divided by year of IVIG initiation (year 2014 is up to June), and by central and peripheral indications. The number of children commenced on IVIG every year increased over the study period, mostly because of an increase of IVIG administration for central indications, while peripheral indications were relatively stable over time.

Other immune therapies

Data on other immune therapies are detailed in Table SI (online supporting information). The IVIG was the only immune therapy given in 25.5% of patients from the total cohort (50 of 196). The sole use of IVIG varied according to the clinical indication, and was highest in Guillain–Barré syndrome (41 of 55, 74.5%). Immune therapies other than IVIG were given in 74.5% of patients (146 of 196), most commonly corticosteroids (144 of 196, 73.5%; oral prednisone 121 of 196, 61.7%, and intravenous methylprednisolone 84 of 196, 42.8%). Plasma exchange was used in a limited number of cases (4 of 196, 2%). Second-line immune therapies were administered in 26.7% of patients (39 of 146), and included mycophenolate mofetil (16 of 146, 10.9%), rituximab (12 of 146, 8.2%), cyclophosphamide (7 of 146, 4.8%), azathioprine (7 of 146, 4.8%), and others (Table SI).

Immunoglobulin measurement before IVIG administration

Before commencement of IVIG treatment, IgG, IgA, and IgM were measured in 37.2% of patients (73 of 196), and some minor reductions in baseline immunoglobulin values were noted (IgG [2 of 73, 2.7%], IgA [2 of 73, 2.7%], and IgM [4 of 73, 5.5%]).

Number of courses and quantity of IVIG administered

A total of 1669 IVIG courses (mean 8.5 courses per patient, median 1, range 1–150) was administered in the 196 patients during the total cohort treatment time of 144.2 years (mean 1.7y, median 0.5, range 0.02–10.5) (with exclusion of the IVIG courses administered for Guillain–Barré syndrome: total 1603 IVIG courses, mean 11.4, median 2, range 1–150). The corresponding total quantity of IVIG was 57 221g in the whole cohort (mean 291.9g per patient, median 78, range 12–5748). Data on IVIG courses and quantity by clinical diagnosis are detailed in Table I and Figure S1 (online supporting information). In the indication groups with at least five patients, chronic demyelinating neuropathies were the indication with highest median number of IVIG courses per patient, followed by opsoclonus-myoclonus ataxia syndrome, epilepsies, and Rasmussen's encephalitis; the highest median quantity of IVIG per patient was administered in chronic demyelinating polyneuropathies, opsoclonus-myoclonus ataxia syndrome, myasthenia gravis, Rasmussen's encephalitis, epilepsies, and relapsing inflammatory demyelinating diseases (Table I).

Dose of IVIG and days of treatment

High dose IVIG (2g/kg given over 2–5d) was given for 408 courses in 177 patients, typically as the first course. In chronic therapy, lower doses were given per course: 1.2 to 1.8g/kg (116 courses in eight patients), 1g/kg (254 courses in 27 patients), and 0.2 to 0.8g/kg (891 courses in 25 patients).

Type of IVIG and cost

Intragam (CSL Pharma) accounted for over half of the total quantity of IVIG (32 100g/57 221g, 56.1%). Other types of IVIG used were Octagam (Octapharma) (11 610g/57 221g, 20.3%), Flebogamma (Grifols) (7587g/57 221g, 13.2%), Sandoglobulin (CSL Pharma) (5474g/57 221g, 9.6%),

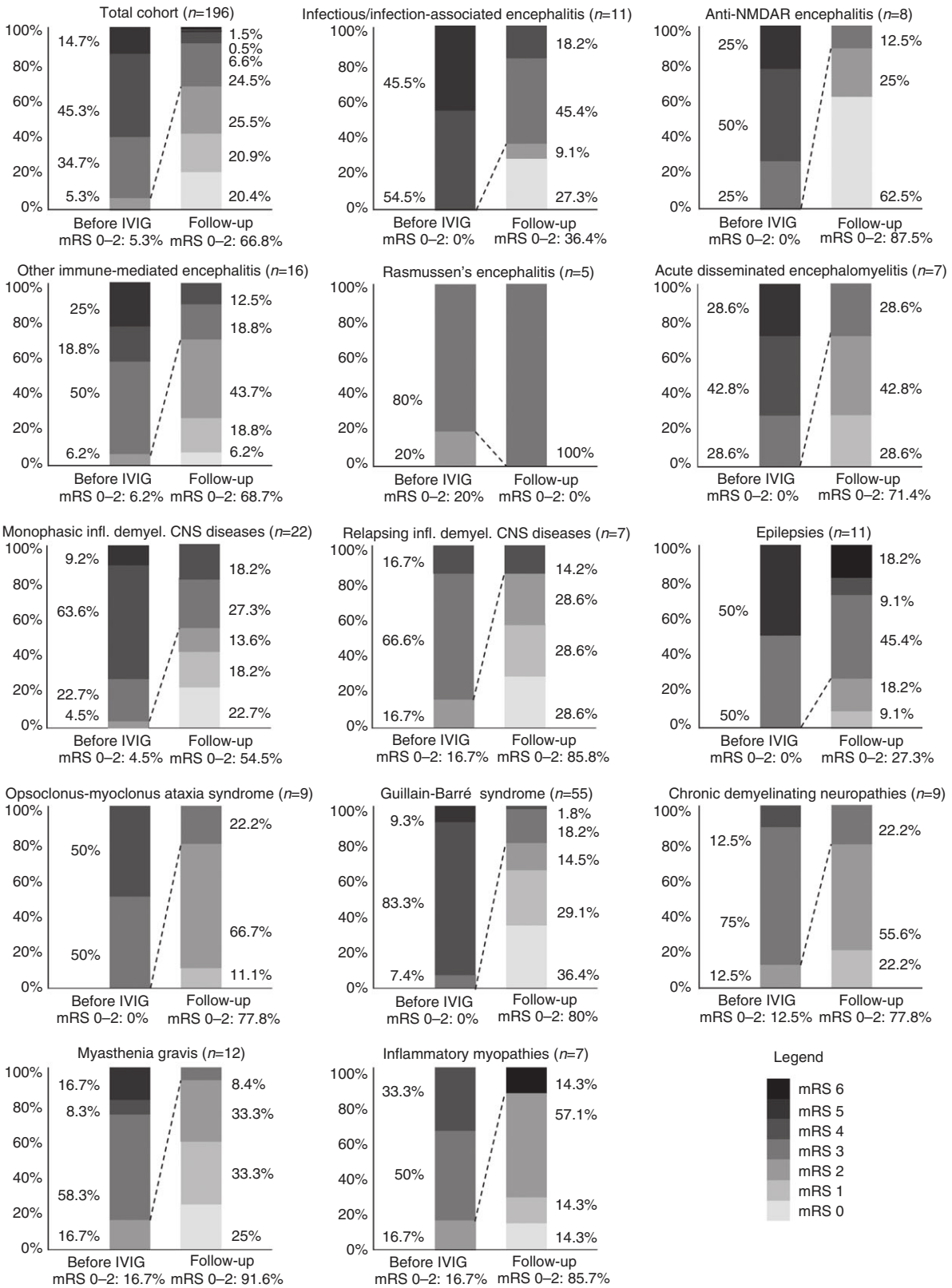


Figure 3: Modified Rankin Scale (mRS) in the acute phase of disease, before IVIG administration, in the total population and according to indication group (only the indications with at least five patients are represented, see Fig. 1). The change in mRS 0 to 2 is presented at IVIG administration, and at final follow-up. CNS, central nervous system; infl. demyel., inflammatory demyelinating; IVIG, intravenous immunoglobulin; neuropsych., neuropsychiatric; NMDAR, *N*-methyl-D-aspartate receptor; PNS, peripheral nervous system.

Table I: Number of IVIG courses and quantity of IVIG (g) administered by clinical indication

Indications for IVIG administration	Number of IVIG courses				Quantity of IVIG (g)				Cost per patient (USD)
	Total	Mean	Median	Range	Total	Mean	Median	Range	Mean (median)
CNS indications (*n*=113)									
Encephalitis (*n*=47)									
Infectious and infection-associated encephalitis (*n*=11)	14	1.3	1	1–3	530	48.2	24	12–246	2186 (1089)
Anti-NMDAR encephalitis (*n*=8)	51	6.4	3.5	1–23	1626.5	203.3	68	30–1020	9223 (3085)
Acute disseminated encephalomyelitis (*n*=7)	9	1.3	1	1–3	454	64.8	30	24–200	2940 (1361)
Rasmussen's encephalitis (*n*=5)	28	5.6	6	2–11	1147	229.4	220	54–420	10 407 (9981)
Other autoimmune or immune-mediated encephalitis (*n*=16)	111	6.9	1	1–56	3316	207.2	60	18–1661	9400 (2722)
Inflammatory demyelinating CNS diseases (*n*=29)									
Monophasic inflammatory demyelinating CNS diseases (*n*=22)	23	1	1	1–2	1367	62.1	36	12–275	2817 (1633)
Relapsing inflammatory demyelinating CNS diseases (*n*=7)	119	17	4	1–79	3022	431.7	180	90–1846	19 584 (8166)
Epilepsies (*n*=11)									
Epilepsies (*n*=11)	416	37.9	11	1–150	6748	613.4	180	48–2298	27 828 (8166)
Autoimmune CNS syndromes (*n*=10)									
Opsoclonus-myoclonus ataxia syndrome (*n*=9)	236	26.2	13	3–147	5237	581.9	260	60–2592	26 399 (11 795)
ROHHAD syndrome (*n*=1)	17	17	17	N/A	1200	1200	1200	N/A	54 440 (54 440)
Postinfectious movement disorders (*n*=6)									
Sydenham chorea (*n*=4)	8	2	1	1–5	482	120.5	90	40–262	5467 (4083)
Other (*n*=2)	4	2	2	1–3	129	64.5	64.5	24–105	2926 (2926)
Paediatric acute neuropsychiatric syndromes (*n*=3)									
Paediatric acute neuropsychiatric syndromes (*n*=3)	20	6.7	5	3–12	1917	639	321	150–1446	28 989 (14 562)
Genetic autoinflammation (*n*=2)									
Genetic autoinflammation (*n*=2)	8	4	4	3–5	260	130	130	60–200	5898 (5898)
CNS involvement in systemic inflammatory diseases (*n*=2)									
Neuropsych. systemic lupus erythematosus (*n*=2)	15	7.5	7.5	3–12	1707	853.5	853.5	267–1440	38 720 (38 720)
Undiagnosed complex autoimmune disorders (*n*=3)									
Undiagnosed complex autoimmune disorders (*n*=3)	21	7	10	1–10	2078	692.7	1010	48–1020	31 425 (45 820)
PNS indications (*n*=83)									
Demyelinating neuropathies (*n*=64)									
Acute demyelinating neuropathy (Guillain–Barré syndrome) (*n*=55)	66	1.2	1	1–4	4081.5	74.2	45	12–407	3366 (2041)
Chronic demyelinating neuropathies (*n*=9)	285	31.7	24	3–90	12504	1389.3	900	50–5748	63 028 (40 830)
Disorders of the neuromuscular junction (*n*=12)									
Myasthenia gravis (*n*=12)	100	8.3	2.5	1–29	4886	407.2	227.5	24–1299	18 473 (10 321)
Inflammatory myopathies (*n*=7)									
Inflammatory myopathies (*n*=7)	117	16.7	3	1–88	4529	647	141	75–3500	29 352 (6397)

CNS, central nervous system; IVIG, intravenous immunoglobulin; N/A, not applicable; NMDAR, *N*-methyl-D-aspartate receptor; PNS, peripheral nervous system; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; USD, US dollars.

Intraglobin F (Paviour Pharma) (325g/57 221g, 0.6%), and Kiovig (Baxter) (125g/57 221g, 0.2%). Based on a mean of the IVIG prices as at July 2015 in AUD (mean 620 AUD/10g=453.7 USD/10g), the total cost for IVIG in the whole cohort in the study period 2000 to 2014 was 2 595 907 USD (mean 13 244 USD per patient, median 3538, range 544–260 766). The IVIG cost per patient according to clinical indication group, reflecting the IVIG quantity administered per patient, is detailed in Table I. In the indication groups with at least five patients, the highest median costs per patient were in chronic demyelinating neuropathies, opsoclonus-myoclonus ataxia syndrome, myasthenia gravis, Rasmussen's encephalitis, epilepsies, and relapsing inflammatory demyelinating diseases. The lowest median costs per patient were in infectious and infection-associated encephalitis, acute disseminated encephalomyelitis, monophasic inflammatory demyelinating CNS diseases, Guillain–Barré syndrome, other autoimmune or immune-mediated encephalitis, and anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis.

IVIG tolerability

Adverse reactions or infusion reactions to IVIG of any severity were reported in 25.5% of the total cohort (50 of 196). Severe or medically significant (but not life-threatening) adverse events (grade 3), according to the National Institutes of Health Common Terminology Criteria for Adverse Events,[12] occurred in 2% of the total patients (4 of

196), whereas no life-threatening consequences (grade 4) or deaths related to adverse events (grade 5) occurred. Grade 3 adverse events included aseptic meningitis (defined as the presence of at least three of the following: fever, headache, altered mental status, stiff neck, photophobia) in 1.5% of cases (3 of 196), and by aseptic meningitis and hypotension requiring intervention in 0.5% of cases (1 of 196).

In the remaining 23.5% of patients (46 of 196), adverse events were mild or moderate (grade 1–2).[12] The most commonly reported adverse reactions were headache (12 of 196, 6.1%), vomiting, or nausea (11 of 196, 5.6%), local skin reactions or problems at the site of cannula insertion (9 of 196, 4.6%), fever (9 of 196, 4.6%), and hypotension not requiring intervention (3 of 196, 1.5%). Rarer adverse reactions were bradycardia (3 of 196, 1.5%), rash (3 of 196, 1.5%), hypertension, tachycardia, shortness of breath, flushing (each 2 of 196, 1%), pallor, abdominal pain, drowsiness, derangement of liver function tests, evidence of hepatitis B immunity (passive transfer of immunoglobulin, not infection), haemolytic reaction with fever and lethargy, increased respiratory rate, and intermittent apnoea, and sweatiness during infusion (each 1 of 196, 0.5%). Of the patients who received multiple IVIG courses, side effects most commonly occurred during the first course only (14 of 24, 58.3%).

Outcome

Data on outcome at last follow-up are detailed in Table II (and its extended legend provided in Appendix S1, online supplementary information), Table SII (online supplementary information), and Figure 3. The mean length of follow-up in the total cohort was 52 months (median 36, range 0.25–186). Of the patients, 173 of 196 (88.3%) had follow-up of more than 12 months. In the indication groups with at least five cases, patients with epilepsy and inflammatory myopathies had the longest follow-up periods, whereas patients with anti-NMDAR encephalitis and myasthenia gravis had the shortest follow-up (Table II). At last available follow-up, mean mRS in the total cohort was 1.8 (median 2, range 0–6). Of the patients, 20.4% (40 of 196) had mRS 0 (no symptoms at all), 20.9% (41 of 196) had mRS 1 (no significant disability despite symptoms), 25% (49 of 196) had mRS 2 (slight disability), 25% (49 of 196) had mRS 3 (moderate disability), 6.6% (13 of 196) had mRS 4 (moderately severe disability), 0.5% (1 of 196) had mRS 5 (severe disability), and 1.5% (3 of 196) of patients had died (mRS 6: one with febrile infection-related epilepsy syndrome, one with Lennox-Gastaut syndrome, one with dermatomyositis) (Table SII). At last follow-up, 20.4% (40 of 196) of patients reported ongoing cognitive or learning problems, 9.2% (18 of 196) behavioural problems, 46.9% (92 of 196) motor problems, 3.6% (7 of 196) visual impairment, 12.7% (25 of 196) epilepsy, and 37.2% (73 of 196) other problems.

In the indication groups with at least five cases, patients with anti-NMDAR encephalitis, Guillain–Barré syndrome, and myasthenia gravis had the lowest mean and median mRS at last follow-up, the highest proportion of good outcome (mRS 0–2), and the greatest change to mRS 0 to 2 from the acute phase to the last follow-up (see Fig. 3, Table II, and Appendix S1). By contrast, patients with Rasmussen's encephalitis and epilepsy had the highest mean and median mRS at follow-up, the lowest proportions of good outcome (mRS 0–2), and the smallest change to mRS 0 to 2 between the acute phase and the follow-up (Fig. 3).

Clinical indications for IVIG administration in our cohort: comparison with existing guidelines on the use of IVIG

Table III presents the role of IVIG according to different guidelines, in each of the clinical indications for which IVIG were administered in our cohort. With reference to the guidelines including both CNS and PNS indications,[4–7,9] the proportion of patients in our cohort who received IVIG for indications not strongly recommended or not listed in the guidelines ranged between 45.4% and 57.1%. Table SIII (online supporting information) gives details with regard to the Australian criteria for the clinical use of IVIG.[9]

DISCUSSION

To review the clinical practice regarding the use of IVIG in paediatric neurology, we carried out a retrospective study at the Children's Hospital at Westmead, Sydney, for the period 2000 to 2014. Kawasaki disease was the clinical indication for which IVIG was most commonly administered, outnumbering all neurological indications, which represented about one-sixth of all patients given IVIG in our institution.

Neurological indications for IVIG treatment were similarly distributed between CNS and PNS indications in our cohort, but the increase in use of IVIG for neurological disorders over the study period is mostly a result of the rise in CNS indications. This is at least partly because the description of some of these disorders, including anti-NMDAR encephalitis, is relatively recent. The understanding of the immunological basis for anti-NMDAR encephalitis and other cell surface autoimmune encephalitis has likely resulted in an increased willingness to use immune therapy in patients with encephalitis.

These observations may also partly explain why about half of the patients in our cohort (45.4–57.1%) received IVIG for indications not strongly recommended or not listed in the most recent available international guidelines for the use of IVIG. Besides, some of these disorders are very rare, such as rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation syndrome, and the evidence on the efficacy of immune therapy is limited. Others, such as transverse myelitis, are more common, but quality evidence on the efficacy of IVIG is lacking; a randomized controlled trial is currently under way.[13] Given that transverse myelitis can have a poor prognosis, with less than 50% making a full recovery,[14] it is understandable that clinicians are more likely to

Table II: Length of follow-up and neurological outcome by clinical indication

Indications for IVIG administration	Mean length of follow-up in months (median, range)	Mean mRS at follow-up (median, range)	Proportion of patients with complete recovery and good outcome	
			mRS 0, complete recovery (%)	mRS 0–2, good outcome (%)
CNS indications (*n*=113)				
Encephalitis (*n*=47)				
Infectious and infection-associated encephalitis (*n*=11)	48.3 (32, 13–160)	2.3 (3, 0–4)	3/11 (27.3)	4/11 (36.4)
Anti-NMDAR encephalitis (*n*=8)	36 (23.5, 10–98)	0.9 (0, 0–3)	5/8 (62.5)	7/8 (87.5)
Acute disseminated encephalomyelitis (*n*=7)	54 (51, 27–99)	2 (2, 1–3)	0/7 (0)	5/7 (71.4)
Rasmussen's encephalitis (*n*=5)	80.4 (83, 8–164)	3 (3, 3)	0/5 (0)	0/5 (0)
Other autoimmune or immune-mediated encephalitis (*n*=16)	39.1 (33, 14–117)	2.1 (2, 0–4)	1/16 (6.2)	11/16 (68.7)
Inflammatory demyelinating CNS diseases (*n*=29)				
Monophasic inflammatory demyelinating CNS diseases (*n*=22)	45.9 (30.5, 0.5–169)	2 (2, 0–4)	5/22 (22.7)	12/22 (54.5)
Relapsing inflammatory demyelinating CNS diseases (*n*=7)	59.4 (36, 7–139)	1.4 (1, 0–4)	2/7 (28.6)	6/7 (85.7)
Epilepsies (*n*=11)				
Epilepsies (*n*=11)	89.4 (94, 25–151)	3.3 (3, 1–6)	0/11 (0)	3/11 (27.3)
Autoimmune CNS syndromes (*n*=10)				
Opsoclonus-myoclonus ataxia syndrome (*n*=9)	64.9 (40, 10–181)	2.1 (2, 1–3)	0/9 (0)	7/9 (77.8)
ROHHAD syndrome (*n*=1)	18	4	0/1 (0)	0/1 (0)
Postinfectious movement disorders (*n*=6)				
Sydenham chorea (*n*=4)	10.1 (11.5, 0.25–17)	1.5 (1.5, 1–2)	0/4 (0)	4/4 (100)
Other (*n*=2)	43 (43, 38–48)	2 (2, 1–3)	0/2 (0)	1/2 (50)
Paediatric acute neuropsychiatric syndromes (*n*=3)				
Paediatric acute neuropsychiatric syndromes (*n*=3)	33.7 (29, 13–59)	2.3 (3, 1–3)	0/3 (0)	1/3 (33.3)
Genetic autoinflammation (*n*=2)				
Genetic autoinflammation (*n*=2)	12.5 (12.5, 6–19)	4.5 (4.5 (4–5)	0/2 (0)	0/2 (0)
CNS involvement in systemic inflammatory diseases (*n*=2)				
Neuropsych. systemic lupus erythematosus (*n*=2)	44.5 (44.5, 29–60)	2.5 (2.5 (2–3)	0/2 (0)	1/2 (50)
Undiagnosed complex autoimmune disorders (*n*=3)				
Undiagnosed complex autoimmune disorders (*n*=3)	20 (18, 17–25)	2.3 (3, 1–3)	0/3 (0)	1/3 (33.3)
PNS indications (*n*=83)				
Demyelinating neuropathies (*n*=64)				
Acute demyelinating neuropathy (Guillain–Barré syndrome) (*n*=55)	55.7 (44, 0.25–186)	1.2 (1, 0–4)	20/55 (36.4)	44/55 (80)
Chronic demyelinating neuropathies (*n*=9)	49 (32, 15–110)	2 (2, 1–3)	0/9 (0)	7/9 (77.8)
Disorders of the neuromuscular junction (*n*=12)				
Myasthenia gravis (*n*=12)	37.7 (30, 4.5–123)	1.25 (1, 0–3)	3/12 (25)	11/12 (91.7)
Inflammatory myopathies (*n*=7)				
Inflammatory myopathies (*n*=7)	84.3 (85, 1.5–175)	2.1 (2, 0–6)	1/7 (14.3)	6/7 (85.7)

In the indication groups with at least five cases, the greatest change to mRS 0–2 from the acute phase to the last follow-up occurred in patients with anti-NMDAR encephalitis, Guillain–Barré syndrome, and myasthenia gravis (see also Fig. 3). By contrast, Rasmussen's encephalitis and epilepsy had the lowest proportions of patients with good outcome (mRS 0–2) and the smallest change to mRS 0–2 between the acute phase and the follow-up. See Appendix S1 for an extended version of Table II legend. CNS, central nervous system; IVIG, intravenous immunoglobulin; mRS, modified Rankin Scale; NMDAR, *N*-methyl-D-aspartate receptor; PNS, peripheral nervous system; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation.

treat these patients more aggressively with multiple immune therapies including IVIG. Furthermore, some of the indication categories in our cohort are poorly defined entities (such as 'suspected autoimmune encephalitis' and 'undiagnosed complex autoimmune disorders'), and these are therefore not dealt with in the available guidelines, as expected. It is likely that future revisions of the existing recommendations will include some of these currently unlisted diagnostic entities, or accommodate for the uncertainty in some of the disorders in which an autoimmune mechanism is suspected but unproven.

In general, the available evidence for the benefit of IVIG in neurological conditions is limited, and Cochrane reviews are available only for Guillain–Barré syndrome,[15] chronic inflammatory demyelinating polyneuropathy,[16] myasthenia gravis,[17] dermatomyositis,[18] and multiple sclerosis.[19] A Cochrane review on the use of IVIG in childhood encephalitis, the second most common indication category for IVIG administration in our cohort, is under way.[20] Given the increasing description of autoantibody-associated encephalitis syndromes and the emerging evidence of improved outcomes with early immune therapy, it seems fair to consider IVIG treatment for these.[21]

In our cohort, the proportion of patients who received IVIG for indications not strongly recommended or not listed in the current available guidelines was higher than in previous studies.[22–24] In an audit on the use of IVIG in clinical practice in adults, conducted in Sydney about 12 years ago,[23] 25.5% of patients received IVIG for indications not strongly recommended in the existing criteria at the time.[25] Similarly, 30% of patients in a more recent French study in adults also received IVIG 'off-label'.[24,26]

Table III: Indications for IVIG administration in our cohort: role for IVIG according to different guidelines

Role for IVIG in different guidelines including CNS and PNS indications	2012, NBA	2011, Wimperis	2008, Elovaara[a]	2007, Feasby[b]	2006, Orange[c]
Committee issuing the guidelines (Country) (see legend for details on the recommendations in each guideline)	National Blood Authority Australia (NBA) (Australia)	Department of Health (UK)	EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases (Europe)	IVIG Hematology and Neurology Expert Panels (Canada)	Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma And Immunology (USA)
Recommendations for the use of IVIG (subdivided into stronger and weaker by the authors)					
Stronger recommendation categories	Established Emerging	Highest priority Appropriate	Established effective (LoE A) Probably effective (LoE B)	Recommended (based on LoE 1a to 6)	Definitely beneficial Probably beneficial Might provide benefit (A, B)
Weaker recommendation categories/Not recommended	Exceptional circumstances only Not supported	Limited/little/no evidence Not recommended	Possibly effective (LoE C) Good practice point (class IV evidence)	Not recommended (based on LoE 1a to 6)	Might provide benefit (C, D)
Indications for IVIG administration in our cohort: role for IVIG according to different guidelines					
Central indications (*n*=113)					
Encephalitis (*n*=47)					
Infectious/infection-associated encephalitis (*n*=11): Enterovirus (*n*=7), Mycoplasma (*n*=1), HSV (*n*=1), Influenza (*n*=1), Acute necrotizing encephalopathy (*n*=1)	–	–	–	–	–
Anti-NMDAR encephalitis (*n*=8)	–	Limited evidence	–	–	–
Acute disseminated encephalomyelitis (*n*=7)	Emerging	Limited evidence	Good practice point (class IV)	Recommended (LoE 4)	Might provide benefit (III C)
Rasmussen's encephalitis (*n*=5)	Exceptional	Appropriate	Good practice point (class IV)	Recommended	Might provide benefit (IIb B)
Basal ganglia (*n*=4)	–	–	–	–	–
Anti-VGKC encephalitis (*n*=1)	Exceptional	Limited evidence	–	–	–
Other suspected autoimmune encephalitis (*n*=11)	–	Limited evidence	–	–	–
Inflammatory demyelinating diseases (*n*=29)					
Transverse myelitis (*n*=21)	–	–	–	–	–
Optic neuritis (*n*=1)	Not supported	–	–	–	–
Multiple sclerosis (*n*=4)	Emerging	Not recommended	Probably effective (LoE B)	Recommended (LoE 1a)	–
Neuromyelitis optica (*n*=3)	Exceptional	–	Good practice point (class IV)	–	–
Epilepsies (*n*=11)					
FIRES (*n*=3), Lennox-Gastaut (*n*=2), Landau-Kleffner (*n*=1), Other (*n*=5)	Exceptional	Limited evidence	Good practice point (class IV)	Not recommended (LoE 1b)	Might provide benefit (Ia A)
Autoimmune CNS syndromes (*n*=10)					
Opsoclonus-myoclonus ataxia syndrome (*n*=9)	Emerging	Limited evidence	–	Recommended (LoE 4)	Might provide benefit (III C)
ROHHAD syndrome (*n*=1)	–	–	–	–	–
Postinfectious movement disorders (*n*=6)					
Sydenham chorea (*n*=4)	–	–	–	–	–
Other (*n*=2)	–	–	–	–	–
Paediatric acute neuropsychiatric syndromes (*n*=3)					
PANDAS/Tourette syndrome (*n*=2)	Exceptional	Little/No evidence	–	Recommended (LoE 1b)	Might provide benefit (IIb B)

Table III: Continued

Role for IVIG in different guidelines including CNS and PNS indications	2012, NBA	2011, Wimperis	2008, Elovaara[a]	2007, Feasby[b]	2006, Orange[c]
PANS (*n*=1)	Not supported	–	–	–	–
Genetic autoinflammation (*n*=2)					
Aicardi–Goutiéres syndrome (*n*=1), Suspected autoinflammatory neurodegen. brain disorder (*n*=1)	–	–	–	–	–
CNS involvement in systemic inflammatory diseases (*n*=2)					
Neuropsychiatric systemic lupus erythematosus (*n*=2)	Not supported	Little/no evidence	–	–	Might provide benefit (III D)
Undiagnosed complex autoimmune disorders (*n*=3)					
Undiagnosed complex autoimmune disorders (*n*=3)	–	–	–	–	–
Peripheral indications (*n*=83)					
Demyelyinating neuropathies (*n*=64)					
Acute demyelinating neuropathy (Guillain–Barré syndrome) (*n*=55)	Established	Highest priority	Established effective (LoE A)	Recommended (LoE 1a)	Definitely beneficial (Ia A)
Chronic inflammatory demyelinating polyneuropathy (*n*=7)	Established	Highest priority	Established effective (LoE A)	Recommended (LoE 1a)	Definitely beneficial (Ia A)
Mononeuritis (*n*=2)	–	–	–	–	–
Disorders of the neuromuscular junction (*n*=12)					
Myasthenia gravis (*n*=12)	Established	Appropriate	Established effective (LoE A)	Recommended (LoE 1b)	Probably beneficial (Ib-IIa B)
Inflammatory myopathies (*n*=7)					
Dermatomyositis (*n*=6)	Established	Appropriate	Probably effective (LoE B)	Recommended (LoE 1b)	Probably beneficial (IIa B)
Orbital myositis (*n*=1)	–	–	–	–	–
Total quantity of IVIG (g) given for weaker indications, or not recommended/not listed	41.4% (23 682.5g/ 57 221g)	53% (30 349g/ 57 221g)	48.8% (27 928.5g/57 221g)	36.4% (20 858.5g/57 221g)	38.4% (22 004.5g/57 221g)
Total patients who received IVIG for weaker indications, or not recommended/not listed	49% (96/196)	56.6% (111/196)	57.1% (112/196)	45.4% (89/196)	50% (98/196)

See Appendix S1 for an extended version of Table III legend. [a–c] EFNS, European Federation of Neurological Societies; FIRES, febrile infection-related epilepsy syndrome; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; LoE, level of evidence; NMDAR, *N*-methyl-D-aspartate receptor; PANDAS, paediatric autoimmune neuropsychiatric disorder associated with group A streptococci; PANS, paediatric acute-onset neuropsychiatric syndrome; PNS, peripheral nervous system; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; VGKC, voltage-gated potassium channel.

In these studies,[23,24] the most common neurological indications for IVIG included chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, multifocal motor neuropathy, and dermatomyositis, reflecting the different age in the study population (adult only) compared with ours.

The dose of IVIG used in our cohort was variable, but generally 2g/kg was used in acute diseases that required only one course (i.e. Guillain–Barré syndrome), whereas smaller doses and a high number of courses were used in chronic diseases, such as chronic inflammatory demyelinating polyneuropathy. Adverse reactions to IVIG occurred in 25.5% of patients in our cohort, but serious events were rare. It is possible that the actual rate of non-serious adverse reactions is higher because of under-reporting given the retrospective design of this study, especially in the case of patients who were discharged soon after receiving IVIG. Most of the patients were very impaired before receiving IVIG (mRS 3–5 in 94.7%), and most were given other immune therapies, with the exception of patients with Guillain–Barré syndrome in whom most received IVIG monotherapy. The length of follow-up was relatively long in our population, and generally there was a good recovery, with mRS 0 to 2 in 66.8% of cases, although three patients did die. The improvement at last follow-up was most marked in the patients with anti-NMDAR encephalitis, Guillain–Barré syndrome, and myasthenia gravis. It is significant that some of these entities, such as anti-NMDAR encephalitis, are not specifically mentioned in most of the existing guidelines for the use of IVIG, even though their description predates the publication date of the guideline.

The least marked improvement at follow-up was observed in patients with Rasmussen's encephalitis and epilepsy (Fig. 3), questioning the role of IVIG in these conditions. It is the personal experience of the authors that some patients with Rasmussen's encephalitis and epilepsy do benefit from IVIG and other immune therapies, whereas other patients get no apparent benefit. Even though some evidence for a role of IVIG in epilepsy is available,[27] according to two Cochrane reviews no reliable conclusions can be drawn regarding the efficacy of IVIG in epilepsy.[28,29] Recently, the efficacy of immune therapy over antiepileptic drugs has been reported in specific types of seizures with autoimmune aetiology, such as faciobrachial dystonic seizures,[30] and in patients with positive neuronal surface antibodies with exclusive or prevalent seizure presentations.[31] Therefore, IVIG likely does have a role in some types of immune-mediated epilepsy, although our data suggest the benefits are equivocal outside of proven autoimmune encephalitis with seizures. Even though IVIG does seem to have a role in adult-onset Rasmussen's encephalitis,[32,33] the results of our study support other data in the literature suggesting limited efficacy of IVIG in paediatric Rasmussen's encephalitis.[34,35] It is noteworthy that the subgroups receiving less benefit (Rasmussen's encephalitis, epilepsies) received a large amount of IVIG at a high financial cost. Therefore when using IVIG for less accepted indications, clinicians should try to define clear outcome targets, and be willing to stop IVIG if those targets are not met; this is not easy to achieve in patients with refractory syndromes when families describe modest benefits.

A very limited number of patients in our cohort were treated with plasma exchange. The use of plasma exchange in children may present unique challenges and higher complication rates compared with adults, especially in patients who are poorly cooperative or have autonomic instability.[36] In addition, the use of plasma exchange is at least partly subject to the experience and expertise of individual centres, and our centre has generally used IVIG rather than plasma exchange. We have only recently started using plasma exchange in neurological patients.

The long study period, large cohort, long follow-up, and comparison with different guidelines are among the strengths of this study. Its limitations are primarily a result of its retrospective nature, including the retrospective assignment of mRS disability score and the detection of side effects to IVIG. In addition, the natural history of different clinical conditions and the use of other immune therapies as well as IVIG will have influenced the clinical outcomes at last follow-up, and make the efficacy of IVIG difficult to define with confidence in our study. We decided to exclude the 23 patients initially treated with IVIG for suspected neuroimmunological conditions who were subsequently found to have other disease mechanisms (Fig. 1), because the natural disease history in these patients may be different.

In summary, IVIG represents an expensive resource, and demand has increased worldwide in recent years. Updated guidelines for the clinical use of IVIG are essential to rationalize the use of IVIG in an evidence-based fashion, ensuring availability for the conditions for which IVIG use is clearly beneficial, and limiting unnecessary expenses. Our study captures the recent clinical practice as regards the use of IVIG in a large paediatric neurology centre, further highlighting an imbalance between generally accepted clinical practice (e.g. use of IVIG for transverse myelitis and anti-NMDAR encephalitis), and clinical guidelines that are usually generated based on randomized controlled trial evidence. Furthermore, future studies to prove efficacy of IVIG, such as IVIG versus placebo, are likely to be considered unethical for most of these conditions, whereas 'head-to-head' studies comparing IVIG with other first-line agents may require large numbers to generate statistical significance.

APPENDIX: MEMBERS OF THE IVIG IN NEUROLOGY STUDY GROUP

In addition to the authors listed at the top of this article, the IVIG in Neurology Study Group consists of:

Peter Barclay, Pharmacy Department, the Children's Hospital at Westmead, University of Sydney;

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SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Number of IVIG courses per patient (mean, median range) by clinical indication group (only the indications with at least five patients are represented, see Fig. 1).

Table SI: First-line and second-line immune therapies administered beside IVIG according to indication group.

Table SII: Detailed data on outcome at last follow-up by clinical indications.

Table SIII: Role for IVIG in the clinical indications of our cohort according to the National Blood Authority Australia, Criteria for the clinical use of intravenous immunoglobulin in Australia, 2nd edition, July 2012.

Appendix S1: Patients with undiagnosed complex autoimmune disorders; extended legends to Tables II and III.

REFERENCES

1. Živković S. Intravenous immunoglobulin in the treatment of neurologic disorders. *Acta Neurol Scand* 2015. doi: 10.1111/ane.12444 [Epub ahead of print].
2. Lünemann JD, Nimmerjahn F, Dalakas MC. Intravenous immunoglobulin in neurology–mode of action and clinical efficacy. *Nat Rev Neurol* 2015; **11**: 80–89.
3. Wong PH, White KM. Impact of immunoglobulin therapy in pediatric disease: a review of immune mechanisms. *Clin Rev Allergy Immunol* 2015. doi: 10.1007/s12016–015–8499–2 [Epub ahead of print].
4. Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006; **117**: S525–53.
5. Feasby T, Banwell B, Benstead T, et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 2007; **21**: S57–107.
6. Elovaara I, Apostolski S, van Doorn P, et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. *Eur J Neurol* 2008; **15**: 893–908.
7. Wimperis J, Lunn M, Jones A, et al. (2011) Clinical Guidelines for Immunoglobulin Use (Second Edition Update). https://www.gov.uk/government/publications/clinical-guidelines-for-immunoglobulin-use-second-edition-update (accessed 1 December 2015).
8. Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2012; **78**: 1009–15.
9. National Blood Authority Australia. Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia. 2nd edn. 2012. http://www.blood.gov.au/ivig-criteria (accessed 1 December 2015).
10. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; **19**: 604–07.
11. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013; **12**: 157–65.
12. National Cancer Institute. The National Institutes of Health Common Terminology Criteria for Adverse Events. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 (accessed 7 December 2015).
13. Absoud M, Gadian J, Hellier J, et al. Protocol for a multicentre randomiSed controlled TRial of IntraVEnous immunoglobulin versus standard therapy for the treatment of transverse myelitis in adults and children (STRIVE). *BMJ Open* 2015; **5**: e008312.
14. Pidcock FS, Krishnan C, Crawford TO, Salorio CF, Trovato M, Kerr DA. Acute transverse myelitis in childhood: center-based analysis of 47 cases. *Neurology* 2007; **68**: 1474–80.
15. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain–Barré syndrome. *Cochrane Database Syst Rev* 2014; **9**: CD002063.
16. Eftimov F, Winer JB, Vermeulen M, de Haan R, van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2013; **12**: CD001797.
17. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. *Cochrane Database Syst Rev* 2012; **12**: CD002277.
18. Gordon PA, Winer JB, Hoogendijk JE, Choy EH. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Cochrane Database Syst Rev* 2012; **8**: CD003643.
19. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev* 2015; **9**: CD011381.
20. Iro MA, Martin NG, Absoud M, Pollard AJ. Intravenous immunoglobulin for the treatment of childhood encephalitis. *Cochrane* 2014. http://www.cochrane.org/CD011367/MS_intravenous-immunoglobulin-for-the-treatment-of-childhood-encephalitis (accessed 1 December 2015).
21. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. *Expert Rev Neurother* 2015; **15**: 1391–419.

22. Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature. *Transfusion* 2006; **46**: 741–53.

23. Lin MW, Kirkpatrick PE, Riminton DS. How intravenous immunoglobulin is used in clinical practice: audits of two Sydney teaching hospitals. *Intern Med J* 2007; **37**: 308–14.

24. Frauger E, Grassi J, Pradel V, et al. Use of intravenous immunoglobulins in clinical practice: data from three French university hospitals. *Fundam Clin Pharmacol* 2011; **25**: 753–61.

25. Australian Health Ministers' Advisory Council. Review of the Use and Supply of Intravenous Immunoglobulins in Australia. A Report by the Blood and Blood Products Committee. 2000. http://www.nba.gov.au/PDF/IVIg.pdf [cited June 2000] (accessed 1 December 2015).

26. European Medicines Agency (EMA). Guideline on the Clinical Investigation of Human Normal. Immunoglobulin for Intravenous Administration (IVIg). 2009. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000388.jsp&mid=WC0b01ac0580032ec8#Normal%20immunoglobulins (accessed 22 April 2016).

27. van Rijckevorsel-Harmant K, Delire M, Schmitz-Moorman W, Wieser HG. Treatment of refractory epilepsy with intravenous immunoglobulins. Results of the first double-blind/dose finding clinical study. *Int J Clin Lab Res* 1994; **24**: 162–66.

28. Geng J, Dong J, Li Y, et al. Intravenous immunoglobulins for epilepsy. *Cochrane Database Syst Rev* 2011; **1**: CD008557.

29. Walker L, Pirmohamed M, Marson AG. Immunomodulatory interventions for focal epilepsy syndromes. *Cochrane Database Syst Rev* 2013; **6**: CD009945.

30. Irani SR, Stagg CJ, Schott JM, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. *Brain* 2013; **136**: 3151–62.

31. Quek AM, Britton JW, McKeon A, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. *Arch Neurol* 2012; **69**: 582–93.

32. Hart YM, Cortez M, Andermann F, et al. Medical treatment of Rasmussen's syndrome (chronic encephalitis and epilepsy): effect of high-dose steroids or immunoglobulins in 19 patients. *Neurology* 1994; **44**: 1030–36.

33. Villani F, Spreafico R, Farina L, et al. Positive response to immunomodulatory therapy in an adult patient with Rasmussen's encephalitis. *Neurology* 2001; **56**: 248–50.

34. Granata T, Fusco L, Gobbi G, et al. Experience with immunomodulatory treatments in Rasmussen's encephalitis. *Neurology* 2003; **61**: 1807–10.

35. Ramesha KN, Rajesh B, Ashalatha R, et al. Rasmussen's encephalitis: experience from a developing country based on a group of medically and surgically treated patients. *Seizure* 2009; **18**: 567–72.

36. Michon B, Moghrabi A, Winikoff R, et al. Complications of apheresis in children. *Transfusion* 2007; **47**: 1837–42.

37. Pillai SC, Hacohen Y, Tantsis E, et al. Infectious and autoantibody-associated encephalitis: clinical features and long-term outcome. *Pediatrics* 2015; **135**: e974–84.

38. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006; **66**: 1485–89.

39. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015; **85**: 177–89.

Supplementary material

Supplementary Figure 1

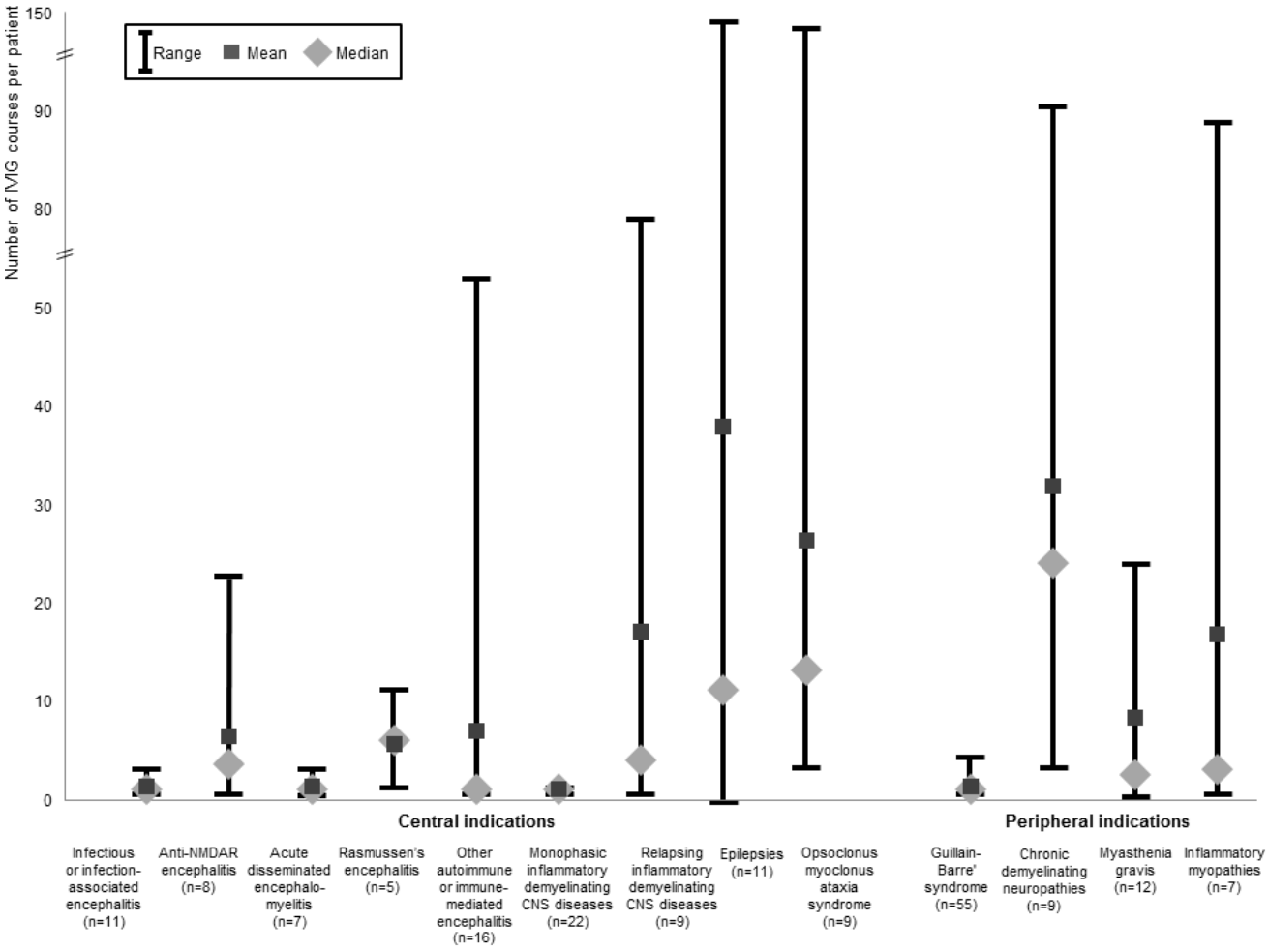

Figure S1: Number of IVIG courses per patient (mean, median range) by clinical indication group (only the indications with at least five patients are represented, see Fig. 1).

Supplementary Table 1

Indication groups	Other first-line immune therapies					Second-line immune therapies					
CNS INDICATIONS (n=113)	**Total**	**Before/ With IVIG**	**After IVIG**	**Steroids**	**PE**	**Total**	**Before/ With IVIG**	**After IVIG**	**RTX**	**CYC**	**Other second-line immune therapies**
Encephalitis (n=47)											
Infectious and infection-associated encephalitis (n=11)	10/11 (90.9%)	8/11 (72.7%)	2/11 (18.2%)	10/11 (90.9%)	-	-	-	-	-	-	-
Anti-NMDAR encephalitis (n=8)	8/8 (100%)	8/8 (100%)	-	8/8 (100%)	-	4/8 (50%)	-	4/8 (50%)	3/8 (37.5%)	-	1/8 (12.5) MMF
Acute disseminated encephalomyelitis (n=7)	7/7 (100%)	7/7 (100%)	-	7/7 (100%)	-	1/7 (14.3%)	-	1/7 (14.3%)	-	-	1/7 (14.3%) MMF
Rasmussen's encephalitis (n=5)	5/5 (100%)	4/5 (80%)	1/5 (20%)	5/5 (100%)	-	-	-	-	-	-	-
Other autoimmune or immune-mediated encephalitis (n=16)	16/16 (100%)	14/16 (87.5%)	2/16 (12.5%)	16/16 (100%)	-	4/16 (25%)	-	4/16 (25%)	2/16 (12.5%)	1/16 (6.25%)	1/16 (6.25%) MMF
Inflammatory demyelinating CNS diseases (n=29)											
Monophasic inflammatory demyelinating CNS diseases (n=22)	20/22 (90.9%)	20/22 (90.9%)	-	20/22 (90.9%)	0/22 (0%)	-	-	-	-	-	-
Relapsing inflammatory demyelinating CNS diseases (n=7)	7/7 (100%)	7/7 (100%)	-	7/7 (100%)	1/7 (14.3%)	4/7 (57.1%)	1/7 (14.3%)	3/7 (42.8%)	-	-	3/7 (42.8%) IFN, 1/7 (14.3%) each MMF, AZA, Mitox
Epilepsies (n=11)											
Epilepsies (n=11)	10/11 (90.9%)	8/11 (72.7%)	2/11 (18.2%)	10/11 (90.9%)	-	2/11 (18.2%)	-	2/11 (18.2%)	2/11 (18.2%)	-	-
Autoimmune CNS syndromes (n=10)											
Opsoclonus myoclonus ataxia syndrome (n=9)	8/9 (88.9%)	8/9 (88.9%)	-	8/9 (88.9%)	-	5/9 (55.5%)	-	5/9 (55.5%)	3/9 (33.3%)	3/9 (33.3%)	-
ROHHAD syndrome (n=1)	1/1 (100%)	1/1 (100%)	-	1/1 (100%)	-	1/1 (100%)	-	1/1 (100%)	1/1 (100%)	1/1 (100%)	-
Postinfectious movement disorders (n=6)											
Sydenham chorea (n=4)	4/4 (100%)	3/4 (75%)	1/4 (25%)	4/4 (100%)	-	-	-	-	-	-	-
Other (n=2)	2/2 (100%)	2/2 (100%)	-	2/2 (100%)	-	-	-	-	-	-	-
Paediatric acute neuropsych. syndromes (n=3)											
Paediatric acute neuropsych. syndromes (n=3)	2/3 (66.7%)	1/3 (33.3%)	1/3, (33.3%)	2/3 (66.7%)	-	-	-	-	-	-	-
Genetic auto-inflammation (n=2)											
Genetic auto-inflammation (n=2)	2/2 (100%)	2/2 (100%)	-	2/2 (100%)	-	1/2 (50%)	1/2 (50%)	-	1/2 (50%)	1/2 (50%)	1/2 (50%) MMF
CNS involvement in systemic inflammatory diseases (n=2)											
Neuropsych. systemic lupus erythematosus (n=2)	2/2 (100%)	2/2 (100%)	0/2 (0%)	2/2 (100%)	0/2 (0%)	2/2 (100%)	2/2 (100%)	-	-	1/2 (50%)	2/2 (100%) MMF, 2/2 (100%) AZA
Undiagnosed complex autoimmune disorders (n=3)											
Undiagnosed complex autoimmune disorders (n=3)	2/3 (66.7%)	-	2/3 (66.7%)	2/3 (66.7%)	-	1/3 (33.3%)	-	1/3 (33.3%)	-	-	1/3 (33.3%) MMF
PNS INDICATIONS (n=83)											
Demyelinating neuropathies (n=64)											
Acute demyelinating neuropathies (n=55)	14/55 (25.4%)	6/55 (10.9%)	8/55 (14.5%)	14/55 (25.4%)	-	-	-	-	-	-	-
Chronic demyelinating neuropathies (n=9)	5/7 (71.4%)	2/7 (28.6%)	3/7 (42.5%)	4/7 (57.1%)	1/7 (14.3%)	1/7 (14.3%)	-	1/7 (14.3%)	-	-	1/7 (14.3%) AZA
Disorders of the neuromuscular junction (n=12)											
Myastenia gravis (n=12)	11/12 (91.7%)	8/12 (66.7%)	3/12 (25%)	11/12 (91.7%)	2/12 (16.7%)	8/12 (66.7%)	1/12 (8.3%)	7/12 (58.3%)	-	-	6/12 (50%) MMF, 3/12 (25%) AZA
Inflammatory myopathies (n=7)											
Inflammatory myopathies (n=7)	7/7 (100%)	7/7 (100%)	-	7/7 (100%)	-	5/7 (71.4%)	4/7 (57.1%)	1/7 (14.3%)	-	-	5/7 (71.4%) MTX, 2/7 (28.6%) MMF

Supplementary Table 1. First-line and second-line immune therapies administered beside IVIG according to indication group. The columns before/with and after IVIG refer to the relative order of first administration of IVIG or other therapy.

Legend: AZA: azathioprine; CNS: central nervous system; CYC: cyclophosphamide; IFN: interferon; IVIG: intravenous immunoglobulin; Mitox: mitoxantrone; MMF: mycophenolate mofetil; MTX: methotrexate; neuropsych: neuropsychiatric; NMDAR: N-methyl-D-aspartate receptor; PE: plasma exchange; PNS: peripheral nervous system; ROHHAD: rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; RTX: rituximab; -: 0%.

Supplementary Table 2

INDICATIONS FOR IVIG ADMINISTRATION	mRS							Type of ongoing problems						
	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6	No problems	Cognitive/learning	Behavioural	Motor	Visual	Epilepsy	Other
CNS INDICATIONS (n=113)														
Encephalitis (n=47)														
Infectious and infection-associated encephalitis (n=11)	27.3%	0%	9.1%	45.4%	18.2%	0%	0%	27.3%	27.3%	0%	54.5%	0%	18.2%	27.3%
Anti-NMDAR encephalitis (n=8)	62.5%	0%	25%	12.5%	0%	0%	0%	62.5%	25%	25%	25%	0%	0%	25%
Acute disseminated encephalomyelitis (n=7)	0%	28.6%	42.5%	28.6%	0%	0%	0%	0%	14.3%	0%	28.6%	0%	28.6%	71.4%
Rasmussen's encephalitis (n=5)	0%	0%	0%	100%	0%	0%	0%	0%	40%	0%	100%	40%	60%	40%
Other autoimmune or immune-mediated encephalitis (n=16)	6.2%	18.7%	43.7%	18.7%	12.5%	0%	0%	6.2%	50%	12.5%	25%	0%	43.7%	56.2%
Inflammatory demyelinating CNS diseases (n=29)														
Monophasic inflammatory demyelinating CNS diseases (n=22)	22.7%	18.2%	13.6%	27.3%	18.2%	0%	0%	22.7%	4.5%	4.5%	68.2%	0%	4.5%	36.4%
Relapsing inflammatory demyelinating CNS diseases (n=7)	28.6%	28.6%	28.6%	0%	14.3%	0%	0%	28.6%	0%	0%	14.3%	28.6%	0%	42.8%
Epilepsies (n=11)														
Epilepsies (n=11)	0%	9.1%	18.2%	45.4%	9.1%	0%	18.2%	0%	63.6%	18.2%	18.2%	0%	63.6%	36.4%
Autoimmune CNS syndromes (n=10)														
Opsoclonus myoclonus ataxia syndrome (n=9)	0%	11.1%	66.7%	22.2%	0%	0%	0%	0%	33.3%	22.2%	55.5%	0%	0%	44.4%
ROHHAD syndrome (n=1)	0%	0%	0%	0%	100%	0%	0%	0%	100%	100%	100%	0%	0%	100%
Postinfectious movement disorders (n=4)														
Sydenham chorea (n=4)	0%	50%	50%	0%	0%	0%	0%	0%	0%	25%	50%	0%	0%	50%
Paediatric acute neuropsych. syndromes (n=3)														
Paediatric acute neuropsych. syndromes (n=3)	0%	33.3%	0%	66.7%	0%	0%	0%	0%	33.3%	0%	0%	0%	33.3%	100%
Genetic autoinflammation (n=2)														
Genetic autoinflammation (n=2)	0%	0%	0%	0%	50%	50%	0%	0%	50%	0%	100%	0%	0%	100%
CNS involvement in systemic inflammatory diseases (n=2)														
Neuropsychiatric systemic lupus erythematosus (n=2)	0%	0%	0%	100%	0%	0%	0%	0%	50%	0%	50%	0%	50%	100%
Undiagnosed complex autoimmune disorders (n=3)														
Undiagnosed complex autoimmune disorders (n=3)	0%	33.3%	66.7%	0%	0%	0%	0%	0%	33.3%	66.7%	0%	0%	0%	100%
Other (n=2)														
Other (n=2)	0%	50%	0%	50%	0%	0%	0%	0%	50%	100%	0%	0%	50%	50%
PNS INDICATIONS (n=83)														
Demyelinating neuropathies (n=64)														
Guillain-Barré syndrome (n=55)	36.4%	29.1%	14.5%	18.2%	1.8%	0%	0%	36.4%	10.9%	3.6%	47.3%	1.8%	0%	20%
Chronic demyelinating neuropathies (n=9)	0%	22.2%	55.5%	22.2%	0%	0%	0%	0%	0%	0%	88.9%	11.1%	0%	22.2%
Disorders of the neuromuscular junction (n=12)														
Myastenia gravis (n=12)	25%	33.3%	33.3%	8.3%	0%	0%	0%	25%	8.3%	0%	66.7%	0%	0%	25%
Inflammatory myopathies (n=7)														
Inflammatory myopathies (n=7)	14.3%	14.3%	57.1%	0%	0%	0%	14.3%	14.3%	0%	0%	28.6%	14.3%	0%	57.1%

Supplementary Table 2. Detailed data on outcome at last follow-up by clinical indications. Legend: CNS: central nervous system; IVIG: intravenous immunoglobulin; mRS: modified Rankin Scale; neuropsych.: neuropsychiatric; NMDAR: N-methyl-D-aspartate receptor; PNS: peripheral nervous system; ROHHAD: rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation.

Supplementary Table 3

Role for IVIG according to the National Blood Authority Australia for the clinical indications in our cohort (the quantity of IVIG administered by clinical indication is detailed)	**Established therapeutic role**	**Emerging therapeutic role**	**Use in exceptional circumstances only**	**Use not supported**	**Not listed in the NBA criteria for IVIG use**
CENTRAL INDICATIONS (n=113)					
Encephalitis (n=47)					
Infectious and infection-associated encephalitis (n=11): Enterovirus (n=7), Mycoplasma (n=1), HSV (n=1), Influenza (n=1), Acute necrotising encephalopathy (n=1)					530 g
Anti-NMDAR encephalitis (n=8)					1626.5 g
Acute disseminated encephalomyelitis (n=7)		454 g			
Rasmussen's encephalitis (n=5)			1147		
Basal ganglia (n=4)					426 g
Anti-VGKC encephalitis (n=1)			60 g		
Other suspected autoimmune encephalitis (n=11)			2830 g*		
Inflammatory demyelinating diseases (n=29)					
Transverse myelitis (n=21)					1327 g
Optic neuritis (n=1)				40 g	
Multiple sclerosis (n=4)		2203 g			
Neuromyelitis optica MOG+ or AQP4+ (n=3)			819 g		
***Epilepsies* (n=11)**					
FIRES (n=3), Lennox-Gastaut (n=2), Landau-Kleffner (n=1), Other (n=5)			6748 g		
***Autoimmune CNS syndromes* (n=10)**					
Opsoclonus myoclonus ataxia syndrome (n=9)		5237 g			
ROHHAD syndrome (n=1)					1200 g
***Postinfectious movement disorders* (n=4)**					
Sydenham chorea (n=4)					482 g
Other (n=2): Acute cerebellar ataxia (n=1), Complex movement disorder (n=1)					129 g
***Paediatric acute neuropsychiatric syndromes* (n=3)**					
PANDAS/Tourette syndrome (n=2)			1596 g		
PANS (n=1)				321 g	
***Genetic autoinflammation* (n=2)**					
Aicardi-Goutieres syndrome (n=1), Suspected autoinflammatory neurodegenerative brain disorder (n=1)					260 g
***CNS involvement in systemic inflammatory diseases* (n=2)**					
Neuropsychiatric systemic lupus erythematosus (n=2)				1707 g	
***Undiagnosed complex autoimmune disorders* (n=3)**					
Undiagnosed complex autoimmune disorders (n=3)					2078 g
***Other* (n=2)**					
Acute cerebellar ataxia (n=1), Complex movement disorder (n=1)					129 g
PERIPHERAL INDICATIONS (n=83)					
***Demyelyinating neuropathies* (n=64)**					
Acute demyelinating neuropathy (Guillain-Barré syndrome) (n=55)	4081.5 g				
Chronic inflammatory demyelinating polyneuropathy (n=7)	12229 g				
Mononeuritis (n=2)					275 g
***Disorders of the neuromuscular junction*(n=12)**					
Myastenia gravis (n=12)	4886 g				
***Inflammatory neuropathies* (n=7)**					
Dermatomyositis (n=6),	4529 g				
Orbital myositis (n=1)					81 g
Quantity of IVIG (total: 57221 g)	**25644.5 g (44.8%)**	**7894 g (13.8%)**	**13200 g (23.1%)**	**2068 g (3.6%)**	**8414.5 g (14.7%)**
Number of patients (total: 196)	**80/196 (40.8%)**	**20/196 (10.2%)**	**33/196 (16.8%)**	**4/196 (2%)**	**59/196 (30.1%)**

Supplementary Table 3. Role for IVIG in the clinical indications of our cohort according to the National Blood Authority Australia, Criteria for the clinical use of intravenous immunoglobulin in Australia, 2nd edition July 2012. http://www.blood.gov.au/ivig-criteria. Only for a minority of the diagnoses present in our cohort IVIG has an established (n=4 diagnoses, n=80 patients, total 25644.5 g administered in our cohort) or emerging (n=3 diagnoses, n=20 patients, total 7894 g administered in our cohort) therapeutic role according to the NBA recommendations, whereas for the remaining diagnoses the use of IVIG was recommended in exceptional circumstances only (n=6 diagnoses, n=33 patients, total 13200 g administered in our cohort), not supported (n=3 diagnoses, n=4 patients, total 2068 g administered in our cohort) or not listed in the NBA criteria (n=10 diagnoses, n=59 patients, total 8414.5 g administered in our cohort). 49% (96/196) of the patients in our cohort received IVIG for indications that are not listed in the NBA Criteria, or for which the use of IVIG is not supported or is recommended in exceptional circumstances only. Legend: CNS: central nervous system; IVIG: intravenous immunoglobulin; neuropsych.: neuropsychiatric; NMDAR: N-methyl-D-aspartate receptor; PNS: peripheral nervous system; ROHHAD: rapid-onset obesity with hypothalamic dysfunction,

hypoventilation, and autonomic dysregulation; VGKC: voltage-gated potassium channel; *Limbic encephalitis, non-paraneoplastic.

Supplementary information: Patients with undiagnosed complex autoimmune disorders

The three cases included in the group “undiagnosed complex autoimmune disorders” were patients with a complex history not fitting a known pattern. In these children, alternative diagnoses had been excluded, and clues to an autoimmune etiology were represented by a combination of factors including the family history of autoimmunity, the presence of other known autoimmune diagnoses in the patient, the exacerbation of symptoms with infection, and the inflammatory CSF findings in one patient, and by the history and the positive response to IVIG in the two other patients.

Of the three patients in the category “undiagnosed complex autoimmune disorder”, the first was a boy with type 1 diabetes, idiopathic thrombocytopenia and neutropenia, obstructive sleep apnoea, recurrent tonsillitis, recurrent paroxysmal episodes of neurological disturbance (mostly characterised by visual disturbances), and tics exacerbated by infections. He had normal brain MRI and EEG, and evidence of chronic inflammation in the CSF (persistent finding of pleocytosis and raised neopterin and ESR). The patient’s mother had possible Hashimoto's disease.

The two other patients were two challenging twin boys with a very similar acute onset then progressive history of stereotypic hand movements, posturing, repetitive ritualistic behaviour associated with anxiety, obsessive-compulsive behaviours, social anxiety and withdrawal, bursts of anger and rage, progressive decline in functioning (soiling, inability to write, decline in ability to perform mathematical calculations, on a background of previously good academic ability). The boys had raised anti-DNAse and anti-streptolysin titres, normal CSF and EEG, and brain MRI demonstrating minor cerebellar atrophy, minor thinning of the corpus callosum and minor widening of the posterior horn of the lateral ventricles. A diagnosis of PANDAS had been considered, even though their clinical course was not completely typical. Given the reported mild improvement in symptoms after commencement of antibiotics, a trial with IVIG was done, which associated with sustained improvement based on the family's observations and clinical examination (decrease in anxiety and obsessive compulsive type behaviours, decreased defiance, decreased anger and rage, improved sleep, toileting and participation in family life, increased participation in clinical examination as opposed to a firm refuse and withdrawal before treatment, better performance in simple arithmetic). The cases had features reminiscent of PANDAS but were atypical, and therefore put in this ‘undiagnosed category’.

3.3.3 Therapeutic plasma exchange in paediatric anti-NMDAR encephalitis

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Review article

Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review

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Abstract

Objective: To clarify the most frequent modalities of use of plasma exchange (PE) in pediatric anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis and to establish the most effective association with other immunotherapies.

Methods: Systematic literature review on PE in pediatric anti-NMDAR encephalitis (2007–2015).

Results: Seventy-one articles were included (mostly retrospective), reporting a total of 242 subjects (73.2%, 93/127 females; median age at onset 12 years, range 1–18). Median time to immunotherapy was 21 days (range 0–190). In most cases, PE was given with steroids and IVIG (69.5%, 89/128), or steroids only (18%, 23/128); in a minority, it was associated with IVIG only (7%, 9/128), or was the only first-line treatment (5.5%, 7/128). In 54.5% (65/119), PE was the third treatment after steroids and IVIG, in 31.1% (37/119) the second after steroids or IVIG; only in 14.3% (17/119) was it the first treatment. Second-line immunotherapies were administered in 71.9% (100/139). Higher rates of full/substantial recovery at follow-up were observed with immunotherapy given ⩽30 days from onset (69.4%, 25/36) compared to later (59.2%, 16/27), and when PE was associated with steroids (66.7%, 70/105) rather than not (46.7%, 7/15). Significant adverse reactions to PE were reported in 6 patients.

Conclusion: Our review disclosed a paucity of quality data on PE in pediatric anti-NMDAR encephalitis. PE use in this condition has been increasingly reported, most often with steroids and IVIG. Despite the limited number of patients, our data seem to confirm the trend towards a better outcome when PE was administered early, and when given with steroids.
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Keywords: Anti-NMDAR; Encephalitis; Plasma exchange; Plasmapheresis; Apheresis; Children; Immune therapy

1. Introduction

Since its description in 2007, anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis has been increasingly recognized also in pediatric age, even in the absence of tumor. Although treatment strategies have

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been suggested in adults [1], to date there is no established treatment algorithm in children.

A direct pathogenic role of antibodies against the GluN1 subunit of the NMDAR has been demonstrated in anti-NMDAR encephalitis, resulting in immunoglobulin-induced NMDAR internalization [2,3], and supporting the rationale of antibody removal for the treatment of the disease.

Therapeutic plasma exchange (PE) is an established intervention as a first-line, often life-saving treatment in several conditions [4]. In view of its potential for removal of the pathogenic antibodies, PE is one of the immune therapies so far commonly used in pediatric anti-NMDAR encephalitis. Though, the extent of PE use, timing, and therapeutic protocols in pediatric anti-NMDAR encephalitis vary greatly in the literature. The use of PE in children partly relies on the expertise of the individual centers [1].

We searched the literature for children with anti-NMDAR encephalitis treated with PE, in order to clarify the most frequent modalities of use of PE in this disease and to investigate the most effective protocols, especially as regards the association with other immune therapies and the relative timing. In particular, we studied the relationship between outcome at last follow-up and overall first-line immune therapy strategy, use of second-line immune therapy, and timing of initiation of the first immune therapy, regardless of the type.

2. Materials and methods

2.1. Systematic review criteria

We performed an extensive search of the literature for children with anti-NMDAR encephalitis treated with PE. The literature search was conducted through MEDLINE, updated to December 2015, using the search terms "NMDAR", "Anti-N-methyl-D-Aspartate Receptor Encephalitis", "N-methyl-D-Aspartate receptor", "anti-NMDAR encephalitis" and "NMDA receptor encephalitis". No randomized controlled trials are available on the use of PE for anti–NMDAR encephalitis. Given the retrospective nature of published data, and the variable reporting in the publications, the data regarding treatment and timing was not always available. Therefore, the number of reported patients with available data is provided in brackets for each criteria. When the same patients reported in different articles were clearly identifiable, we counted them only once to avoid duplication.

2.2. Inclusion and exclusion criteria

We included in the present study published pediatric patients (age $\leqslant$18 years) with anti-NMDAR encephalitis treated with PE. Exclusion criteria were lack of treatment with PE, negative search for anti-NMDAR antibodies, or age >18 years.

2.3. Demographics and clinical data

We searched in the literature cohort a comprehensive set of data, including gender, age at onset, presence of tumor and symptoms of anti-NMDAR encephalitis. Based on the pertinent literature, we categorized symptoms in: prodromal flu-like symptoms; behavioral/psychiatric symptoms; movement disorder; speech disturbances/aphasia; psychomotor agitation; paroxysmal spells/epileptic seizures; consciousness disturbances/unresponsiveness/bed ridden/catatonia; autonomic instability.

2.4. Immune therapy

First-line immune therapy was defined as steroids, intravenous immunoglobulin (IVIG) and/or PE; second-line immune therapy included cyclophosphamide, rituximab, mycophenolate mofetil, azathioprine, methotrexate or other. Timing of initiation of immune therapy with respect to disease onset was registered, when explicitly reported in the original papers or when it could be inferred with a certain degree of confidence from the available data.

To enable comparison between treatment strategies involving PE, these were categorized according to the timing of PE compared to other first-line immune therapies (PE as first treatment; PE after steroids; PE after IVIG; PE after steroids and IVIG), and to the overall first-line immune therapy strategy, regardless of the order (PE + steroids + IVIG; PE + steroids; PE + IVIG; PE only). We defined the time point for "early" immune therapy as $\leq$30 days, in order to split the literature cohort in two similar sized subgroups – similar time thresholds have been used in other previous studies of autoimmune encephalitis [5–7].

2.5. Outcome

Based on the explicit comments of the authors, or to the best of our interpretation of the case description, clinical response to treatment in three major categories was performed by MN: full/substantial recovery (modified Rankin Scale (mRS) 0–2, asymptomatic or only mild deficits), similarly to the "good outcome" category used in one of the major studies on treatment in this condition [8]; partial improvement (mRS 3, moderate impairments); and limited/no improvement (mRS 4–6, severe deficits or death). Outcome was assessed at three different time stages: immediately after PE (regardless of the administration of other therapies), after completion of all first-line treatments, and at last available follow-up.

The clinical outcome was evaluated with respect to overall first-line immune therapy strategy, use of

second-line immune therapy, and timing of initiation of immune therapy (any) and of PE.

3. Results

3.1. Literature cohort

The literature search led to the identification of 71 articles meeting inclusion criteria, published between January 2007 and December 2015 (literature search updated to 31.12.2015), reporting a total of 242 children treated with PE for anti-NMDAR encephalitis ('literature cohort') [7–77] (Supplementary Table 1). The number of published patients treated with PE for anti–NMDAR encephalitis has increased over the years: 18 in the years 2007–2009, 28 in the years 2010–2012, and 196 in the years 2013–2015.

Most of these articles are case reports describing a restricted number of patients treated with PE (mean 3.4 patients per article, median 1, range 1–50). In particular, 45 of the articles describe only 1 case, 20 articles describe 2–9 cases, and only 6 of the articles are series reporting more than 10 cases treated with PE. In this latter group of larger series [7,8,10,41,54,76], the structure of the article did not allow access to specific data for each patient, therefore a considerable amount of information could not be retrieved. This also occurred in some of the papers reporting a smaller number of patients [20,34,38,72,75]. Therefore, in several cases data was available only in a limited proportion of the total cohort, and the number of cases with available data was specified in brackets.

3.2. Demographics and clinical features

In the patients with available data, female gender was prevalent (93/127, 73.2%), and mean age at disease onset was 10.6 years (median 12, range 1–18; data calculated in 125/242). All symptom categories were frequently represented, with the most frequent ones being behavioral or psychiatric disturbances (117/126, 92.8%), movement disorder (110/120, 91.7%), epileptic or non-epileptic paroxysm (100/119, 84%) and speech disturbances (79/116, 68.1%). Unresponsive phase/catatonia was reported in 58.8% (70/119), and autonomic instability in 50.8% (61/120). Prodromal symptoms were described in 25.5% (26/102), and 3.7% of patients (9/242) had a preceding episode of herpes simplex encephalitis [44,49,53,54,61,62,64]. Tumor was detected in 21.9% of patients with available data (35/160). Patients with tumor were older (mean age 14.9 years, median 16, range 2–18; data available in 19/35 patients with tumor), than patients without tumor (mean age 9.6 years, median 10, range 1–18; data available in 81/120 patients without tumor), and a higher proportion of females had tumor than males (17/75, 22.7% vs. 2/31, 6.4%). Further data on the patients included in the literature cohort are provided in Supplementary Table 1.

3.3. Treatment

Data on treatment in the literature cohort are detailed in Table 1.

3.4. Time from disease onset to initiation of immune therapy

In the patients with available data, first immune therapy (any) was initiated $\leqslant$30 days from disease onset in 57.1% of the cases (36/63). According to available information, mean time to initiation of first immune therapy (any) was 27.5 days (median 21, range 0–190, data available in 37/242 patients).

3.5. Overall first-line immune therapy

According to the inclusion criteria, all patients received PE. The most common combination of first-line immune therapies (regardless of the order of administration) was the association of PE with steroids and IVIG (89/128, 69.5%), followed by the association of PE with steroids only (23/128, 18%) (Table 1).

3.6. Order of PE compared to other first-line immune therapies and to second-line immune therapy

In 54.6% of cases, PE was performed as third treatment, after steroids and IVIG (65/119), in 31.1% as second treatment after steroids (28/119, 23.5%) or after IVIG (9/119, 7.6%), and in a minority of patients as first treatment (17/119, 14.3%). In the great majority of cases, PE was done before initiation of any second-line immune therapies (107/117, 91.4%), but in 10 patients it was done after rituximab, cyclophosphamide, mycophenolate mofetil or interferon-β (10/117, 8.5%) (in 3/10 PE was performed after a subsequent relapse).

3.7. Number of PE exchanges

In the few patients with available data, mean number of PE exchanges was 7.3 (median 6, range 3–21).

3.8. Second-line immune therapy

The majority of patients received second-line immune therapy (100/139, 71.9%). In most cases, this consisted of rituximab (26/82, 31.7%), cyclophosphamide (14/82, 17.1%), or the combination of the two (20/82, 24.4%). Other medications administered were mycophenolate mofetil, azathioprine, methotrexate and interferon-β (Table 1). 41.5% of patients received two or more second-line immune therapies (34/82).

Table 1
Treatment in the literature cohort: time to initiation of immune therapy, first-line immune therapy strategy, number of PE sessions, order of PE compared to other first-line immune therapies and to second-line treatments, and second-line immune therapies.

Treatment		
Time from disease onset to immune therapy		
Initiation of immune therapy (any) before or after 30 days from onset (data in 63/242)		
	⩽30 days	36/63 (57.1%)
	>30 days	27/63 (42.8%)
Time from disease onset to initiation of first immune therapy (any) (data in 37/242)		Mean 27.5 days (median 21, range 0–190)
Time from disease onset to initiation of PE (data in 33/242)		Mean 46.4 days (median 34, range 0–200)
First-line immune therapy		
Overall first-line immune therapy strategy (data in 128/242)		
	PE + Steroids + IVIG (any order)	89/128 (69.5%)
	PE + Steroids (any order)	23/128 (18%)
	PE + IVIG (any order)	9/128 (7%)
	PE only	7/128 (5.5%)
Data on PE		
Number of exchanges (data available in 62/242)		Mean 7.3 (median 6, range 3–21)
Order of PE compared to other first-line immune therapies (data in 119/242)		
	PE as third treatment after Steroids and IVIG	65/119 (54.6%)
	PE as second treatment after Steroids or IVIG	Steroids: 28/119 (23.5%); IVIG: 9/119 (7.6%)
	PE as first treatment	17/119 (14.3%)
Order of PE compared to second-line immune therapies (data in 117/242)		
	PE before initiation of second-line treatments	107/117 (91.4%)
	PE after initiation of second-line treatments	10/117 (8.5%)
Second-line immune therapy		
Second-line immune therapy (data in 139/242)		100/139 (71.9%)
⩾2 second-line immune therapies (data in 82/100)		34/82 (41.5%)
Type of second-line immune therapy (data in 82/100)		
	Rituximab only	26/82 (31.7%)
	Cyclophosphamide + rituximab (any order)	20/82 (24.4%)
	Cyclophosphamide only	14/82 (17.1%)
	Mycophenolate mofetil only	6/82 (7.3%)
	Cyclophosphamide + mycophenolate mofetil (any order)	3/82 (3.6%)
	Cyclophosphamide + rituximab + azathioprine (any order)	3/82 (3.6%)
	Mycophenolate mofetil + rituximab (any order)	3/82 (3.6%)
	Azathioprine only	2/82 (2.4%)
	Rituximab + methotrexate (any order)	2/82 (2.4%)
	Cyclophosphamide + rituximab + mycophenolate mofetil (any order)	1/82 (1.2%)
	Interferon-β + cyclophosphamide (any order)	1/82 (1.2%)
	Rituximab + cyclophosphamide + methotrexate (any order)	1/82 (1.2%)

IVIG: intravenous immunoglobulin; PE: plasma exchange.

3.9. Outcome

With the limitations imposed by the availability of information and the restricted number of cases, data on the clinical outcome in the literature cohort are detailed in Table 2.

3.10. Overall clinical outcome

Full/substantial recovery or partial improvement immediately after PE compared to pre-PE status was reported in 63.5% (33/52) of patients. The rate of full/substantial recovery showed a steady rise along the time

Table 2
Clinical outcome in the study population at different time stages and according to the presence of tumor, first-line immune therapy strategy, second-line immune therapy, time of initiation of immune therapy and of PE.

Clinical outcome				Mean (median) length of follow-up (months)
Clinical outcome at different time stages				
	Full/substantial recovery	Partial improvement	Limited/no improvement	Follow-up
Immediately after PE (data in 52/242)	11/52 (21.1%)	22/52 (42.3%)	19/52 (36.5%)	
After first-line immune therapy (data in 62/242)	15/62 (24.1%)	29/62 (46.8%)	18/62 (29%)	
At last follow-up (data in 120/242)	77/120 (64.2%)	33/120 (27.5%)	10/120 (8.3%)**	18.5 (12) (range 1.7-120, data in 102/120)
Clinical outcome at last follow-up according to the presence of tumor				
	Full/substantial recovery	Partial improvement	Limited/no improvement	Follow-up
Patients without tumor (data in 87/125)	56/87 (64.4%)	26/87 (29.9%)	5/87 (5.7%)	21 (17) (data in 70/87)
Patients with tumor (data in 19/35)	11/19 (57.9%)	4/19 (21%)	4/19 (21%)*	13.1 (8) (data in 19/19)
Clinical outcome at last follow-up according to overall first-line immune therapy strategy				
	Full/substantial recovery	Partial improvement	Limited/no improvement	Follow-up#
PE + Steroids + IVIG (any order) (data in 82/89)	55/82 (67.1%)	20/82 (24.4%)	7/82 (8.5%)**	19.5 (12) (data in 72/82)
PE + Steroids (any order) (data in 23/23)	15/23 (65.2%)	7/23 (30.4%)	1/23 (4.3%)	16.3 (8) (data in 21/23)
PE + IVIG (any order) (data in 8/9)	4/8 (50%)	3/8 (37.5%)	1/8 (12.5%)	23 (24) (data in 3/8)
PE only (data in 7/7)	3/7 (42.8%)	3/7 (42.8%)	1/7 (14.3%)	12 (9.5) (data in 6/7)
Clinical outcome at last follow-up according to second-line immune therapy				
	Full/substantial recovery	Partial improvement	Limited/no improvement	Follow-up
First-line only immune therapy (data in 37/39)	24/37 (64.9%)	11/37 (29.7%)	2/37 (5.4%)*	17.2 (9.5) (data in 32/37)
First + second-line immune therapy (data in 83/100)	53/83 (63.8%)	22/83 (26.5%)	8/83 (9.6%)*	19.1 (12) (data in 70/83)
Clinical outcome at last follow-up according to time of initiation of immune therapy				
	Full/substantial recovery	Partial improvement	Limited/no improvement	Follow-up
First immune therapy $\leqslant$ 30 days (data in 36/36)	25/36 (69.4%)	4/36 (11.1%)	7/36 (19.4%)	12.3 (8) (data in 29/36)
First immune therapy > 30 days (data in 27/27)	16/27 (59.2%)	10/27 (32.2%)	1/27 (3.2%)	14.7 (8.5) (data in 22/27)
Clinical outcome at last follow-up according to time of initiation of PE				
	Full/substantial recovery	Partial improvement	Limited/no improvement	Follow-up
Initiation of PE $\leqslant$ 30 days (data in 15/15)	12/15 (80%)	1/15 (6.7%)	2/15 (13.3%)	13 (10) (data in 13/15)
Initiation of PE > 30 days (data in 18/18)	11/18 (61.1%)	7/18 (38.9%)	0/18 (0%)	8.9 (6) (data in 17/18)

f-u: follow-up; IVIG: intravenous immunoglobulin; PE: plasma exchange.

* One of these patients had died at last follow-up.

** Two of these patients had died at last follow-up.

Length of follow-up in the patients who received steroids and PE (with or without IVIG): mean 19.2 months, median 12, range 1.7–120; data in 89/101). Length of follow-up in the patients who received IVIG and PE or PE only: mean 15.7, median 12, range 5–36; data in 9/15).

stages, from immediately after PE (11/52, 21.1%) to the last follow-up (77/120, 64.2%). The overall outcome at last follow-up was slightly better in the patients without tumor than in those with tumor, with longer follow-up in the patients without tumor (Table 2).

3.11. Clinical outcome at last follow-up according to overall first-line immune therapy strategy

A trend towards a higher rate of full/substantial recovery at follow-up was observed with first-line immune therapy strategy (regardless of the order of administration) consisting of PE, steroids and IVIG (55/82, 67.1%), or PE and steroids (15/23, 65.2%), compared to PE and IVIG (4/8, 50%) or PE alone (3/7, 42.8%) (similar median length of follow-up) (Table 2).

3.12. Clinical outcome at last follow-up according to second-line immune therapy

Patients who received second-line immune therapies had similar rates of full/substantial recovery to patients treated with first-line immune therapy only (53/83, 63.8%, vs. 24/37, 64.9%), with similar length of follow-up (Table 2).

3.13. Clinical outcome at last follow-up according to time of initiation of first-line immune therapy (any) and of PE

A higher rate of full/substantial recovery at last follow-up occurred in patients in whom immune therapy was started within a month from disease onset (25/36, 69.4%) as opposed to patients in whom it was started later (16/27, 59.2%) (Table 2) (with similar length of follow-up). Similar trends were observed as regards the timing of initiation of PE (12/15, 80%, vs. 11/18, 61.1%, respectively) (length of follow-up slightly longer in the group who received PE early).

3.14. Adverse reactions to PE

Significant side effects to PE were described only in 6 cases, and consisted of transient hypotensive episodes responding to either a fluid bolus or a vasopressor treatment in 2 patients [22], anaphylactic reaction in 1 patient [51], worsening of autonomic instability resulting in hypotensive shock in 1 patient [67], and pulmonary artery thromboembolism in 1 patient [65] (in 1 case, PE had to be stopped due to nontolerance, but the type of reaction was not described [53]).

4. Discussion

In the absence of definite guidelines on the treatment of pediatric anti-NMDAR encephalitis, we conducted a literature review with the aim of clarifying the most frequent modalities of use of PE in this condition and the most effective protocols as regards the association with other immune therapies and the relative timing.

Our results show that schemes of utilization of PE are greatly heterogeneous in the literature; though, we observed that in the majority of cases PE is used after steroids and IVIG. In the cases with available information, our data seem to suggest a better outcome at follow-up in patients in whom first-line immune therapy consisted of the association of PE with steroids (with or without IVIG), as opposed to other treatment strategies without steroids, possibly supporting a role of the combination of immune therapies with peripheral and central action. The potential role for antibody removal via PE in anti-NMDAR encephalitis is supported by the direct pathogenic role of anti-NMDAR antibodies [2,3]. Though, since the production of antibodies occurs intrathecally in this disease [78], the removal of antibodies from the peripheral circulation via PE, while altering peripheral immunology and possibly reducing to a certain extent the traffic of antibody and lymphocytes into the central nervous system, should also be associated with other therapies that modify the intrathecal immune disease, such as steroids. However, in the subgroup of patients who received PE and steroids, the possibility that better outcome primarily due to steroids (rather than PE) cannot be excluded.

Of primary importance in clinical practice, our results also seem to point to the role of early initiation of immune therapy in favoring a better outcome. Data in the literature on this and other autoimmune encephalitis are consistent with these observations [5,7,8,22,72,78–80]. The possibility of a better outcome with early immune therapy should encourage a high level of suspicion towards this condition, whose prompt recognition may be challenging in view of its rarity and of its sometimes subtle and variegated initial features, in order to promote early diagnosis and initiation of therapy.

Previous data in the literature support the role of second-line immune therapy in terms of improvement of the neurological outcome and of reduction of subsequent relapses [8,80], even though in our review the outcome was similar in patients who received second-line treatments or not. This may be possibly ascribed to a severity bias, with predominant use of second-line immune therapies in more severe patients.

PE was administered after second-line immune therapy only in a small proportion of the cases included in our literature review, sometimes to treat a relapse, or as a last resource in severe cases not responding to other treatments. This may at least partly reflect the lack of available evidence on PE efficacy and safety and the absence of definite guidelines in pediatric anti-NMDAR encephalitis.

Reflecting the complexity of the general picture and the natural history of anti-NMDAR encephalitis, it

should be noted that this condition may have different degrees of clinical severity, and a spontaneous gradual and slow recovery may occur in the course of several months [8]. In our study, the rate of full recovery was remarkably higher at last follow-up as opposed to the previous stages of disease (after PE and after first-line therapy), possibly reflecting these observations and the crucial role of time in the recovery from this condition.

Overall, a considerable number of published patients treated with PE were identified, mostly derived from case reports, small case series and only few larger series. We observed that the number of published pediatric cases of anti-NMDAR encephalitis treated with PE has been rising steadily; though, the proportion of use of PE compared to other immune interventions cannot be estimated in the present work.

Despite the general characteristics of the literature cohort studied are in overall agreement with the pertinent pediatric literature, a relatively high rate of tumor was reported in this cohort, similar to that reported in adult cases [8,10,34]. A reporting bias in the original reports may at least partly explain this observation, with data on the presence of tumor explicitly reported more frequently than its absence. Similarly to what observed by other authors, patients with tumor were older than those without, and had a higher proportion of females. In the patients without tumor, the overall outcome at last follow-up was slightly better than the oncologic cases, in contrast with the literature stating that tumor patients generally do better [21,81]; whether this may be ascribed to the use of PE is not clear, since our study did not include literature on patients not treated with PE.

The main limitation of the present study is the restricted number of patients, largely dependent on the relative rarity of this condition in children and the availability of information as reported in the original articles. In relation to this, certain aspects relative to the treatment with PE, such as side effects, were subject to reporting bias and were likely under-reported, and could not be fully evaluated. As pointed out by other authors, PE in children presents unique challenges and higher complication rates compared to adults, especially in patients who are poorly cooperative or have autonomic instability, and should therefore be performed in specialized centers [1,64,66,82]. On the other hand, research on PE use in other conditions suggests a relatively safe profile also in the pediatric age [83,84]. Further studies specifically investigating PE safety in children with anti-NMDAR encephalitis are warranted.

The outcome in our study was evaluated retrospectively by one of the authors, representing a methodological limitation to our work – multiple raters would have strengthened the data. In a recent pediatric case series from the United Kingdom [75], 89% (8/9) patients who received PE during their initial treatment made a full eventual recovery compared with 47% receiving IVIG and steroids. Similarly, compelling preliminary data from another recent retrospective review comparing intravenous methylprednisolone and PE suggested that corticosteroids may not be as effective compared to steroids followed by PE [85]. Despite these recent papers, data specifically comparing the outcome in subgroups of patients receiving PE are generally lacking in the literature and would be of high clinical importance – this aspect could not be addressed in our study due to the selection criteria including only patients who received PE, and represents one of the main limitations of our work.

Despite the fact that we tried to avoid duplication when the same patient reported in different articles was clearly identifiable, we cannot exclude the possibility that duplication of cases may have inadvertently occurred in a few instances, though possibly in a limited number of cases.

In conclusion, treatment with PE has been reported in increasing numbers recently in pediatric anti-NMDAR encephalitis; though, its extent of utilization, timing, and therapeutic protocols vary greatly. Stronger scientific evidence on the added clinical value of PE is warranted. Our literature review, conducted only on patients receiving PE, suggests improved efficacy of PE when used with steroids, and confirms other data in the literature reporting a positive role of early commencement of immune therapy in autoimmune encephalitis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.braindev.2016.01.009.

References

[1] Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63–74.
[2] Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8.
[3] Moscato EH, Peng X, Jain A, Parsons TD, Dalmau J, Balice-Gordon RJ. Acute mechanisms underlying antibody effects in anti-N-methyl-D-aspartate receptor encephalitis. Ann Neurol 2014;76:108–19.
[4] Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the writing committee of the American society for apheresis: the sixth special issue. J Clin Apher 2013;28:145–284.
[5] Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 2010;133:1655–67.

[6] Shin YW, Lee ST, Shin JW, Moon J, Lim JA, Byun JI, et al. VGKC-complex/LGI1-antibody encephalitis: clinical manifestations and response to immunotherapy. J Neuroimmunol 2013;265:75–81.
[7] Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 2014;83:142–50.
[8] Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–65.
[9] Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25–36.
[10] Seki M, Suzuki S, Iizuka T, Shimizu T, Nihei Y, Suzuki N, et al. Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry 2008;79:324–6.
[11] Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66:11–8.
[12] Schimmel M, Bien CG, Vincent A, Schenk W, Penzien J. Successful treatment of anti-N-methyl-D-aspartate receptor encephalitis presenting with catatonia. Arch Dis Child 2009;94:314–6.
[13] Agrawal S, Vincent A, Jacobson L, Milford D, Gupta R, Wassmer E. Successful treatment of anti N-methyl-D-aspartate receptor limbic encephalitis in a 22-monthold child with plasmapheresis and pharmacological immunomodulation. Arch Dis Child 2010;95:312.
[14] Kruer MC, Koch TK, Bourdette DN, Chabas D, Waubant E, Mueller S, et al. NMDA receptor encephalitis mimicking seronegative neuromyelitis optica. Neurology 2010;74:1473–5.
[15] Schmiedeskamp M, Cariga P, Ranta A. Anti-NMDA-receptor autoimmune encephalitis without neoplasm: a rare condition? N Z Med J 2010;123:67–71.
[16] Sonn TS, Merritt DF. Anti-NMDA-receptor encephalitis: an adolescent with an ovarian teratoma. J Pediatr Adolesc Gynecol 2010;23:e141–4.
[17] Consoli A, Ronen K, An-Gourfinkel I, Barbeau M, Marra D, Costedoat-Chalumeau N, et al. Malignant catatonia due to anti-NMDA-receptor encephalitis in a 17-year-old girl: case report. Child Adolesc Psychiatry Ment Health 2011;5:15.
[18] Gataullina S, Plouin P, Vincent A, Scalais E, Nuttin C, Dulac O. Paroxysmal EEG pattern in a child with N-methyl-D-aspartate receptor antibody encephalitis. Dev Med Child Neurol 2011;53:764–7.
[19] Greiner H, Leach JL, Lee KH, Krueger DA. Anti-NMDA receptor encephalitis presenting with imaging findings and clinical features mimicking Rasmussen syndrome. Seizure 2011;20:266–70.
[20] Hollódy K, Csábi G, Láng A, Rózsai B, Komáromy H, Bors L, et al. Anti-NMDA-receptor encephalitis: description of the syndrome in connection with the first Hungarian patient (in Hungarian). Ideggyogy Sz 2011;64:119–25.
[21] Mirza MK, Pogoriler J, Paral K, Ananthanarayanan V, Mandal S, Mazin A, et al. Adjunct therapeutic plasma exchange for anti-N-methyl-D-aspartate receptor antibody encephalitis: a case report and review of literature. J Clin Apher 2011;26:362–5.
[22] Pham HP, Daniel-Johnson JA, Stotler BA, Stephens H, Schwartz J. Therapeutic plasma exchange for the treatment of anti-NMDA receptor encephalitis. J Clin Apher 2011;26:320–5.
[23] Taguchi Y, Takashima S, Takano S, Mori H, Tanaka K. A case of anti-N-methyl-D-aspartate receptor encephalitis with ovarian teratoma showing excellent recovery with decreasing of anti-N-methyl-D-aspartate receptor antibody (in Japanese). Rinsho Shinkeigaku 2011;51:499–504.
[24] Tamma PD, Agwu AL, Hartman AL. Behavior outbursts, orofacial dyskinesias, and CSF pleocytosis in a healthy child. Pediatrics 2011;128:e242–5.
[25] Sameshima A, Hidaka T, Shima T, Nakashima A, Hasegawa T, Saito S. Anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian immature teratoma. J Obstet Gynaecol Res 2011;37:1883–6.
[26] Bseikri MR, Barton JR, Kulhanjian JA, Dalmau J, Cohen RA, Glaser CA, et al. Anti-N-methyl D-aspartate receptor encephalitis mimics viral encephalitis. Pediatr Infect Dis J 2012;31:202–4.
[27] Frawley KJ, Calvo-Garcia MA, Krueger DA, McMasters RL. 'Benign' ovarian teratoma and N-methyl-D-aspartate receptor (NMDAR) encephalitis in a child. Pediatr Radiol 2012;42:120–3.
[28] Houtrow AJ, Bhandal M, Pratini NR, Davidson L, Neufeld JA. The rehabilitation of children with anti-N-methyl-D-aspartate-receptor encephalitis: a case series. Am J Phys Med Rehabil 2012;91:435–41.
[29] Kashyape P, Taylor E, Ng J, Krishnakumar D, Kirkham F, Whitney A. Successful treatment of two paediatric cases of anti-NMDA receptor encephalitis with cyclophosphamide: the need for early aggressive immunotherapy in tumour negative paediatric patients. Eur J Paediatr Neurol 2012;16:74–8.
[30] Kataoka H, Takatani T, Ueno S. Low-voltage EEG activity presenting from psychotic stage in a patient with anti-NMDA receptor encephalitis. BMJ Case Rep 2012;2012 (pii: bcr2012007045).
[31] Mann A, Machado NM, Liu N, Mazin AH, Silver K, Afzal KI. A multidisciplinary approach to the treatment of anti-NMDA-receptor antibody encephalitis: a case and review of the literature. J Neuropsychiatry Clin Neurosci 2012;24:247–54.
[32] Nunez-Enamorado N, Camacho-Salas A, Belda-Hofheinz S, Cordero-Castro C, Simon-De Las Heras R, Saiz-Diaz R, et al. Fast and spectacular clinical response to plasmapheresis in a paediatric case of anti-NMDA encephalitis (in Spanish). Rev Neurol 2012;54:420–4.
[33] Slettedal IÖ, Dahl HM, Sandvig I, Dalmau J, Strømme P. Young girl with psychosis, cognitive failure and seizures. Tidsskr Nor Laegeforen 2012;132:2073–6.
[34] Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr 2013;162(850–6):e2.
[35] Baizabal-Carvallo JF, Stocco A, Muscal E, Jankovic J. The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Mov Disord 2013;28:543–7.
[36] Finné Lenoir X, Sindic C, van Pesch V, El Sankari S, de Tourtchaninoff M, Denays R, et al. Anti-N-methyl-D-aspartate receptor encephalitis with favorable outcome despite prolonged status epilepticus. Neurocrit Care 2013;18:89–92.
[37] Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti-N-methyl-D-aspartate receptor encephalitis. JAMA Neurol 2013;70:1133–9.
[38] Pérez E, Ruggieri V, Monges S, Loos M, Caraballo R, Yerga A, et al. Acute encephalitis anti-ionotropic glutamate receptor activated N-methyl-D-aspartate (NMDAR): analysis of eleven pediatric cases in Argentina (Benito Yelín Award) (in Spanish). Medicina (B Aires) 2013;73:1–9.
[39] van de Riet EH, Esseveld MM, Cuypers L, Schieveld JN. Anti-NMDAR encephalitis: a new, severe and challenging enduring entity. Eur Child Adolesc Psychiatry 2013;22:319–23.
[40] Verfaillie L, Bissay V, Vanderbruggen N, Van Eetvelde E, Honoré PM, Spapen H. An unusual case of acute psychosis in an adolescent. Acta Clin Belg 2013;68:138–9.
[41] Adang LA, Lynch DR, Panzer JA. Pediatric anti-NMDA receptor encephalitis is seasonal. Ann Clin Transl Neurol 2014;1:921–5.

[42] Appu M, Noetzel M. Clinically significant response to zolpidem in disorders of consciousness secondary to anti-N-methyl-D-aspartate receptor encephalitis in a teenager: a case report. Pediatr Neurol 2014;50:262–4.
[43] Barros P, Brito H, Ferreira PC, Ramalheira J, Lopes J, Rangel R, et al. Resective surgery in the treatment of super-refractory partial status epilepticus secondary to NMDAR antibody encephalitis. Eur J Paediatr Neurol 2014;18:449–52.
[44] Bektaş Ö, Tanyel T, Kocabaş BA, Fitöz S, Ince E, Deda G. Anti-N-methyl-D-aspartate receptor encephalitis that developed after herpes encephalitis: a case report and literature review. Neuropediatrics 2014;45:396–401.
[45] Ben Azoun M, Tatencloux S, Deiva K, Blanc P. Two pediatric cases of anti-NMDA receptor antibody encephalitis (in French). Arch Pediatr 2014;21:1216–9.
[46] Byrne S, McCoy B, Lynch B, Webb D, King MD. Does early treatment improve outcomes in N-methyl-D-aspartate receptor encephalitis? Dev Med Child Neurol 2014;56:794–6.
[47] Chakrabarty B, Tripathi M, Gulati S, Yoganathan S, Pandit AK, Sinha A, et al. Pediatric anti-N-methyl-D-aspartate (NMDA) receptor encephalitis: experience of a tertiary care teaching center from north India. J Child Neurol 2014;29:1453–9.
[48] Cohen AL, Wong-Kisiel LC. Case of a two-year-old boy with recurrent seizures, abnormal movements, and central hypoventilation. Semin Pediatr Neurol 2014;21:114–8.
[49] Desena A, Graves D, Warnack W, Greenberg BM. Herpes simplex encephalitis as a potential cause of anti-N-methyl-D-aspartate receptor antibody encephalitis: report of 2 cases. JAMA Neurol 2014;71:344–6.
[50] DeSena AD, Greenberg BM, Graves D. Three phenotypes of anti-N-methyl-D-aspartate receptor antibody encephalitis in children: prevalence of symptoms and prognosis. Pediatr Neurol 2014;51:542–9.
[51] Guo YH, Kuan TS, Hsieh PC, Lien WC, Chang CK, Lin YC. Rehabilitation for a child with recalcitrant anti-N-methyl-D-aspartate receptor encephalitis: case report and literature review. Neuropsychiatr Dis Treat 2014;10:2263–7.
[52] Hayashi M, Motegi E, Honma K, Masawa N, Sakuta H, Hirata K, et al. Successful laparoscopic resection of 7 mm ovarian mature cystic teratoma associated with anti-NMDAR encephalitis. Case Rep Obstet Gynecol 2014;2014:618742.
[53] Hacohen Y, Deiva K, Pettingill P, Waters P, Siddiqui A, Chretien P, et al. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. Mov Disord 2014;29:90–6.
[54] Hacohen Y, Absoud M, Hemingway C, Jacobson L, Lin JP, Pike M, et al. NMDA receptor antibodies associated with distinct white matter syndromes. Neurol Neuroimmunol Neuroinflamm 2014;1:e2.
[55] Le Moigno L, Ternant D, Paintaud G, Thibault G, Cloarec S, Tardieu M, et al. N-methyl-D-aspartate receptor antibody encephalitis: value of immunomodulatory therapy. Arch Pediatr 2014;21:620–3.
[56] Salvucci A, Devine IM, Hammond D, Sheth RD. Pediatric anti-NMDA (N-methyl D-Aspartate) receptor encephalitis. Pediatr Neurol 2014;50:507–10.
[57] Sommeling C, Santens P. Anti-N-methyl-D-aspartate (anti-NMDA) receptor antibody encephalitis in a male adolescent with a large mediastinal teratoma. J Child Neurol 2014;29:688–90.
[58] Titulaer MJ, Höftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, et al. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. Ann Neurol 2014;75:411–28.
[59] Venâncio P, Brito MJ, Pereira G, Vieira JP. Anti-N-methyl-D-aspartate receptor encephalitis with positive serum antithyroid antibodies, IgM antibodies against mycoplasma pneumoniae and human herpesvirus 7 PCR in the CSF. Pediatr Infect Dis J 2014;33:882–3.
[60] Almuslamani A, Mahmood F. First Bahraini adolescent with anti-NMDAR-Ab encephalitis. Qatar Med J 2015;2015:2.
[61] Armangue T, Moris G, Cantarín-Extremera V, Conde CE, Rostasy K, Erro ME, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. Neurology 2015;85:1736–43.
[62] Bamford A, Crowe BH, Hacohen Y, Lin JP, Clarke A, Tudor-Williams G, et al. Pediatric herpes simplex virus encephalitis complicated by N-Methyl-D-aspartate receptor antibody encephalitis. J Pediatric Infect Dis Soc 2015;4:e17–21.
[63] Cleland N, Lieblich S, Schalling M, Rahm C. A 16-year-old girl with anti-NMDA-receptor encephalitis and family history of psychotic disorders. Acta Neuropsychiatr 2015;27:375–9.
[64] Ellul MA, Griffiths MJ, Iyer A, Avula S, Defres S, Baborie A, et al. Anti-N-methyl-D-aspartate receptor encephalitis in a young child with histological evidence on brain biopsy of coexistent herpes simplex virus type 1 infection. Pediatr Infect Dis J 2015;35:347–9.
[65] Kramina S, Kevere L, Bezborodovs N, Purvina S, Rozentals G, Strautmanis J, et al. Acute psychosis due to non-paraneoplastic anti-NMDA-receptor encephalitis in a teenage girl: case report. Psych J 2015;4:226–30.
[66] Lagarde S, Lepine A, Caietta E, Pelletier F, Boucraut J, Chabrol B, et al. Cerebral 18FluoroDeoxy-Glucose Positron Emission Tomography in paediatric anti N-methyl-D-aspartate receptor encephalitis: a case series. Brain Dev 2016;38:461–70.
[67] Miyauchi A, Monden Y, Osaka H, Takahashi Y, Yamagata T. A case of anti-NMDAR encephalitis presented hypotensive shock during plasma exchange. Brain Dev 2016;38:427–30.
[68] Mohammad SS, Jones H, Hong M, Nosadini M, Sharpe C, Pillai SC, et al. Symptomatic treatment of children with anti-NMDAR encephalitis. Dev Med Child Neurol 2015. http://dx.doi.org/10.1111/dmcn.12882 (in press).
[69] Nosadini M, Boniver C, Zuliani L, de Palma L, Cainelli E, Battistella PA, et al. Longitudinal electroencephalographic (EEG) findings in pediatric anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis: the Padua experience. J Child Neurol 2015;30:238–45.
[70] Reilly-Shapiro C, Fendrick S. Anti-NMDA receptor encephalitis: a case study of recovery through art. J Pediatr Health Care 2016;30:78–83.
[71] Sands TT, Nash K, Tong S, Sullivan J. Focal seizures in children with anti-NMDA receptor antibody encephalitis. Epilepsy Res 2015;112:31–6.
[72] Sartori S, Nosadini M, Cesaroni E, Falsaperla R, Capovilla G, Beccaria F, et al. Paediatric anti-N-methyl-D-aspartate receptor encephalitis: the first Italian multicenter case series. Eur J Paediatr Neurol 2015;19:453–63.
[73] Scharko AM, Panzer J, McIntyre CM. Treatment of delirium in the context of anti-N-methyl-D-aspartate receptor antibody encephalitis. J Am Acad Child Adolesc Psychiatry 2015;54:233–4.
[74] Tatencloux S, Chretien P, Rogemond V, Honnorat J, Tardieu M, Deiva K. Intrathecal treatment of anti-N-Methyl-D-aspartate receptor encephalitis in children. Dev Med Child Neurol 2015;57:95–9.
[75] Wright S, Hacohen Y, Jacobson L, Agrawal S, Gupta R, Philip S, et al. N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. Arch Dis Child 2015;100:521–6.
[76] Zekeridou A, Karantoni E, Viaccoz A, Ducray F, Gitiaux C, Villega F, et al. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. J Neurol 2015;262:1859–66.
[77] Zubkov S, Aggarwal Joshi P, Shepherd TM, Kothare SV. Teaching NeuroImages: NMDA encephalomyelitis with MRI

abnormalities isolated to ventral spinal cord gray matter. Neurology 2015;85:e55–6.
[78] Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 2011;77:589–93.
[79] Byrne S, Walsh C, Hacohen Y, Muscal E, Jankovic J, Stocco A, et al. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. Neurol Neuroimmunol Neuroinflamm 2015;2:e130.
[80] Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother 2015:1–29.
[81] Vincent A, Bien CG. Anti-NMDA-receptor encephalitis: a cause of psychiatric, seizure, and movement disorders in young adults. Lancet Neurol 2008;7:1074–5.
[82] Michon B, Moghrabi A, Winikoff R, Barrette S, Bernstein ML, Champagne J, et al. Complications of apheresis in children. Transfusion 2007;47:1837–42.
[83] Kim YA, Sloan SR. Pediatric therapeutic apheresis: rationale and indications for plasmapheresis, cytapheresis, extracorporeal photopheresis, and LDL apheresis. Pediatr Clin North Am 2013;60:1569–80.
[84] De Silvestro G, Tison T, Vicarioto M, Bagatella P, Stefanutti C, Marson P. The Italian Registry of Pediatric Therapeutic Apheresis: a report on activity during 2005. J Clin Apher 2009;24:1–5.
[85] DeSena AD, Noland DK, Matevosyan K, King K, Phillips L, Qureshi SS, et al. Intravenous methylprednisolone versus therapeutic plasma exchange for treatment of anti-N-methyl-D-aspartate receptor antibody encephalitis: a retrospective review. J Clin Apher 2015;30:212–6.

Supplementary material

Supplementary Table 1

Authors, year [reference] (nº of reported children with anti-NMDAR encephalitis treated with PE)	Sex	Age (years)	Prodromal cold or viral-like symptoms	Behaviour / Psychiatric disorder	Movement disorder	Speech problems	Epileptic seizures / Paroxysmal episodes	Unresponsive phase / Catatonia	Autonomic instability	Tumour (type if available)	Anti-NMDAR antibodies
Dalmau et al, 2007 [9] (2 cases)	F	17	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (OT)	Positive in serum and CSF
	F	14	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (OT)	Positive in serum and CSF
Seki et al, 2008 [10] (1 case)	F	18	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (OT)	Positive in serum and CSF
Florance et al, 2009 [11] (14 cases)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Positive in CSF and/or serum*
Schimmel et al, 2008 [12] (1 case)	F	12	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
Agrawal et al, 2010 [13] (1 case)	F	1.8	No	Yes	Yes	Yes	Yes	Yes	Yes	No	NR
Kruer et al, 2010 [14] (1 case)	F	15	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in CSF, negative in serum
Schmiedeskamp et al, 2010 [15] (1 case)	F	17	No	Yes	Yes	Yes	Yes	No	Yes	No	Positive in serum and CSF
Sonn et al, 2010 [16] (1 case)	F	14	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (OT)	Positive CSF (serum NR)
Consoli et al, 2011 [17] (1 case)	F	17	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
Gataullina et al, 2011 [18] (1 case)	M	8	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
Greiner et al, 2011 [19] (1 case)	F	11	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (OT)	Positive in CSF, negative in serum
Hollódy et al, 2011 [20] (1 case)	F	15	NR	NR	NR	NR	NR	NR	NR	No	NR
Mirza et al, 2011 [21] (1 case)	F	14	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in CSF, negative in serum
Pham et al, 2011 [22] (3 cases)	F	18	Yes	Yes	NR	NR	NR	Yes	NR	Yes (OT)	Positive in serum (CSF NR)
	F	17	No	Yes	NR	NR	Yes	NR	NR	Yes (OT)	Positive in serum (CSF NR)
	M	3	No	NR	NR	NR	NR	NR	NR	No	Positive in serum (CSF NR)
Taguchi et al, 2011 [23] (1 case)	F	17	NR	Yes	NR	NR	NR	NR	NR	Yes (OT)	Positive in serum and CSF
Tamma et al, 2011 [24] (1 case)	M	7	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
Sameshima et al, 2011 [25] (1 case)	F	17	Yes	Yes	No	No	No	Yes	No	Yes (OT)	Positive in serum (CSF NR)
Bseikri et al, 2012 [26] (2 cases)	F	15	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes (OT)	Positive in CSF (serum NR)
	F	9	No	Yes	Yes	Yes	Yes	No	No	No	Positive in CSF (serum NR)
Frawley et al, 2012 [27] (1 case)	F	11	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes (OT)	Positive in CSF, negative in serum
Houtrow et al, 2012 [28] (4 cases)	F	2	No	Yes	Yes	Yes	Yes	Yes	No	No	Positive in serum or CSF*
	M	9	No	Yes	Yes	Yes	No	Yes	Yes	No	Positive in serum or CSF*
	F	9	No	Yes	Yes	Yes	Yes	No	No	No	Positive in serum or CSF*
	F	15	No	Yes	No	Yes	Yes	Yes	No	Yes (OT)	Positive in serum or CSF*
Kashyape et al, 2012 [29] (2 cases)	F	2.3	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum (CSF NR)
	F	14	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum (CSF NR)
Kataoka et al, 2012 [30] (1 case)	F	17	NR	Yes	Yes	NR	Yes	NR	Yes	Yes (OT)	Positive in CSF (serum NR)
Mann et al, 2012 [31] (1 case)	F	14	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in CSF (serum NR)
Nunez-Enamorado et al, 2012 [32] (1 case)	M	2.5	NR	Yes	Yes	Yes	Yes	NR	Yes	No	Positive in serum or CSF*
Slettedal et al, 2012 [33] (1 case)	F	School age	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in CSF and serum

Armangue et al, 2013 [34] (3 cases)	NR	< 12	NR	NR	NR	NR	NR	NR	NR	No	Positive in CSF (serum NR)
	NR	12-18	NR	NR	NR	NR	NR	NR	NR	No	Positive in CSF (serum NR)
	NR	12-18	NR	NR	NR	NR	NR	NR	NR	No	Positive in CSF (serum NR)
Baizabal-Carvallo et al, 2013 [35] (3 cases)	F	13	No	Yes	Yes	No	Yes	No	Yes	No	Positive in serum and/or CSF*
	M	8	No	Yes	Yes	Yes	Yes	Yes	No	No	Positive in serum and/or CSF*
	F	8	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in CSF (serum NR)
Finné Lenoir et al, 2013 [36] (1 case)	M	17	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
Kayser et al, 2013 [37] (3 cases)	F	12	NR	Yes	NR	NR	NR	NR	NR	No	Positive in CSF, negative in serum
	F	13	NR	Yes	NR	NR	NR	NR	NR	No	Positive in CSF and serum
	F	17	NR	Yes	NR	NR	NR	NR	NR	No	Positive in CSF and serum
Pérez et al, 2013 [38] (2 cases)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Titulaer et al, 201 [8] (50 cases)	NR	NR	NR	NR	NR	NR	NR	NR	NR	34/50: No 16/50: Yes	NR
van de Riet et al, 2013 [39] (1 case)	F	17	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
Verfaillie et al, 2013 [40] (1 case)	NR	18	NR	Yes	Yes	NR	NR	Yes	Yes	No	Positive in serum or CSF*
Adang et al, 2014 [41] (20 cases)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Appu et al, 2014 [42] (1 case)	F	16	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes (OT)	Positive in CSF (serum NR)
Barros et al, 2014 [43] (1 case)	M	7	Yes	Yes	Yes	Yes	Yes	No	No	No	Positive in serum and CSF
Bektaş et al, 2014 [44] (1 case)	F^	1.7	No	Yes	Yes	No	No	No	No	No	Positive in serum and CSF
Ben Azoun et al, 2014 [45] (1 case)	F	12	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Positive in serum and CSF
Byrne et al, 2014 [46] (1 case)	F	11	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Positive in serum and CSF
Chakrabarty et al, 2014 [47] (3 cases)	F	10	NR	No	Yes	Yes	Yes	No	Yes	No	Positive in serum and CSF
	F	10	NR	No	Yes	No	Yes	No	No	No	Positive in serum and CSF
	F	5	NR	Yes	Yes	Yes	Yes	No	No	No	Positive in serum and CSF
Cohen et al, 2014 [48] (1 case)	M	2	No	Yes	Yes	Yes	Yes	No	Yes	No	Positive in CSF (serum NR)
Dale et al, 2014 [7] (11 cases)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Desena et al, 2014 [49] (1 case)	M^	Infant	No	No	Yes	Yes	Yes	Yes	No	No	Positive in CSF (serum NR)
DeSena et al, 2014 [50] (7 cases)	M	11	No	Yes	Yes	Yes	Yes	Yes	No	No	Positive in CSF (serum NR)
	M	4	No	Yes	Yes	Yes	Yes	No	No	No	Positive in serum (CSF NR)
	M	17	No	Yes	No	No	Yes	No	No	No	Positive in CSF, negative in serum
	F	4	No	Yes	Yes	No	Yes	No	No	No	Positive in serum (CSF NR)
	F	2	No	Yes	Yes	Yes	No	No	No	No	Positive in serum (CSF NR)
	M	2	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes (testicular tumor, detected after 4 years)	Positive in serum (CSF NR)
	F	5	No	No	Yes	Yes	Yes	Yes	No	No	Positive in serum and CSF
Guo et al, 2014 [51] (1 case)	F	3.1	NR	Yes	Yes	Yes	No	Yes	Yes	No	Positive in CSF (serum NR)
Hayashi et al, 2014 [52] (1 case)	F	18	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Positive in serum and CSF
Hacohen et al, 2014 [53] (1 case)	F^	3.1	No	Yes	Yes	No	Yes	Yes	No	No	Positive in serum (CSF NR)
Hacohen et al, 2014 [54] (14 cases)	M	18	No	Yes	Yes	No	No	Yes	Yes	No	Positive in serum (CSF NR)
	M	5	No	No	No	No	No	Yes	No	No	Positive in CSF (serum NR)

	F^	16	No	No	Yes	No	No	Yes	No	No	Positive in CSF and serum
	F	14	No	Yes	No	Yes	No	No	No	Yes (OT)	Positive in serum (CSF NR)
	F	2	No	No	Yes	Yes	Yes	No	No	No	Positive in serum (CSF NR)
	M	16	No	Yes	No	Yes	Yes	No	Yes	No	Positive in serum (CSF NR)
	F	17	No	Yes	Yes	No	No	No	Yes	No	Positive in serum and CSF
	F	16	No	No	No	Yes	Yes	No	No	No	Positive in serum (CSF NR)
	M	4	No	Yes	Yes	Yes	Yes	No	Yes	No	Positive in serum (CSF NR)
	F	13	No	Yes	Yes	Yes	Yes	No	Yes	No	Positive in serum (CSF NR)
	F	11	No	Yes	Yes	No	Yes	No	Yes	No	Positive in serum and CSF
	M	13	No	Yes	Yes	No	Yes	No	No	No	Positive in serum and CSF
	F	14	No	Yes	Yes	Yes	Yes	No	Yes	No	Positive in serum and CSF
	F	16	No	Yes	Yes	Yes	Yes	No	No	No	Positive in serum and CSF
Le Moigno et al, 2014 [55] (1 case)	F	6	No	Yes	Yes	Yes	Yes	Yes	No	No	Positive in CSF (serum NR)
Salvucci et al, 2014 [56] (1 case)	F	7	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Positive in CSF and serum
Sommeling et al, 2014 [57] (1 case)	M	16	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes (mature terato-ma)	Positive in serum and CSF
Titulaer et al, 2014 [58] (2 cases)	F	8	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Positive in serum and CSF
	F	18	Yes	Yes	Yes	Yes	Yes	No	No	NR	Positive in serum and CSF
Venancio et al, 2014 [59] (1 case)	M	9	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Positive in CSF (serum NR)
Almuslamani et al, 2015 [60] (1 case)	F	13	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in CSF, negative in serum
Armangue et al, 2015 [61] (3 cases)	M^	1	No	Yes	Yes	No	Yes	Yes	No	No	Positive in CSF, negative in serum
	M^	1.3	No	Yes	Yes	No	Yes	Yes	No	No	Positive in serum and CSF
	F^	1.8	No	Yes	Yes	No	Yes	Yes	No	No	Positive in serum and CSF
Bamford et al, 2015 [62] (1 case)	F^	1.3	NR	No	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
Cleland et al, 2015 [63] (1 case)	F	16	No	Yes	Yes	Yes	Yes	No	No	No	Positive in CSF, negative in serum
Ellul et al, 2015 [64] (1 case)	M^	3	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Positive in serum and CSF
Kramina et al, 2015 [65] (1 case)	F	15	No	Yes	Yes	Yes	No	Yes	Yes	No	Positive in serum and CSF
Lagarde et al, 2015 [66] (6 cases)	F	10	NR	Yes	Yes	Yes	Yes	No	No	No	Positive in serum and CSF#
	F	17	NR	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF#
	F	14	NR	Yes	Yes	Yes	Yes	Yes	No	No	Positive in serum and CSF#
	M	3	NR	Yes	Yes	Yes	Yes	Yes	No	No	Positive in serum and CSF#
	F	11	NR	Yes	Yes	Yes	Yes	Yes	No	No	Positive in serum and CSF#
	M	5	NR	Yes	Yes	Yes	Yes	Yes	No	No	Positive in serum and CSF#
Miyauchi et al, 2015 [67] (1 case)	M	11	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
Mohammad et al, 2015 [68] (7 cases)	F	14	NR	Yes	Yes	No	Yes	No	No	NR	Positive in serum or CSF*
	F	14	NR	Yes	Yes	No	Yes	No	No	NR	Positive in serum or CSF*
	F	5.1	NR	Yes	Yes	No	Yes	No	No	NR	Positive in serum or CSF*
	M	2.2	NR	Yes	Yes	No	Yes	No	No	NR	Positive in serum or CSF*
	F	16	NR	Yes	Yes	No	Yes	No	No	NR	Positive in serum or CSF*
	M	1.8	NR	Yes	Yes	No	Yes	No	No	NR	Positive in serum or CSF*
	M	15	NR	Yes	Yes	No	Yes	No	No	NR	Positive in serum or CSF*
Nosadini et al, 2015	F	9	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in CSF

[69] (4 cases)											(serum NR)
	M	12	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in CSF (serum NR)
	F	8	No	Yes	Yes	Yes	No	Yes	Yes	No	Positive in CSF (serum NR)
	M	6	No	Yes	Yes	Yes	No	Yes	Yes	No	Positive in CSF (serum NR)
Reilly-Shapiro et al, 2015 [70] (1 case)	F	18	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in CSF (serum NR)
Sands et al, 2015 [71] (3 cases)	F	2	No	Yes	Yes	No	Yes	No	No	NR	Positive in CSF (serum NR)
	F	14	No	Yes	No	No	Yes	No	Yes	NR	Positive in CSF (serum NR)
	F	14	No	Yes	Yes	No	No	No	No	NR	Positive in CSF (serum NR)
Sartori et al, 2015 [72] (3 cases)	M	3.8	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
	F	4.3	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
	F	12	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum (CSF NR)
Sharko et al, 2015 [73] (1 case)	F	13	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in CSF (serum NR)
Tatencloux et al, 2015 [74] (3 cases)	M	10	No	Yes	Yes	Yes	Yes	Yes	No	No	Positive in serum and CSF
	F	11	No	Yes	Yes	No	Yes	No	No	No	Positive in serum and CSF
	F	14	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive in serum and CSF
Wright et al, 2015 [75] (9 cases)	F	n.a.	No	Yes	Yes	No	Yes	No	No	NR	Positive in serum and/or CSF*
	F	14	No	Yes	Yes	No	Yes	No	No	NR	Positive in serum and/or CSF*
	F	14	No	Yes	Yes	No	Yes	No	No	NR	Positive in serum and/or CSF*
	F	2	No	Yes	Yes	No	Yes	No	No	NR	Positive in serum and/or CSF*
	F	14	No	Yes	Yes	No	Yes	No	No	NR	Positive in serum and/or CSF*
	F	3	No	Yes	Yes	No	Yes	No	No	NR	Positive in serum and/or CSF*
	F	2	No	Yes	Yes	No	No	No	No	NR	Positive in serum and/or CSF*
	F	17	No	Yes	No	No	Yes	No	No	NR	Positive in serum and/or CSF*
	F	15	No	Yes	No	No	No	No	No	NR	Positive in serum and/or CSF*
Zekeridou et al, 2015 [76] (14 cases)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zubkov et al, 2015 [77] (1 case)	F	17	NR	Yes	Yes	No	Yes	Yes	Yes	Yes (OT)	Positive in CSF (serum NR)

Supplementary Table 1. Articles included in our literature review and relative reported pediatric patients treated with PE for anti-NMDAR encephalitis. Demographic and clinical features of the patients and data on anti-NMDAR antibodies are reported too. For the case series with >10 patients and in which most of the information was not available, we reported all the cases in a single row [7,8,11,41,73]. See main text for list of References.

Legend: anti-NMDAR: anti-N-methyl-D-aspartate receptor; CSF: cerebrospinal fluid; NR: not reportde (data not available); OT: ovarian teratoma; PE: plasma exchange;

*Not specified

#All patients showed anti-NMDAR antibody positivity at low titre in serum and with relatively higher titre in CSF, suggesting an intrathecal synthesis of anti-NMDAR antibodies

^Preceding episode of herpes simplex virus encephalitis

3.3.4 Rituximab in paediatric neuromyelitis optica spectrum disorders

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Rituximab monitoring and redosing in pediatric neuromyelitis optica spectrum disorder.

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Rituximab monitoring and redosing in pediatric neuromyelitis optica spectrum disorder

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ABSTRACT

Objective: To study rituximab in pediatric neuromyelitis optica (NMO)/NMO spectrum disorders (NMOSD) and the relationship between rituximab, B cell repopulation, and relapses in order to improve rituximab monitoring and redosing.

Methods: Multicenter retrospective study of 16 children with NMO/NMOSD receiving ≥2 rituximab courses. According to CD19 counts, events during rituximab were categorized as "repopulation," "depletion," or "depletion failure" relapses (repopulation threshold CD19 $\geq 10 \times 10^6$ cells/L).

Results: The 16 patients (14 girls; mean age 9.6 years, range 1.8–15.3) had a mean of 6.1 events (range 1–11) during a mean follow-up of 6.1 years (range 1.6–13.6) and received a total of 76 rituximab courses (mean 4.7, range 2–9) in 42.6-year cohort treatment. Before rituximab, 62.5% had received azathioprine, mycophenolate mofetil, or cyclophosphamide. Mean time from rituximab to last documented B cell depletion and first repopulation was 4.5 and 6.8 months, respectively, with large interpatient variability. Earliest repopulations occurred with the lowest doses. Significant reduction between pre- and post-rituximab annualized relapse rate (ARR) was observed ($p = 0.003$). During rituximab, 6 patients were relapse-free, although 21 relapses occurred in 10 patients, including 13 "repopulation," 3 "depletion," and 4 "depletion failure" relapses. Of the 13 "repopulation" relapses, 4 had CD19 10–50 $\times 10^6$ cells/L, 10 had inadequate monitoring (≤1 CD19 in the 4 months before relapses), and 5 had delayed redosing after repopulation detection.

Conclusion: Rituximab is effective in relapse prevention, but B cell repopulation creates a risk of relapse. Redosing before B cell repopulation could reduce the relapse risk further.

Classification of evidence: This study provides Class IV evidence that rituximab significantly reduces ARR in pediatric NMO/NMOSD. This study also demonstrates a relationship between B cell repopulation and relapses. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e188; doi: 10.1212/NXI.0000000000000188

GLOSSARY

AQP4 = aquaporin-4; **ARR** = annualized relapse rate; **EDSS** = Expanded Disability Status Scale; **IVIg** = IV immunoglobulin; **MS** = multiple sclerosis; **MOG** = myelin oligodendrocyte glycoprotein; **NMO** = neuromyelitis optica; **NMOSD** = NMO spectrum disorders; **ON** = optic neuritis; **TM** = transverse myelitis.

Neuromyelitis optica (NMO) is an autoimmune inflammatory demyelinating disease of the CNS.[1] Although previously considered a multiple sclerosis (MS) variant, IgG autoantibody targeting aquaporin-4 (AQP4) channel (NMO-IgG) has clearly demonstrated that NMO is a separate entity.[2] NMO lesions are characterized by humoral inflammatory response and astrocytic cell death with AQP4 loss, followed by inflammatory demyelination and axonal damage.[3]

Supplemental data at Neurology.org/nn

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The course of NMO is characterized by a high relapse rate with accumulation of neurologic disability, potentially causing permanent blindness and paralysis. Therefore, relapse prevention is crucial. Differentiation from MS is important because some MS therapies fail to control or may aggravate NMO.[4–6] Even though the optimal therapeutic regimen has not been established, acute NMO attacks are mainly treated with corticosteroids, plasma exchange, and IV immunoglobulin (IVIg); azathioprine, methotrexate, mycophenolate mofetil, rituximab, mitoxantrone, cyclophosphamide, and tocilizumab have been used to prevent relapses.[7]

Rituximab is an anti-CD20 chimeric monoclonal antibody that depletes B cells that is used in severe autoimmune and inflammatory CNS disorders despite the risk of infections, as recently demonstrated in a large pediatric study.[8] One prospective and 3 retrospective adult NMO studies demonstrated reduced annualized relapse rate (ARR) and significantly improved Expanded Disability Status Scale (EDSS) score with rituximab.[9–12] Pediatric data are more limited and retrospective.[13–16] No study specifically addresses optimal rituximab monitoring and redosing to prevent relapses and reduce disability. To clarify these aspects, we retrospectively studied 16 children with NMO who received ≥2 rituximab courses in order to establish rituximab efficacy, the time from rituximab to B cell repopulation, and the relationship between B cell repopulation and relapses.

METHODS

Patients. We identified 16 patients with NMO who received ≥2 rituximab courses (<18 years at first dose) from 9 international pediatric neuroimmunology centers. NMO was defined according to the revised Wingerchuk criteria for NMO[17] and NMO spectrum disorders (NMOSD).[18] In 13 of 16 patients, diagnosis of definite NMO was met based on the presence of both optic neuritis (ON) and transverse myelitis (TM).[19] The remaining 3 children had NMOSD (1 had a single attack of isolated TM, 1 had an attack of TM and brainstem manifestations, and 1 had recurrent ON), and these patients were all NMO-IgG positive. Regarding serologic status, 15 of 16 patients were positive for NMO-IgG or AQP4 antibodies: 12 were tested and positive for NMO-IgG using immunofluorescence, and 3 were tested and positive for both NMO-IgG (using immunofluorescence) and anti-AQP4 antibodies (using cell-based assay). One patient was negative for NMO-IgG but positive for anti–myelin oligodendrocyte glycoprotein (MOG) antibodies using cell-based assay (not tested for anti-AQP4 antibodies) (patient 7).

Data collection. Data were retrospectively collected by the main investigator (R.C.D.) through telephone interviews to the physicians using a structured questionnaire created for this study. Information recorded included demographics, clinical characteristics of disease, immune therapies received besides rituximab, rituximab regimen, CD19 count measurements, and outcome. Data collection focused on the relationship between rituximab administration (timing, dose, number of courses, adverse reactions), CD19 counts, and relapses. First-line immune therapy was defined as corticosteroids, IVIg, and plasma exchange, whereas second-line immune therapy included rituximab, cyclophosphamide, azathioprine, and mycophenolate mofetil. Disease duration pre-rituximab was defined as the time between onset (first event) and initiation of rituximab treatment. Rituximab treatment duration was defined as the time between rituximab initiation and last follow-up (for patients with ongoing rituximab) or the date of final CD19 repopulation (for patients who stopped rituximab).

CD19 values and relationship to relapses. The threshold for B cell repopulation was defined as CD19 count $\geq 10 \times 10^6$ cells/L, as previously proposed.[16,20] In order to study the B cell status during relapses, we used the CD19 count closest to the clinical event (mean 4.6 days before or after the event, median 1, range 0–22). We categorized a relapse as a "repopulation" relapse when it was associated with B cell repopulation $\geq 10 \times 10^6$ cells/L, as a "depletion" relapse when it occurred despite B cell depletion $< 10 \times 10^6$ cells/L, or as a "depletion failure" relapse when it occurred following a rituximab course failing to deplete B cells despite conventional rituximab doses and adequate CD19 monitoring. In order to examine the timing of CD19 repopulation, we used data only from rituximab courses with evidence of both B cell depletion and subsequent repopulation (31 courses from 13 patients).

Therapeutic efficacy. We used ARR as a clinical indicator of therapeutic efficacy by comparing the ARR pre-rituximab and during rituximab. ARR was calculated only when a time span of ≥6 months was available.[12] One relapse (patient 13) occurred 14 days after the first rituximab course and was considered to occur before treatment effect because B cell depletion may take up to 1 month after rituximab administration.[21] Pre- and post-rituximab ARR were compared using the Wilcoxon 2-sample test (only patients with both pre- and post-rituximab ARR were included). EDSS score was calculated retrospectively to assess the neurologic outcome at the last follow-up. We used Spearman correlation coefficient (nonparametric) for correlating relapse number with EDSS score at last follow-up.

Research questions and classification of evidence. Our primary research objectives were to determine the efficacy of rituximab using ARR and to determine the relationship of relapses to B cell repopulation. Given the retrospective nature of our study and lack of a control group, our study represents Class IV evidence.

Standard protocol approvals, registrations, and patient consents. Patient data were acquired after local ethical approval or using preexisting approved studies to collect deidentified clinical data.

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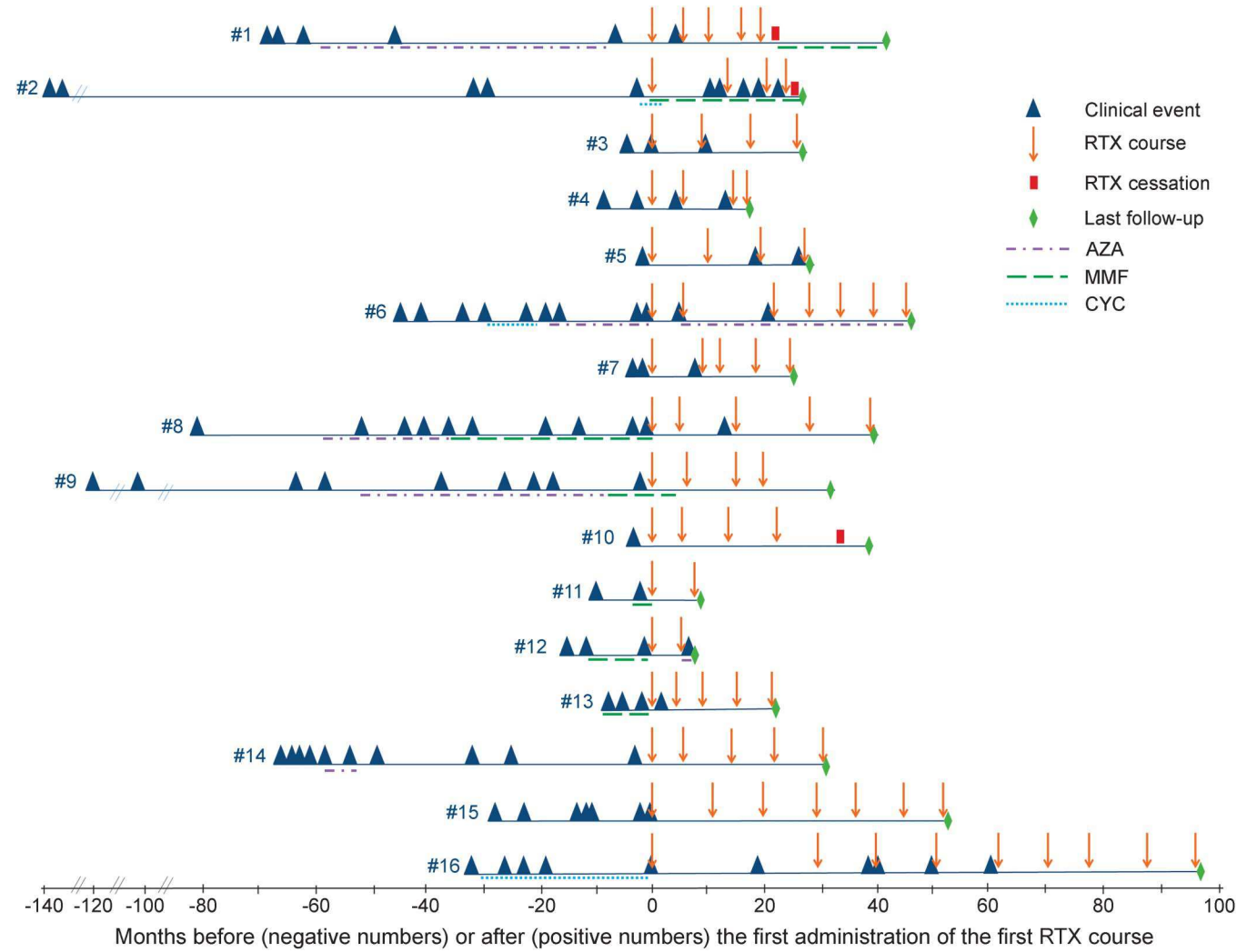
RESULTS **Demographics.** Sixteen children (14 girls) with NMO or NMOSD treated with ≥2 rituximab courses were included in our study (mean age 9.6 years, median 10.9, range 1.8–15.3). The patient race was white (n = 8), black or African American (n = 5), Native Pacific Islander (n = 1), mixed white and Native Pacific Islander (n = 1), and mixed African, Asian, and white (n = 1).

Clinical presentation and disease course. Disease onset was between 2000 and 2012. Ten patients had ON and/or TM at onset (ON: n = 4; TM: n = 4; both ON and TM: n = 2). The other presentations were brainstem disease only (n = 3), TM and brainstem disease (n = 2), and ON and brainstem disease (n = 1). The mean total duration of disease (time from onset to last follow-up) was 6.1 years (median 5.1, range 1.6–13.6). In the 16 children, 98 total events occurred (mean 6.1, median 5, range 1–11), most of which (71 of 98) were monosymptomatic attacks (isolated ON: n = 29; isolated TM: n = 38; isolated brainstem disease: n = 4). The remaining attacks were concurrent ON and TM (n = 13); TM and brainstem disease (n = 9); ON, TM, and brainstem disease (n = 2); ON and brainstem disease (n = 1); or other (n = 2). Figure 1 illustrates the clinical course of the 16 patients (clinical events, second-line immune therapies, and rituximab courses).

Immune therapies before rituximab. Before rituximab, all patients received IV methylprednisolone followed by oral prednisolone tapers; 8 patients received plasma exchange and 8 received IVIg. Ten patients received other second-line immune treatments before rituximab (figure 1 and table 1): mycophenolate mofetil (n = 5; 2 of 5 also received azathioprine), azathioprine (n = 5; 2 of 5 also received mycophenolate mofetil and 1 of 5 also received cyclophosphamide), and cyclophosphamide (n = 3; 1 of 3 also received azathioprine).

Figure 1 Clinical course of the 16 patients: Clinical events, second-line immune treatments, and rituximab courses



AZA = azathioprine; CYC = cyclophosphamide; MMF = mycophenolate mofetil; RTX = rituximab.

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Table 1 First-line and second-line immune treatments administered before rituximab

Patient	Sex	Age at disease onset, yr	First-line immune treatments before RTX				Second-line immune treatments before RTX			Age at RTX initiation, yr
			IVMP	OP	PE	IVIg	MMF	AZA	CYC	
1	F	7.25	+ (5 courses)	+	–	–	–	+	–	12.92
2	M	1.83	+ (5 courses)	+	+ (1 cycle)	+ (1 course)	–	–	+	13.33
3	F	15.33	+ (2 courses)	+	+ (1 cycle)	–	–	–	–	15.92
4	F	9.58	+ (2 courses)	+	–	+ (2 courses)	–	–	–	10.25
5	F	8.08	+ (1 course)	+	–	+ (1 course)	–	–	–	8.17
6	F	10.83	+ (8 courses)	+	–	–	–	+	+	14.58
7	F	11	+ (1 course)	+	–	+ (2 courses)	–	–	–	11.25
8	F	7.75	+ (8 courses)	+	+ (3 cycles)	–	+	+	–	14.58
9	F	3.92	+ (6 courses)	+	–	+ (1 course)	+	+	–	13.92
10	F	12.42	+ (1 course)	+	–	–	–	–	–	12.67
11	F	11.75	+ (2 courses)	+	+ (1 cycle)	+ (1 course)	+	–	–	12.58
12	F	14.08	+ (2 courses)	+	+ (1 cycle)	–	+	–	–	15.33
13	M	11.17	+ (3 courses)	+	+ (1 cycle)	+ (8 courses)	+	–	–	11.75
14	F	5.67	+ (7 courses)	+	–	+ (1 course)	–	+	–	11.17
15	F	11.33	+ (3 courses)	+	+ (15 cycles)	–	–	–	–	13.67
16	F	11.25	+ (4 courses)	+	+ (3 cycles)	–	–	–	+	14

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; IVIg = IV immunoglobulin; IVMP = IV methylprednisolone; MMF = mycophenolate mofetil; OP = oral prednisolone; PE = plasma exchange; RTX = rituximab.
When available, the number of treatment courses and cycles is provided in parentheses. Before rituximab, all patients received IV methylprednisolone (total 60 courses; mean 3.7 courses per patient, median 3, range 1–8) followed by oral prednisolone. Plasma exchange was administered in 8/16 patients (total 26 cycles; mean 3.2 cycles per patient, median 1, range 1–15; in data available, there were mean 5.2 exchanges per cycle, median 5, range 1–10). IVIg was administered in 8/16 patients (total 17 courses; mean 2.1 courses per patient, median 1, range 1–8).

Rituximab administration. A total of 76 rituximab courses were administered in the 16 patients (mean 4.7, median 4.5, range 2–9) (figure 1). The mean time between the first infusion of the first and last rituximab courses was 29.8 months (median 23.5, range 5.7–93). The protocols for administration (in descending order of frequency) were as follows: 1,000 mg × 2 infusions 2–4 weeks apart (n = 31 courses), 375 mg/m^2 × 4 weekly infusions (n = 19 courses), 375 mg/m^2 × 1 infusion (n = 10 courses), 375 mg/m^2 × 2 infusions 2 weeks apart (n = 9 courses), 750 mg/m^2 × 2 infusions 2 weeks apart (n = 5 courses), and 500 mg/m^2 × 2 infusions 2 weeks apart (n = 2 courses). Rituximab was redosed at a mean of 7.9 months (median 7.6, range 2.2–28.3). In some patients it was redosed after a relapse, in others after detection of B cell repopulation, and in a minority at regular intervals regardless of B cell status. At last available follow-up, rituximab was ongoing in 13 patients. Rituximab was discontinued in the 3 remaining patients because of difficulty coming to the hospital (patient 1), treatment failure (patient 2), and relapse freedom for ≥2 years (patient 10).

Infusion reactions and adverse events. Data on infusion reactions to rituximab and adverse events were available in 14 of 16 patients. Infusion reactions occurred in 6 of 14 children (dyspnea: n = 2; rash: n = 2; chest pain: n = 1; lightheadedness: n = 1; tingling and stinging sensation in mouth and throat: n = 1). Other adverse reactions occurred in 3 of 14 children, including infections in 2 (skin infection: n = 1; mastoiditis: n = 1) and immunoglobulin deficiency without infectious complications in 1 (this patient received 4 rituximab courses of 750 mg/m^2 × 2).

Rituximab efficacy. Six patients were relapse-free during rituximab treatment (patients 9, 10, 11, 13, 14, and 15) (table 2; figure 1). In these 6 relapse-free patients, the rate of use of other immune therapies during rituximab (corticosteroids: n = 4; IVIg: n = 2; plasma exchange: n = 0; second-line immune therapies: n = 0) was similar to the rate in the other 10 patients (corticosteroids: n = 9; IVIg: n = 4; plasma exchange: n = 4; mycophenolate mofetil + cyclophosphamide: n = 1; azathioprine: n = 1). In the 10 relapsing patients, a total of 21 events occurred during rituximab treatment (mean 2.1, median 1.5, range 1–5) (table 2). Relapses occurred a mean of 9.1 months (median 8.1, range 1.2–27.8) after the last rituximab course (figure 2A). There was a statistically significant reduction between

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Table 2 Duration of disease, number of events, and ARR pre- and post-rituximab

Patient	Disease duration pre-RTX, mo	Duration of RTX treatment, mo	No. events pre-RTX (including first event)	No. events during RTX treatment	ARR pre-RTX including first event (excluding first event)	ARR during RTX	ARR in the year before RTX	ARR in the year after RTX
1	67.5	22	5	1	0.89 (0.71)	0.54	1	1
2	137	23	5	5	0.44 (0.35)	2.61	1	0
3	4	26	2	1	—	0.46	—	1
4	8	17.3	2	2	3.00 (1.50)	1.39	—	1
5	1.3	27.5	1	2	—	0.87	—	0
6	45	46	9	2	2.40 (2.13)	0.52	3	1
7	3.2	31	2	1	—	0.39	—	1
8	82.3	26	10	1	1.46 (1.31)	0.46	3	0
9	123.7	39.5	9	0	0.88 (0.78)	0	1	0
10	2.5	33.5	1	0	—	0	—	0
11	9.7	9.2	2	0	2.47 (1.24)	0	—	0
12	15	7	3	1	2.40 (1.60)	1.71	2	1
13	7.5	22.7	4	0	6.40 (4.80)	0	—	0
14	66	30	10	0	1.82 (1.64)	0	1	0
15	28	52.7	7	0	3.00 (2.57)	0	3	0
16	33	98	5	5	1.82 (1.45)	0.61	1	0
	Mean 39.6	Mean 32	Mean 4.8	Mean 1.3	Mean 2.2 (1.5)	Mean 0.6	Mean 1.7	Mean 0.4
	Median 21.5	Median 26.7	Median 4.5	Median 1	Median 2.1 (1.5)	Median 0.5	Median 1	Median 0
	Range 1.3–137	Range 7–98	Range 1–10	Range 0–5	Range 0.4–6.4 (0.3–3.2)	Range 0–2.6	Range 1–3	Range 0–1

Abbreviations: ARR = annualized relapse rate; RTX = rituximab.
There was a statistically significant reduction between pre- and post-rituximab ARR when first events were included ($p = 0.003$) or excluded ($p = 0.014$). There was also a significant reduction in the ARR in the year before and after rituximab initiation ($p = 0.002$).

pre- and post-rituximab ARR when first events were included ($p = 0.003$) or excluded ($p = 0.014$) (table 2). There was also a significant reduction in the ARR in the year after rituximab initiation compared to the year before ($p = 0.002$).

CD19 count monitoring and repopulation on rituximab. During the total 42.6 years of cohort rituximab treatment, a total of 196 CD19 counts were measured (mean 12.2 per patient, median 9, range 1–36). All patients had documented B cell depletion after at least 1 rituximab course. In the 31 rituximab courses (in 13 patients) with documented B cell depletion followed by repopulation, the mean time from rituximab administration to the last demonstrated depleted CD19 count was 4.5 months (median 5.1, range 0.9–8.7), and the mean time to the first demonstrated repopulated CD19 count was 6.8 months (median 6.7, range 2.7–12.2). The 2 shortest times to repopulation occurred 2.7 and 2.9 months after rituximab (375 mg/m^2 × 1 and 375 mg/m^2 × 2, respectively) in 2 different patients. We observed notable interpatient variability in the time to B cell repopulation and some intrapatient variability (figure 2B). The mean time to repopulation in the first rituximab courses (mean 7.4 months, median 7.2, range 3.6–12.2; calculated in 8 courses) was similar to that in subsequent courses (mean 6.7 months, median 6.8, range 2.7–11.2; calculated in 23 courses). Time to B cell repopulation was faster in the younger patients (18 courses in 5 patients with adequate data; age range 8.2–11.7 years at rituximab initiation) than in the older patients (12 courses in 7 patients; age range 13.3–15.9 years at rituximab initiation) (mean 5.9 vs 8.1 months, median 5.6 vs 8.5 months). Where adequate data were available (n = 10 courses), once B cells repopulated over the threshold of 10 × 10^6 cells/L, B cell counts never redepleted spontaneously. In contrast, according to available data (n = 9 courses), only 22% of CD19 counts 1–9 × 10^6 cells/L were followed by repopulated CD19 values ≥10 × 10^6 cells/L within 1 month.

CD19 count and relationship to relapses. The 21 relapses that occurred in 10 children during rituximab treatment are detailed in table e-1 at Neurology.org/nn (adequate CD19 data in 20 of 21 relapses). Most of the events (13 of 20) occurred with B cell repopulation and are defined as "repopulation" relapses. In these 13 "repopulation" relapses, the mean CD19 value at relapse was 192.3 × 10^6 cells/L (median 130, range 10–449), and in 4 of these 13 events the CD19 count was 10–50 × 10^6 cells/L

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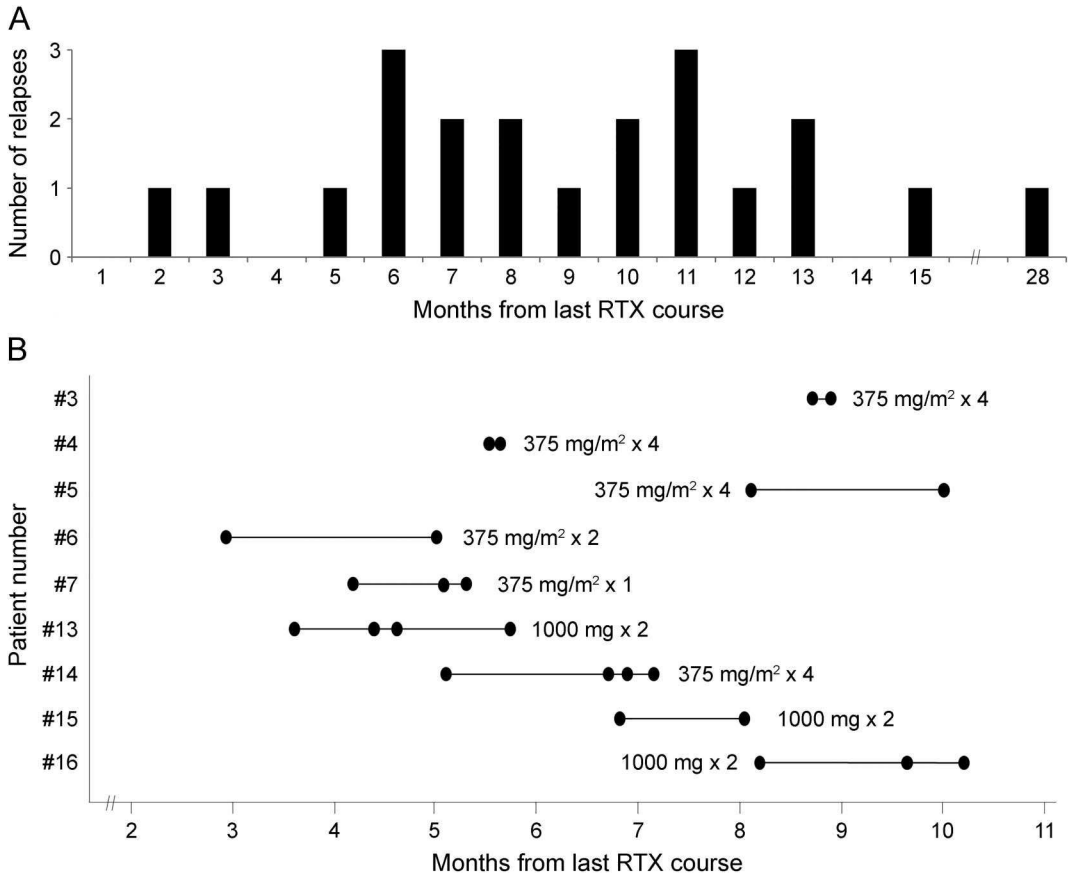
Figure 2 Time to relapse and time to B cell repopulation after rituximab



(A) Relapses during rituximab (RTX) treatment according to the time from last rituximab course (total 21 relapses in 10 patients). (B) Inter- and intraindividual variability in the time to B cell repopulation after rituximab in 9 patients. To assess the variability in the intraindividual time to repopulation, these 9 patients were selected based on the availability of at least 2 rituximab courses with evidence of a repopulated CD19 count after demonstrated depletion and the fact that the same dose regimen was administered (rituximab regimen specified for each patient next to the bar). The horizontal bars represent the range of intraindividual variability in the time to repopulation, and the dots represent the actual measurements. There is significant variability between patients, although the intrapatient variability appears to be less.

(10, 16, 37, and 40 × 10^6 cells/L). Of the 13 "repopulation" relapses, there was a lack of monitoring (defined as ≤1 CD19 count in the 4 months preceding the relapse) in 10, a delay in redosing (defined as ≥10 days between detection of repopulation and rituximab redosing) during which the relapse occurred in 5, and there was no inadequate monitoring or delayed redosing in 2.

The remaining 7 clinical events occurred in 2 patients: 3 relapses in patient 2 (rituximab 750 mg/m² × 2 infusions 2 weeks apart) occurred despite B cell depletion and were defined as "depletion" relapses, whereas the 4 relapses in patient 16 (rituximab 1,000 mg × 2 infusions 4 weeks apart) occurred with documented persistent nondepleted CD19 counts (mean 6.2 CD19 counts/relapse, median 6, range 2–11) and were defined as "depletion failure" relapses. Examples of relapse freedom after treatment and of "repopulation," "depletion," and "depletion failure" relapses are presented in figures 3 and e-1.

Outcome. At a mean follow-up of 6.1 years from disease onset (median 5.1 years, range 1.6–13.6), mean EDSS score was 2.4 (median 2.5, range 0–6.5), and no ongoing problems (EDSS 0) were reported in 5 patients. There was a trend of worse EDSS scores at follow-up in the patients who had more relapses during the disease course, but this was not statistically significant ($r = 0.49$, $p = 0.051$). The most common neurologic problem at follow-up was reduced visual acuity, reported in 10 of 16 cases; in 6 of these 10 patients visual acuity was severely reduced (worse eye with maximal visual acuity corrected less than 20/200). Pyramidal signs in the lower limbs were reported in 2 of 16 cases, upper limb involvement in 0 of 16, and bowel or bladder impairment in 1 of 16.

DISCUSSION We retrospectively studied 16 children with NMO treated with ≥2 rituximab courses with the aim of optimizing rituximab monitoring and

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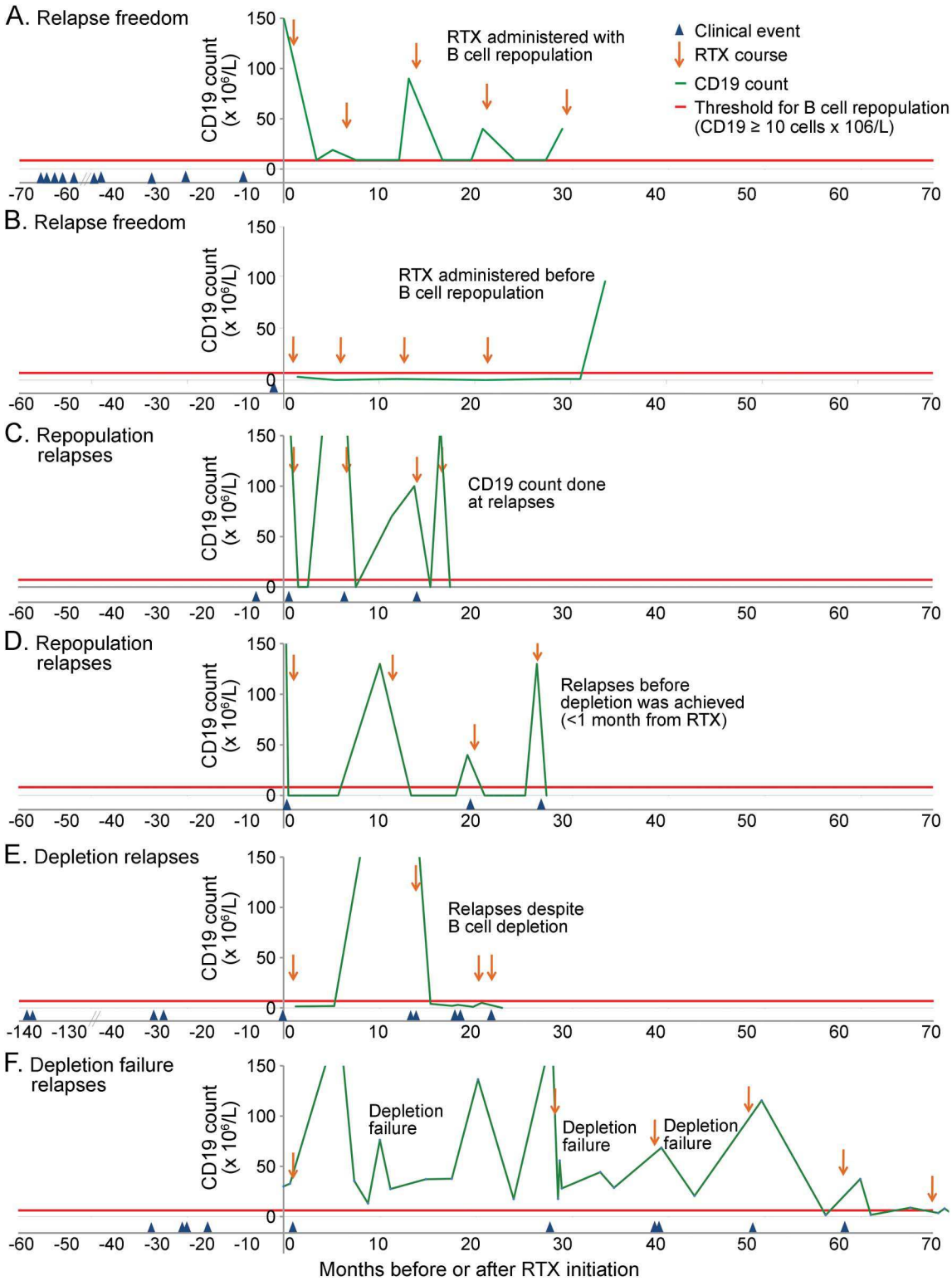
Figure 3 Summary figure exemplifying 4 different types of response to rituximab treatment observed in our patients



Relapse freedom with rituximab (RTX) (A, B), occurrence of relapses with a repopulated B cell count ("repopulation" relapses; C, D), occurrence of relapses with a depleted B cell count ("depletion" relapses; E), occurrence of relapses in association with failure to reach B cell depletion ("depletion failure" relapses; F). (A) Relapse freedom (no relapses during rituximab): rituximab redosing after B cell repopulation (patient 14). (B) Relapse freedom (no relapses during rituximab): rituximab redosing before B cell repopulation (patient 10). (C) "Repopulation" relapses (relapses with B cell repopulation): repopulation was detected only at the time of the relapse (third and fourth relapses); subsequent rituximab courses were administered after the relapse (second and third rituximab courses) (patient 4). (D) "Repopulation" relapses (relapses with B cell repopulation): repopulation was noticed at CD19 count monitoring and rituximab was administered, but clinical relapse occurred a few days after rituximab, before depletion was achieved (second and third relapses) (patient 5). (E) "Depletion" relapses (relapses despite B cell depletion in

Continued

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redosing to prevent relapses. This represents the largest reported therapeutic study of pediatric NMO.

Confirming published literature, there was a female predominance in our cohort, and most of the clinical events were monosymptomatic TM, ON, and brainstem events. Our patients had a high relapse rate and a long disease course before rituximab initiation. Fifteen of the 16 patients were NMO-IgG positive, although the single MOG-IgG-positive patient had 2 events in the 3 months preceding rituximab initiation and 1 relapse during rituximab, suggesting a highly relapsing disease. Although long-term data regarding MOG-IgG-associated disease are lacking, early reports suggest that MOG-IgG-associated NMOSD is more reversible and less severe and carries less risk of permanent disability compared to NMO-IgG-associated NMOSD.[19,22]

All patients received immunosuppressive therapies before rituximab: all received IV methylprednisolone and oral steroids, half received IVIg, half received plasma exchange, and 62.5% were given other second-line immune therapies before rituximab. Rituximab was generally initiated after $\geq$2 events, although it was started after the first event in 3 cases. Overall, our cohort likely represents a more severe end of the pediatric NMO spectrum.

In our cohort, the protocols of rituximab induction, redosing, and monitoring were heterogeneous, reflecting the multicenter nature of our cohort and the lack of guidelines and consensus opinion. Rituximab was redosed at a mean of 7.9 months, although with considerable variability (range 2.2–28.3 months). Redosing occurred for different reasons, including occurrence of relapses, detection of B cell repopulation, or, more rarely, planned redosing (figures 3 and e-1).

Rituximab treatment was relatively well tolerated with no major complications in 42.6-year cohort treatment. There was evidence of efficacy in our cohort; 6 of the patients were relapse-free during treatment (figures 3, A and B and e-1). There was a significant reduction in ARR using all measures, although it is important to note that the ARR may decline during the course of disease regardless of treatment.[23] The use of other immune therapies was similar in the 6 relapse-free patients compared to the other patients, suggesting that the lack of relapses was not due to other concomitant therapies administered with rituximab.

The clinical events during rituximab occurred a mean of 9.1 months after the last rituximab course, although the timing of relapses was very widely distributed.

We chose a CD19 count of 10×10^6 cells/L as a threshold for B cell repopulation, as previously used,[16,20] partly because absolute values (rather than percentages) would allow adequate comparison across centers. The observation that 4 of the 13 "repopulation" relapses in our cohort occurred during early repopulation ($10–50 \times 10^6$ cells/L) confirms the clinical validity of 10×10^6 cells/L as a threshold. We also observed that once B cells repopulated beyond 10×10^6 cells/L, CD19 counts continued to rise and there was no spontaneous return to B cell redepletion.

We confirmed a relationship between B cell repopulation and relapses. Most relapses occurred with CD19 repopulation, and only 1 patient had relapses with depleted CD19 counts, confirming that depletion appears to be protective in most patients. In most of the 13 "repopulation" relapses, CD19 monitoring was inadequate and B cell repopulation went unnoticed until subsequent clinical relapse. In 5 of the "repopulation" relapses, there was delayed rituximab redosing after detection of B cell repopulation and relapses occurred while waiting to admit the patient for redosing. Furthermore, B cell depletion can take up to 1 month after rituximab administration,[21] allowing for a "window of vulnerability" for relapses (as shown in figure 3D). The remaining 7 relapses occurred in 2 patients, defined as "depletion" relapse in one patient (figure 3E) and "depletion failure" relapse in the other (figure 3F). Therefore, only 1 of the 16 patients (patient 2) had relapses despite adequate monitoring and documented B cell depletion and can therefore be defined as having true rituximab failure. The reason for the different response to rituximab in these 2 patients with "depletion" and "depletion failure" relapses is not clear, although some investigators have suggested that B cell activating factor of the tumor necrosis factor family may be relevant.[20,24–26] Some studies in adult patients have shown a relationship of anti-AQP4 antibodies with B cell status and clinical relapses,[11,27,28] although others have not found a convincing relationship.[20] Unfortunately, longitudinal anti-AQP4 antibodies were not available in our cohort.

In light of the above considerations on the relationship between B cell repopulation and relapses, understanding the timing of repopulation after rituximab is critical for preventing relapses. The mean time for B cell repopulation in our cohort was between 4.5 (mean time of last depletion) and 6.8 months (mean time of first repopulation) after the last rituximab course. However, repopulation as early as

Figure 3 legend, continued:
the last 3 relapses) (patient 2). (F). "Depletion failure" relapses (relapses associated with failure to reach B cell depletion in the first, second, and third rituximab courses). In this patient, B cell depletion was achieved in subsequent rituximab courses (total 9 courses; same rituximab regimen used in all the courses, 1,000 mg $\times$ 2). The figure shows only the first 5 courses; no relapses occurred subsequently.

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2.7 months post-rituximab and persistent B cell depletion up to 8.7 months were observed, suggesting large interpatient variability in CD19 count effects (figure 2B), similar to other published data.[29] In contrast, the intrapatient variability appeared to be smaller, implying a relative predictability of B cell repopulation in individuals, which will help monitoring. We noted that the shortest time to repopulation occurred with the lowest rituximab doses and the longest with the highest doses, as previously observed,[29] although other variables likely play a role in B cell repopulation. We also observed that younger patients repopulated faster than older patients.

In our study, we observed that genuine treatment failure with rituximab occurred in only 1 patient, whereas relapses were otherwise attributable to the challenges associated with monitoring and redosing. We confirm that rituximab efficacy is associated with CD19 depletion, and our data suggest that the detection of repopulation over 10×10^6 cells/L should alert the clinician to the likely possibility of further B cell rise and relapse risk. Considering the significant variability observed in the time to B cell repopulation, further efforts should be made to optimize rituximab monitoring. A possible individualized strategy to minimize relapses involves rigorous CD19 monitoring (i.e., monthly, especially after the third month), particularly during first courses, and rapid redosing on repopulation detection. Given the latency of B cell depletion after rituximab infusion, there is a risk of relapse during this repopulated period, especially when there is delay in redosing. In view of this, an alternative strategy involves planned rituximab redosing at regular intervals, before B cell repopulation occurs, as previously described[9,10,20] and shown in figure 3B, which may reduce the relapse risk but will result in increased therapy cost. As shown in figure 2B, there is significant variability in B cell repopulation between patients, including early repopulation (3–6 months) even for higher dose regimens (375 mg/m^2 $\times$ 4 and 1,000 mg/m^2 $\times$ 2). Therefore, planned redosing would need to be at short intervals (3–4 months) to minimize the chance of B cell repopulation.

The retrospective design, the lack of standardization, and the relatively small number of patients are the main limitations of our study. However, we have confirmed rituximab efficacy, demonstrated challenges in monitoring, and provided data on B cell repopulation. This will improve redosing of rituximab in children with NMO and other serious autoimmune disorders of the CNS.

AUTHOR CONTRIBUTIONS

Dr. Margherita Nosadini: data analysis and first draft, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Gulay Alper: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Catherine J. Riney: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Leslie A. Benson: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Shekeeb S. Mohammad: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Sudarshini Ramanathan: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Melinda Nolan: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Richard Appleton: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Richard J. Leventer: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Kumaran Deiva: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Fabienne Brilot: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Mark P. Gorman: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Amy T. Waldman: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Brenda Banwell: acquisition of data, critical revision of the manuscript for important intellectual content, editing and approval of final draft. Dr. Russell C. Dale: project conception, design, and modification; data analysis and first draft; critical revision of the manuscript for important intellectual content; study supervision.

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for *Neurology* and *Multiple Sclerosis and Related Disorders*; has consulted for Biogen Idec, Eli Lilly, and Sanofi; has spoken at an event supported by the Consortium of MS Centers; received research support from Canadian Institute of Health Research, Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Research Foundation, and National Multiple Sclerosis Society. R.C. Dale served on the scientific advisory board for Queensland Children's Medical Institute, received speaker honoraria from Biogen Idec and Bristol-Myers-Squibb, is an editorial advisory board member for *Multiple Sclerosis and Related Disorders* and an editorial board member for *Neurology: Neuroimmunology & Neuroinflammation* and *European Journal of Paediatric Neurology*, received publishing royalties from Biogen and Bristol-Myers-Squibb, and received research support from NHMRC and Multiple Sclerosis Research Australia. Go to Neurology.org/nn for full disclosure forms.

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REFERENCES

1. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica (Devic's syndrome). Handb Clin Neurol 2014;122:581–599.
2. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;364:2106–2112.
3. Wegner C. Recent insights into the pathology of multiple sclerosis and neuromyelitis optica. Clin Neurol Neurosurg 2013;115:S38–S41.
4. Kim SH, Kim W, Li XF, Jung IJ, Kim HJ. Does interferon beta treatment exacerbate neuromyelitis optica spectrum disorder? Mult Scler 2012;18:1480.
5. Kleiter I, Hellwig K, Berthele A, et al. Failure of natalizumab to prevent relapses in neuromyelitis optica. Arch Neurol 2012;69:239–245.
6. Min JH, Kim BJ, Lee KH. Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder. Mult Scler 2012;18:113–115.
7. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol 2014;261:1–16.
8. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 2014;83:142–150.
9. Jacob A, Weinshenker BG, Violich I, et al. Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. Arch Neurol 2008;65:1443–1448.
10. Bedi GS, Brown AD, Delgado SR, Usmani N, Lam BL, Sheremata WA. Impact of rituximab on relapse rate and disability in neuromyelitis optica. Mult Scler 2011;17:1225–1230.
11. Kim SH, Huh SY, Lee SJ, Joung A, Kim HJ. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurol 2013;70:1110–1117.
12. Mealy MA, Wingerchuk DM, Palace J, Greenberg BM, Levy M. Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: multicenter study of treatment efficacy. JAMA Neurol 2014;71:324–330.
13. Lotze TE, Northrop JL, Hutton GJ, Ross B, Schiffman JS, Hunter JV. Spectrum of pediatric neuromyelitis optica. Pediatrics 2008;122:e1039–e1047.
14. McKeon A, Lennon VA, Lotze T, et al. CNS aquaporin-4 autoimmunity in children. Neurology 2008;71:93–100.
15. Beres SJ, Graves J, Waubant E. Rituximab use in pediatric central demyelinating disease. Pediatr Neurol 2014;51:114–118.
16. Longoni G, Banwell B, Filippi M, Yeh EA. Rituximab as a first-line preventive treatment in pediatric NMOSDs: preliminary results in 5 children. Neurol Neuroimmunol Neuroinflamm 2014;1:e46. doi: 10.1212/NXI.0000000000000046.
17. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66:1485–1489.
18. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805–815.
19. Dale RC, Tantsis EM, Merheb V, et al. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. Neurol Neuroimmunol Neuroinflamm 2014;1:e12. doi: 10.1212/NXI.0000000000000012.
20. Pellkofer HL, Krumbholz M, Berthele A, et al. Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. Neurology 2011;76:1310–1315.
21. Kosmidis ML, Dalakas MC. Practical considerations on the use of rituximab in autoimmune neurological disorders. Ther Adv Neurol Disord 2010;3:93–105.
22. Kitley J, Woodhall M, Waters P, et al. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. Neurology 2012;79:1273–1277.
23. Kim SM, Park J, Kim SH, et al. Factors associated with the time to next attack in neuromyelitis optica: accelerated failure time models with random effects. PLoS One 2013;8:e82325.
24. Wang H, Wang K, Zhong X, et al. Cerebrospinal fluid BAFF and APRIL levels in neuromyelitis optica and multiple sclerosis patients during relapse. J Clin Immunol 2012;32:1007–1011.
25. Nakashima I, Takahashi T, Cree BA, et al. Transient increases in anti-aquaporin-4 antibody titers following rituximab treatment in neuromyelitis optica, in association with elevated serum BAFF levels. J Clin Neurosci 2011;18:997–998.
26. Gredler V, Mader S, Schanda K, et al. Clinical and immunological follow-up of B-cell depleting therapy in CNS demyelinating diseases. J Neurol Sci 2013;328:77–82.
27. Jarius S, Aboul-Enein F, Waters P, et al. Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. Brain 2008;131:3072–3080.
28. He D, Yu Y, Yan W, Dai Q, Xu Z, Chu L. Individualized rituximab treatment for relapsing neuromyelitis optica: a pediatric case report. Pediatr Neurol 2014;51:255–258.
29. Greenberg BM, Graves D, Remington G, et al. Rituximab dosing and monitoring strategies in neuromyelitis optica patients: creating strategies for therapeutic success. Mult Scler 2012;18:1022–1026.

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Rituximab monitoring and redosing in pediatric neuromyelitis optica spectrum disorder

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Supplementary material

Supplementary figure e-1

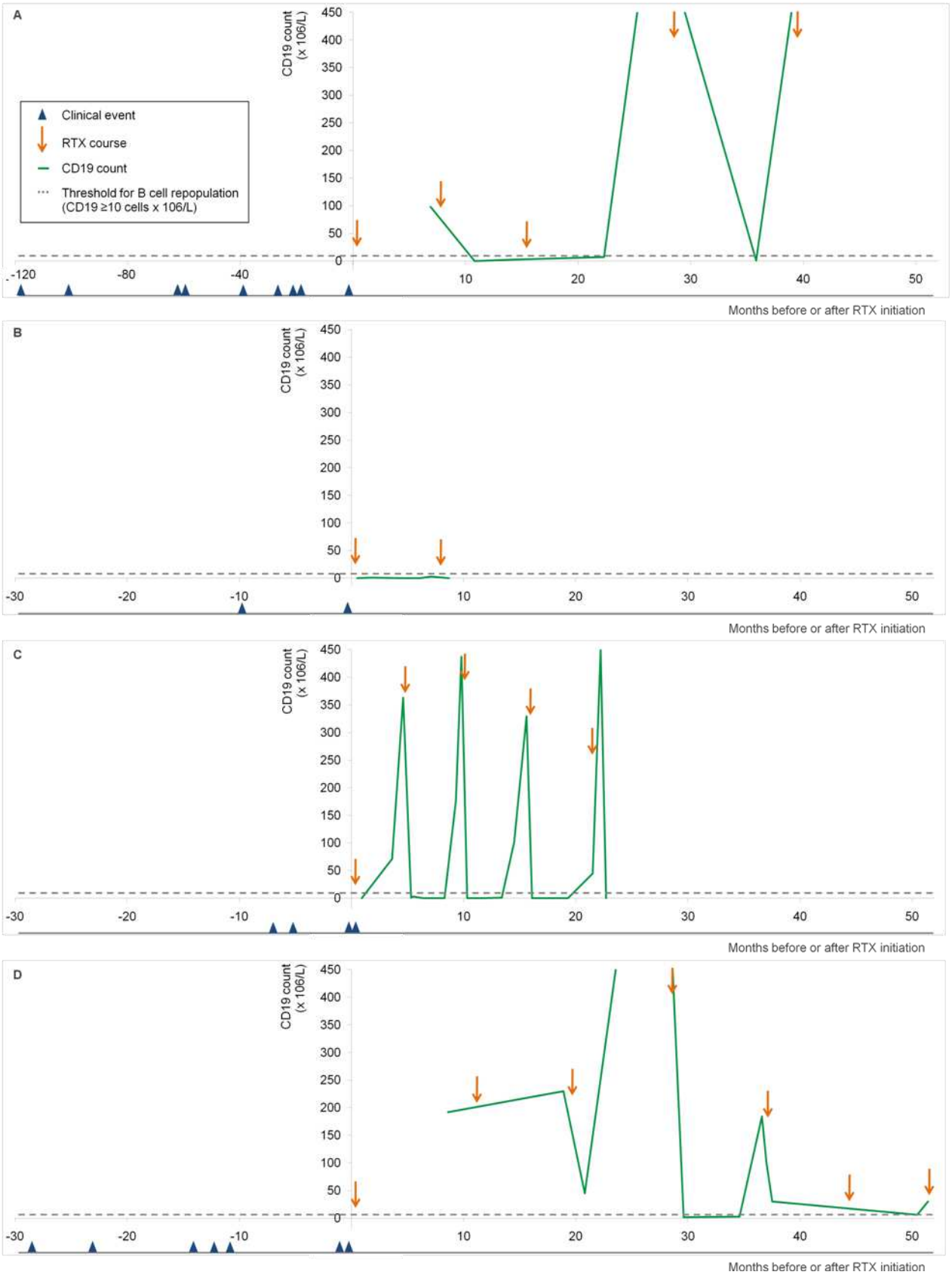

Table e-1

#	Relapse number (including the first event)	RTX regimen at last course	Time from last RTX course to relapse (months)	CD19 count at relapse (timing relative to event)	Repopulation relapse Depletion relapse Depletion failure relapse
1	6	375 mg/m^2 x 2	6.7	340 x 10^6/L (7 days after relapse)	Repopulation relapse^o
2	6	750 mg/m^2 x 2	12.6	388 x 10^6/L (11 days before relapse)	Repopulation relapse
	7	750 mg/m^2 x 2	13	388 x 10^6/L (22 days before relapse)	Repopulation relapse
	8	750 mg/m^2 x 2	4.5	2 x 10^6/L (same day as relapse)	Depletion relapse
	9	750 mg/m^2 x 2	5.5	3 x 10^6/L (9 days before relapse)	Depletion relapse
	10	750 mg/m^2 x 2	2.3	0 x 10^6/L (same day as relapse)	Depletion relapse
3	3	375 mg/m^2 x 4	10	10 x 10^6/L (same day as relapse)	Repopulation relapse
4	3	375 mg/m^2 x 4	5.6	320 x 10^6/L (same day as relapse)	Repopulation relapse
	4	375 mg/m^2 x 4	7.8	100 x 10^6/L (same day as relapse)	Repopulation relapse
5	2	375 mg/m^2 x 4	8.1	40 x 10^6/L (2 days before relapse)	Repopulation relapse
	3	500 mg/m^2 x 2	7.2	130 x 10^6/L (6 days before relapse)	Repopulation relapse
6	10	375 mg/m^2 x 2	5	259 x 10^6/L (same day as relapse)	Repopulation relapse
	11	375 mg/m^2 x 2	14.7	16 x 10^6/L (7 days after relapse)	Repopulation relapse
7	3	375 mg/m^2 x 4	9	60 x 10^6/L (1 day before relapse)	Repopulation relapse
8	11	1000 mg x 2	6.3	449 x 10^6/L (same day as relapse)	Repopulation relapse^o
12	4	1000 mg x 2	1.3	n.a.	n.a.*
16	6	1000 mg x 2	27.8	182 x 10^6/L (1 day after relapse)	Depletion failure relapse
	7	1000 mg x 2	10.8	68 x 10^6/L (same day as relapse)	Depletion failure relapse
	8	1000 mg x 2	11.5	68 x 10^6/L (20 days before relapse)	Depletion failure relapse
	9	1000 mg x 2	10.4	115 x 10^6/L (same day as relapse)	Depletion failure relapse
	10	1000 mg x 2	10.2	37 x 10^6/L (7 days before relapse)	Repopulation relapse

Table e-1 (adapted from [11]). Characteristics of the 21 relapses in 10 patients during rituximab treatment. The clinical events were analysed relative to the preceding rituximab course and CD19 counts. Four of the relapses occurred between 2 and 22 days after rituximab, in the time window when rituximab effect may not be complete yet (patient #3 event number 3, patient #5 event number 3, and patient #16 events number 8 and 10), and were therefore analysed with respect to the previous rituximab course.

Legend: #: patient number; RTX: rituximab.

*For 1 of the 21 clinical events (patient #12) there were inadequate CD19 count data.

ºIn all cases of 'repopulation relapse' there was demonstrated B cell depletion followed by repopulation except in cases #1 and #8, in whom only a single count was performed after rituximab course which showed repopulated B cells, but there was no demonstrated B cell depletion.

3.3.5 Mycophenolate mofetil, azathioprine and methotrexate in paediatric anti-NMDAR encephalitis

In progress

Mycophenolate mofetil, azathioprine and methotrexate in paediatric anti-NMDAR encephalitis: a systematic literature review

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Key words

Anti-NMDAR encephalitis; mycophenolate mofetil; azathioprine; methotrexate; children

Highlights

- The use of steroid sparers for paediatric anti-NMDAR encephalitis is heterogenous
- Severe adverse reactions seem to be rare, although a reporting bias is possible
- Our review highlights the need for improved data in larger cohorts, focused on efficacy and tolerability

Abstract

Background. While first and second-line immune therapy have been increasingly used in paediatric-onset anti-NMDAR encephalitis, expert recommendations and physicians' treating behaviours are still heterogeneous regarding the use of maintenance steroid sparers.

Methods. Systematic literature review on steroid sparers mycophenolate mofetil (MMF), azathioprine (AZA) and methotrexate (MTX) for paediatric-onset anti-NMDAR encephalitis.

Results. 76 patients treated with MMF/AZA/MTX for paediatric-onset anti-NMDAR encephalitis were included (age range at onset 0.8-18 years; 69.7% females; 49.1% had ≥1 relapse), reported in 37 articles. MMF was used in 53.9%, AZA in 25%, MTX in 15.8%; an additional 5.3% received two among MMF/AZA/MTX. MMF/AZA/MTX were not preceded by any second-line therapy (rituximab/cyclophosphamide) in 47.7%, and were administered only after relapses in 46.8%. Among the subgroup treated with MMF/AZA/MTX after the first event, relapses occurred in 8.3% only. Time on MMF/AZA/MTX was median 9 months (range 1-48). Median annualised relapse rate was 0.45 (mean 1, range 0-6.67) before MMF/AZA/MTX (excluding onset), and 0 (mean 0.06, range 0-1.3) during/after MMF/AZA/MTX. Adverse reactions were reported only for MMF (cytomegalovirus colitis and respiratory infection; grade 3 CTCAEv4.0). Relapse rate was significantly higher in patients started on first immune therapy (any) >30 days after onset (85.7%) compared to those treated early (31.2% ($p=0.0272$).

Discussion. Our literature review disclosed heterogeneity in the use of steroid sparers (MMF/AZA/MTX) in paediatric-onset anti-NMDAR encephalitis. Severe adverse reactions were rare, although a reporting bias is possible. While treatment seemed to associate to a slightly lower relapse rate especially when given early, focused data on large prospective cohorts are warranted to study safety and efficacy of MMF/AZA/MTX in paediatric anti-NMDAR encephalitis.

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune syndrome characterised by a constellation of symptoms with multistage progression (psychiatric changes, movement disorder, epileptic seizures, consciousness and vigilance disturbances, sleep-wake cycle disruption, dysautonomias), and the presence of neuronal surface antibodies in the cerebrospinal fluid and serum targeting the anti-N-methyl-D-aspartate receptor [Dalmau, 2007]. Despite the absence of definite guidelines, in recent years a number of expert recommendations have been published on immune therapy for anti-NMDAR encephalitis [Dalmau, 2011; Zuliani, 2012; McKeon, 2013; Gastaldi, 2016; Lancaster, 2016; Dale, 2017; Shin, 2017]. First-line treatments usually include intravenous methylprednisolone, intravenous immunoglobulin (IVIG) [Nosadini, 2015; Nosadini, 2016; Gadian, 2017] and plasma exchange [Suppiej, 2016]. In case of unsatisfactory response or in potentially relapsing disease, second-line therapies are advised, such as rituximab and/or cyclophosphamide. This approach is generally becoming more and more uniform, although major differences between centers and physicians do exist, especially in the use of second-line treatments [Bartolini, 2017; Kahn, 2017]. When it comes to maintenance immune therapy, expert recommendations are less definite and physicians' approaches vary widely as regards the use of maintenance therapy or not, the type of agent, and the duration of treatment [Bartolini, 2017; Kahn, 2017]. Most frequently used agents for maintenance therapy in autoimmune encephalitis include mycophenolate mofetil, azathioprine and methotrexate. These drugs are generally referred to as steroid sparers, and are widely used for prevention of transplant rejection and in a large array of autoimmune diseases, including rheumatologic, dermatologic, gastrointestinal and neurologic conditions [Nosadini, 2017]. The utility and the safety of mycophenolate mofetil, azathioprine and methotrexate in paediatric autoimmune encephalitis have not been thoroughly explored yet. In this context, we carried out a systematic literature review with the aim of collecting available data on the use of steroid sparing agents in paediatric anti-NMDAR encephalitis, with focus on the most frequent modes of use, tolerability and efficacy.

Methods

We conducted a systematic literature review on the use of steroid sparing agents (mycophenolate mofetil, azathioprine and methotrexate) for paediatric-onset anti-NMDAR encephalitis. The search was carried out in Pubmed, up to date to 30.10.2017, with the search terms “anti–N-methyl-D-aspartate receptor encephalitis” OR “N-methyl-D-aspartate antibody encephalitis” OR “anti-NMDAR encephalitis” OR “NMDA receptor encephalitis". The available articles were filtered manually for patients in paediatric age (≤18 years), and searched for “mycophenolate”, "azathioprine", and "methotrexate".

Articles reporting patients who received mycophenolate mofetil, azathioprine and/or methotrexate for paediatric-onset anti-NMDAR encephalitis were included. Articles reporting mixed populations of children and adults, in which the age of the patients treated with mycophenolate mofetil, azathioprine and/or methotrexate was not clear, were excluded.

Articles were searched for data on demographics, disease severity and course, treatment, efficacy and tolerability of mycophenolate mofetil, azathioprine and methotrexate. For disease severity, the modified Rankin Scale (mRS) [van Swieten, 1988] was used, as reported in the original article or scored by one of the main authors (MN), when not available in the text. The annualised relapse rate (ARR) was calculated as number of disease events multiplied by 12 (months), divided by the number of months during which the events occurred (calculated only for time intervals ≥6 months). ARR was calculated before (both including and excluding first events), during and after treatment with mycophenolate mofetil, azathioprine and methotrexate.

Adverse reactions to mycophenolate mofetil, azathioprine and methotrexate were classified using the Common Terminology Criteria for Adverse Events (CTCAE v4.0), into grade 1 (mild), 2 (moderate), 3 (severe or medically significant but not immediately life-threatening), 4 (life-threatening consequences) and 5 (death) [ref].

Data collection was subject to data availability, therefore in the results section of this work denominators may differ.

X^2 or Fisher's tests were used for statistical analysis to compare risk of relapses between different subgroups of patients. The level of statistical significance was set at $p<0.05$.

Results

37 articles reporting a total of 76 patients treated with mycophenolate mofetil, azathioprine and/or methotrexate for paediatric-onset anti-NMDAR encephalitis were included in the literature review [Agrawal, 2010; Kruer, 2010; Shah, 2011; Dale, 2013; Armangue, 2013; Baizabal-Carvallo, 2013; Suleiman, 2013; Kayser, 2013; Bravo-Oro, 2013; Hacohen, 2014; Titulaer, 2014; Hacohen, 2014; Salvucci, 2014; Sommeling, 2014; Guo, 2014; Tatencloux, 2015; Finke, 2015; Nosadini, 2015; Sartori, 2015; Bravo-Oro, 2015; Wright, 2015; DeSena, 2015; Mohammad, 2015; Zekeridou, 2015; Matoq, 2015; Lu, 2016; Suthar, 2016; Liba, 2016; Iizuka, 2016; Brenton, 2016; Hacohen, 2016; Foff, 2017; Hinkle, 2017; Zhang, 2017; Haberlandt, 2017; Jones, 2017; Goldberg, 2017]. Most of the articles were published between 2014 and 2017 (24/37, 64.9%). Data relative to the whole cohort of patients with paediatric-onset anti-NMDAR encephalitis treated with mycophenolate mofetil, azathioprine and/or methotrexate are detailed in Table 1, whereas Table 2 provides efficacy and tolerability data according to treatment group for each of these three agents.

Demographics. Median age at onset of anti-NMDAR encephalitis was 11 years (mean 10.2, range 0.8-18; data available in 65/76), and 69.7% (46/66) of the patients were females. Tumour was reported in 2 patients [Brenton, 2016; Sommeling, 2016].

Disease severity and disease course. In the acute phase, median mRS was 5 (mean 4.4, range 2-5; data available in 51/76), and 49.1% of the patients had relapses (28/57). In the cases with relapsing disease course, median number of total events per patient (including disease onset) was 3 (mean 3.3, range 2-11; data available in 25/28).

Treatment. Immune therapy was started within 30 days from disease onset in 59.2% of patients (16/27). All children in our literature cohort received steroids (65/65, 100%), 80% IVIG (52/65), and 49.2% underwent plasma exchange (32/65). Second-line treatments were used in 62.9% (39/62): rituximab in 50% (31/62), and cyclophosphamide in 34.9% (22/63). As per inclusion criteria, all patients received maintenance immune therapy with steroid sparing agents (76/75, 100%): 53.9% received mycophenolate mofetil (41/76), 25% azathioprine (19/76) and 15.8% methotrexate (12/76); an additional 5.3% of patients received a combination of these treatments (4/76). Methotrexate was administered intrathecally in 3 patients [Tatencloux, 2015; Jones 2017].

Table 1

DEMOGRAPHICS IN THE WHOLE LITERATURE COHORT (patients with paediatric-onset anti-NMDAR encephalitis treated with MMF/AZA/MTX)	
Total number of articles included in the literature review	37
publishing year 2010-2013	13/37 (35.1%)
publishing year 2014-2017	24/37 (64.9%)
Total number of patients	76*
Proportion of females	46/66 (69.7%) (data available in 66/76)
Age at disease onset (years)	Median 11, mean 10.2, range 0.8-18 (data available in 65/76)
Tumour	2/76 (2.6%)°
DISEASE COURSE IN THE WHOLE LITERATURE COHORT	
Worst mRS in the acute phase	Median 5, mean 4.4, range 2-5 (data available in 51/76)
Relapsing disease course	28/57 (49.1%) (data available in 57/76)
TREATMENT IN THE WHOLE LITERATURE COHORT	
Time to first immune therapy ≤30 days	16/27 (59.2%) (data available in 27/76)
First and second-line immune therapies during the whole disease course	
Steroids	65/65 (100%) (data available in 65/76)
IVIG	52/65 (80%) (data available in 65/76)
PE	32/65 (49.2%) (data available in 65/76)
Any second-line immune therapy (RTX and/or CYC)	39/62 (62.9%) (data available in 62/76)
RTX	31/62 (50%) (data available in 62/76)
CYC	22/63 (34.9%) (data available in 63/76)
Maintenance treatment with steroid sparers MMF/AZA/MTX	76/76 (100%)
MMF	41/76 (53.9%)
AZA	19/76 (25%)
MTX	12/76 (15.8%)
AZA + MTX	2/76 (2.6%)
MMF + AZA	1/76 (1.3%)
MMF + MTX	1/76 (1.3%)
MODES OF USE OF MMF, AZA, MTX	
Any second-line immune therapy (RTX and/or CYC) before MMF/AZA/MTX	34/65 (52.3%) (data available in 65/76)
Number of events after which MMF/AZA/MTX were started	Median 1, mean 2, range 1-11 (data available in 47/76)
After ≥2 events	22/47 (46.8%) (data available in 47/76)
Timing of administration of MMF/AZA/MTX from disease onset ≤6 months	17/34 (50%) (data available in 34/76)

Table 1. Demographics, disease course and treatment in the whole literature cohort of patients with paediatric-onset anti-NMDAR encephalitis treated with mycophenolate mofetil, azathioprine and/or methotrexate.
Legend: anti-NMDAR: anti-N-methyl-D-aspartate receptor; AZA: azathioprine; CYC: clyclophosphamide; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; mRS: modified Rankin Scale; MTX: methotrexate; PE: plasma exchange; RTX: rituximab.
*4/76 patients had associated demyelinating episodes: 2/76 patients also had a brainstem syndrome with demyelination [Hacohen, 2014; Titulaer, 2014]; 1/76 patients also had NMOSD [Titulaer, 2014]; 1/76 patient had a single area of demyelination [Titulaer, 2014])
°1 girl had an ovatian teratoma [Brenton, 2016] and 1 boy had a mediastinal teratoma [Sommeling, 2016]

Modes of use of mycophenolate mofetil, azathioprine and methotrexate. Age at commencement of steroid sparing agents was <13 years in 42.8% of patients (24/56), and <6 years in 12.5% (7/56). 47.7% of patients (31/65) did not receive any second-line immune therapy (rituximab and/or cyclophosphamide) before mycophenolate mofetil, azathioprine and/or methotrexate. Timing of initiation of maintenance immune therapy with mycophenolate mofetil, azathioprine and/or methotrexate was within 6 months from onset in 50% only (17/34). In nearly half of the patients, steroid sparers were started only after relapses had occurred (22/47, 46.8%). Median treatment duration with

steroid sparers was highly variable (median 9 months, mean 12.9, range 1-48; data available in 30/76 patients) (Table 2).

Table 2

DISEASE COURSE AND OUTCOME ACCORDING TO TYPE OF MAINTENANCE IMMUNE THERAPY WITH STEROID SPARERS (MMF/AZA/MTX)			
	MMF (n=43)*	**AZA (n=22)****	**MTX (n=15)*****
Worst mRS in the acute phase	Median 5, mean 4.3, range 2-5 (data available in 28/43)	Median 4.5, mean 4.3, range 3-5 (data available in 14/22)	Median 5, mean 4.5, range 3-5 (data available in 12/15)
mRS 2-3	7/28 (25%)	3/14 (21.4%)	1/12 (8.3%)
mRS 4-5	21/28 (75%)	11/14 (78.6%)	11/12 (91.7%)
Relapsing disease course	21/42 (50%) (data available in 42/43)	6/12 (50%) (data available in 12/22)	3/7 (42.8%) (data available in 7/15)
Onset to first immune therapy ≤30 days	10/14 (71.4%) (data available in 14/43)	6/10 (60%) (data available in 10/22)	2/5 (40%) (data available in 5/15)
RTX and/or CYC during disease course	21/41 (51.2%) (data available in 41/43)	9/14 (64.3%) (data available in 14/22)	12/13 (92.3%) (data available in 13/15)
RTX and/or CYC after 1st event	12/20 (60%) (data available in 20/21)	5/6 (83.3%) (data available in 6/9)	2/4 (50%) (data available in 4/12)
Age at MMF/AZA/MTX administration (years)	Median 8.2, mean 10.3, range 2.2-26 (data available in 19/43)	Median 16.4, mean 13.9, range 3.5-18.5 (data available in 9/22)	Median 12.2, mean 11.6, range 6-17.1 (data available in 6/15)
Disease course before treatment with MMF/AZA/MTX			
Time from disease onset to initiation of MMF/AZA/MTX (months)	Median 9.5, mean 16.3, range 1.2-60 (data available in 18/43)	Median 5, mean 4.3, range 2-5 (data available in 13/29)	Median 7.5, mean 16.2, range 5-45 (data available in 4/15)
≤6 months	8/21 (38.1%) (data available in 21/43)	5/10 (50%) (data available in 10/22)	4/6 (66.7%) (data available in 6/15)
Number of events before MMF/AZA/MTX (including 1st events)	Median 1.5, mean 2.2, range 1-11 (data available in 34/43)	Median 1, mean 1.6, range 1-4 (data available in 10/22)	Median 1.5, mean 2.2, range 1-5 (data available in 6/15)
MMF/AZA/MTX after 1st event	17/34 (50%)	6/10 (60%)	3/6 (50%)
ARR before MMF/AZA/MTX (excluding 1st events)#	Median 0.6, median 1.1, range 0-6.7 (data available in 12/43)	Median 0.5, mean 0.8, range 0-2 (data available in 8/22)	Median 0.5, mean 0.5, range 0-1.1 (data available in 2/15)
Disease course during treatment with MMF/AZA/MTX			
Duration of treatment with MMF/AZA/MTX (months)	Median 9, mean 14, range 1-48 (data available in 19/43)	Median 2, mean 13.3, range 1-36 (data available in 7/22)	Median 6, mean 6, range 2-12 (data available in 5/15)
Proportion of patients who relapsed during treatment with MMF/AZA/MTX	4/35 (11.4%) (data available in 35/43)	1/10 (10%) (data available in 10/22)	0/6 (0%) (data available in 6/15)
ARR during treatment with MMF/AZA/MTX	Median 0, mean 0.08, range 0-1.3 (data available in 16/43)	Median 0, mean 0.2, range 0-1 (data available in 4/22)	Median 0, mean 0, range 0-0 (data available in 4/15)
Disease course after discontinuation of MMF/AZA/MTX (if applicable)			
Proportion of patients who discontinued treatment with MMF/AZA/MTX	4/16 (25%) (data available in 16/43)	4/7 (57.1%) (data available in 7/22)	4/5 (80%) (data available in 5/15)
Time between discontinuation to last follow-up (months)	Median 14, mean 14, range 6-22 (data available in 2/4)	Median 6, mean 8.3, range 1-18 (data available in 3/4)	Mean 13, median 13.2, range 2-25 (data available in 4/4)
Proportion of patients who relapsed after MMF/AZA/MTX discontinuation	0/4 (0%) (data available in 4/4)	0/3 (0%) (data available in 3/4)	0/4 (0%) (data available in 4/4)
ARR after MMF/AZA/MTX discontinuation	Median 0, mean 0, range 0-0 (data available in 2/4)	Median 0, mean 0, range 0-0 (data available in 2/4)	Mean 0, median 0, range 0-0 (data available in 3/4)
Adverse reactions to MMF/AZA/MTX and outcome			
Adverse reactions to MMF/AZA/MTX	2/32 (6.2%) (data available in 32/43): CMV colitis; respiratory infection	0/14 (0%) (data available in 14/22)	0/12 (0%) (data available in 12/15)
Length of follow-up from disease onset (years)	Median 1.9, mean 2.5, range 0.2-8.6 (data available in 34/43)	Median 2, median 2.4, range 0.7-5.2 (data available in 25/29)	Mean 2.1, median 2.6, range 1-5.2 (data available in 5/11)
mRS at last follow-up	(data available in 37/43)	(data available in 14/22)	(data available in 5/15)
mRS 0-1	23/37 (62.2%)	8/14 (57.1%)	3/5 (60%)
mRS 2-3	14/37 (37.8%)	4/14 (28.6%)	2/5 (40%)
mRS 4-5	0/37 (0%)	2/14 (14.3%)	0/5 (0%)

Table 2. Disease course and outcome according to type of maintenance immune therapy (mycophenolate mofetil / azathioprine / methotrexate) in the literature cohort of patients with paediatric-onset anti-NMDAR encephalitis treated with mycophenolate mofetil, azathioprine and/or methotrexate. Denominators vary according to data availability.

Legend: anti-NMDAR: anti-N-methyl-D-aspartate receptor; AZA: azathioprine; CMV: cytomegalovirus; CYC: cyclophosphamide; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; mRS: modified Rankin Scale; MTX: methotrexate; PE: plasma exchange; RTX: rituximab.

*1/43 of these patients also received AZA, and 1/43 also received MTX

**2/22 of these patients also received MTX, and 1/22 also received MMF
**2/15 of these patients also received AZA, and 1/15 also received MMF
#In the 72/76 patients who received monotherapy with mycophenolate mofetil, azathioprine or methotrexate, the median ARR before steroid sparers was 1.4 (mean 2.1, range 0.6-7.3; data available in 16/72) (including the first episode) (median 0.45, mean 1, range 0-6.67 after excluding the first episode; data available in 16/72)

Efficacy of mycophenolate mofetil, azathioprine and methotrexate. Among the 25 patients in whom mycophenolate mofetil, azathioprine and/or methotrexate were given after the first event, relapses occurred in 8.3% (2/24; data available in 24/25). Among the 22 patients in whom mycophenolate mofetil, azathioprine and/or methotrexate were given after at least one relapse had occurred, further relapses occurred in 18.2% (4/22; data available in 22/22).

Among the 28 patients with relapsing disease course, in only 8.3% (2/24; data available in 24/28) steroid sparers had been given after the first event. During treatment with these agents, relapses occurred in 10.4% (5/48) patients (total 6 relapses in 5 patients). Proportion of patients who had relapses whilst on treatment with mycophenolate mofetil, azathioprine and/or methotrexate was similar for mycophenolate mofetil (4/35, 11.4%) and azathioprine (1/10, 10%), whereas no patients relapsed whilst on methotrexate (0/6, 0%).

In the 72/76 patients who received monotherapy with mycophenolate mofetil, azathioprine or methotrexate (rather than a combination of these agents), the median ARR before steroid sparers was 0.45 (mean 1, range 0-6.67; data available in 16/72) (excluding the first episode), and median ARR during/after steroid sparers was 0 (mean 0.06, range 0-1.3; data available in 22/72). In the 9/72 patients with monotherapy and availability of both ARR pre and during/after steroid sparing agents, ARR before treatment (excluding first events) was median 0.5 (mean 1.14, range 0-6.67), and ARR during/after treatment was median 0 (mean 0.19, range 0-1.3). ARR data subdivided according to steroid sparing agent received are represented in Table 2, with the limitation imposed by the restricted number of cases.

Tolerability of mycophenolate mofetil, azathioprine and methotrexate. Adverse reactions were reported only for mycophenolate mofetil in 2 cases, with grade 3 severity according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (severe or medically significant, but not immediately life-threatening) (cytomegalovirus colitis and respiratory infection, respectively).

Treatment-related factors influencing relapse risk. The proportion of patients who relapsed was significantly higher among patients in whom the first immune therapy (any) was started late (>30 days after onset) (6/7, 85.7%; second-line treatments used in 5/7 of these, 71.4%) than in patients who were treated early (5/16, 31.2%; second-line treatments used in 9/16 of these, 56.2%) (p=0.0272). Among the patients not treated with second-line immune therapy after the first event, further relapses after second-line therapy occurred in 50% (5/10), while in patients treated with second-line immune therapy after the first event relapses occurred in 16.7% (3/18) (p=0.0913). Relapse rate was only marginally higher among patients in whom mycophenolate mofetil, azathioprine or methotrexate were started after 6 months from onset (10/17, 58.8%; second-line treatments used in 11/17 of these, 64.7%), than in those treated within 6 months from onset (8/16, 50%; second-line treatments used in 6/16 of these, 37.5%) (p=0.7319).

Discussion

Our systematic literature review disclosed that the use of mycophenolate mofetil, azathioprine and methotrexate in paediatric-onset anti-NMDAR encephalitis is quite heterogeneous. Firstly, while all patients in our literature cohort received first-line immune therapy before steroid sparers, second-line treatments (rituximab and/or cyclophosphamide) were administered only in 52.3% (34/65). Secondly, there was a huge variability in the timing of initiation of maintenance immune therapy with mycophenolate mofetil, azathioprine and methotrexate, with only 50% (17/34) of the patients started on one of these agents within 6 months from onset. Similarly, only in 53.2% were these treatments started after the first event (25/47), whereas for the remaining part they were introduced only after one or more relapses had occurred. In this regard, the high relapse rate in our literature cohort (28/57, 49.1%), as compared to that of the largest series available so far (12%) [Titulaer, 2013], confirms that steroid sparers are often used only after relapses have occurred.

The duration of maintenance treatment with steroid sparing agents was also highly variable in our literature cohort, reflecting the lack of recommendations [Shin, 2017]. Indeed, it is unclear how long the inflammatory component of disease lasts for. In this respect, the correlation between anti-NMDAR

antibodies and clinical course is unclear [Mariotto, 2017], while there is some correlation of CXCL13 and disease severity and relapse [Kothur, 2016; Kothur, 2017] that may be useful in guiding treatment.

It is still unclear in the available literature whether long-term immunosuppression with oral agents is effective in reducing the relapse rate of autoimmune encephalitis [Shin, 2017]. In the subset of patients who were started on maintenance immune therapy after the first event, relapse rate (2/24, 8.3%) appeared to be slightly lower than that reported in some of the main literature series, where this figure mostly ranges between 12% [Titulaer, 2013] and 22.7% [Irani, 2010; Wright 2015; Shin, 2017]. Although, our result is limited by the very small number of cases in this subgroup of patients.

In our literature cohort, there was a higher relapse rate among patients in whom the first immune therapy was started late (>30 days after onset) (6/7, 85.7%) than in patients who were treated early (5/16, 31.2%). Similarly, a late start of mycophenolate mofetil, azathioprine or methotrexate (after 6 months from onset) seemed to associate with a slightly higher proportion of patients who relapsed (10/17, 58.8%), as compared to those treated early (8/16, 50%). These results are consistent with previous data in the literature, supporting early commencement of immune therapy [Nosadini, 2015].

In our literature cohort, the use of mycophenolate mofetil prevailed over azathioprine and methotrexate. These agents were administered also in young ages, especially as regards mycophenolate mofetil and azathioprine. Adverse reactions were reported only for mycophenolate mofetil in 2 cases (cytomegalovirus colitis and respiratory infection) [Brenton, 2016]. Although, it should be noticed that side effects were probably under-reported and lacking in details in our review, since none of the articles were focused on drug tolerability.

Our literature review is limited by several factors. The retrospective nature of data collection unavoidably impacts on data accuracy and completeness. Several pieces of information, such as drug doses and monitoring, could not be retrieved in the great majority of papers and therefore were omitted. Severity of disease was estimated via the mRS score, although this scale was not designed to detect and render the vast array of disturbances that characterise anti-NMDAR encephalitis, especially as regards movement disorder, autonomic disturbances, psychiatric symptoms and neuropsychological changes [Matricardi, 2016]. Moreover, when not given in the original report, the mRS was scored by only one of the main authors (MN). ARR (Table 2) was calculated in order to provide data on the tendency to relapse before, during and after treatment with mycophenolate mofetil, azathioprine, or methotrexate;

although, the utility of ARR in this setting is strongly limited by the consideration that, although recurrences are possible, anti-NMDAR encephalitis is typically not a chronic relapsing disease. The analysis of the results of our literature review is also limited by the restricted number of patients, especially when subdivided according to treatment type; therefore, a comparison between efficacy of mycophenolate mofetil, azathioprine and methotrexate could not be carried out. In view of the inclusion criteria, also a direct comparison between disease course in the patients who did and did not receive one of these agents could not be performed; this would be of great clinical interest and warrants further studies. Similarly, the efficacy of steroid sparers for sustained remission and relapse prevention should be explored further in comparison to other approaches proposed in the literature, such as monthly rituximab, IVIG or plasma exchange, or sustained use of oral corticosteroids [Shin, 2017; Dale, 2017].

Despite these important limitations, our literature review is the first work exploring most frequent current treatment modes, efficacy and tolerability of mycophenolate mofetil, azathioprine, and methotrexate in paediatric-onset anti-NMDAR encephalitis. Our review disclosed a huge heterogeneity in the use of these agent in paediatric-onset anti-NMDAR encephalitis, especially as regards the overall associated immune therapies, the timing and the duration of treatment.

Our review highlights the need for improved data in larger cohorts. While paediatric anti-NMDAR encephalitis is usually characterised by a relatively good outcome, relapses are possible. Likewise as highlighted in this review, some clinicians use steroid sparing agents early in disease course, and without relapse, presumably to potentially reduce the steroid burden. However, the ‘risk versus benefit’ of this practice, as this review demonstrates, is unclear.

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References

Agrawal S, Vincent A, Jacobson L, Milford D, Gupta R, Wassmer E. Successful treatment of anti N-methyl-d-aspartate receptor limbic encephalitis in a 22-month old child with plasmapheresis and pharmacological immunomodulation. Arch Dis Child. 2010 Apr;95(4):312.

Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, Dalmau J; Spanish Anti-N-methyl-D-Aspartate Receptor (NMDAR) Encephalitis Work Group. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr. 2013 Apr;162(4):850-856.e2.

Baizabal-Carvallo JF, Stocco A, Muscal E, Jankovic J. The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Mov Disord. 2013 Apr;28(4):543-7.

Bartolini L, Muscal E. Differences in treatment of anti-NMDA receptor encephalitis: results of a worldwide survey. J Neurol. 2017 Apr;264(4):647-653.

Bravo-Oro A, Abud-Mendoza C, Quezada-Corona A, Dalmau J, Campos-Guevara V. [Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis: experience with six pediatric patients. Potential efficacy of methotrexate]. Rev Neurol. 2013 Nov 1;57(9):405-10. Spanish.

Bravo-Oro A, Acosta-Yebra D, Grimaldo-Zapata IP, Reyes-Vaca G. [Reversible cortical atrophy secondary to anti-NMDA receptor antibody encephalitis]. Rev Neurol. 2015 May 16;60(10):447-52. Review. Spanish.

Brenton JN, Kim J, Schwartz RH. Approach to the Management of Pediatric-Onset Anti-N-Methyl-d-Aspartate (Anti-NMDA) Receptor Encephalitis: A Case Series. J Child Neurol. 2016 Aug;31(9):1150-5.

Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 (accessed on 25.09.2017)

Dale RC, Gorman MP, Lim M. Autoimmune encephalitis in children: clinical phenomenology, therapeutics, and emerging challenges. Curr Opin Neurol. 2017 Jun;30(3):334-344.

Dale RC, Pillai S, Brilot F. Cerebrospinal fluid CD19(+) B-cell expansion in N-methyl-D-aspartate receptor encephalitis. Dev Med Child Neurol. 2013 Feb;55(2):191-3.

Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011 Jan;10(1):63-74.

Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007 Jan;61(1):25-36.

DeSena AD, Noland DK, Matevosyan K, King K, Phillips L, Qureshi SS, Greenberg BM, Graves D. Intravenous methylprednisolone versus therapeutic plasma exchange for treatment of anti-N-methyl-D-aspartate receptor antibody encephalitis: A retrospective review. J Clin Apher. 2015 Aug;30(4):212-6.

Finke C, Kopp UA, Pajkert A, Behrens JR, Leypoldt F, Wuerfel JT, Ploner CJ, Prüss H, Paul F. Structural Hippocampal Damage Following Anti-N-Methyl-D-Aspartate Receptor Encephalitis. Biol Psychiatry. 2015 Feb 26. pii: S0006-3223(15)00149-3.

Foff EP, Taplinger D, Suski J, Lopes MB, Quigg M. EEG Findings May Serve as a Potential Biomarker for Anti-NMDA Receptor Encephalitis. Clin EEG Neurosci. 2017 Jan;48(1):48-53.

Gadian J, Kirk E, Holliday K, Lim M, Absoud M. Systematic review of immunoglobulin use in paediatric neurological and neurodevelopmental disorders. Dev Med Child Neurol. 2017 Feb;59(2):136-144.

Gastaldi M, Thouin A, Vincent A. Antibody-Mediated Autoimmune Encephalopathies and Immunotherapies. Neurotherapeutics. 2016 Jan;13(1):147-62.

Goldberg TN, Cellucci MF. New Onset Insomnia in a Pediatric Patient: A Case of Anti-NMDA Receptor Encephalitis. Case Rep Pediatr. 2017;2017:4083785.

Guo YH, Kuan TS, Hsieh PC, Lien WC, Chang CK, Lin YC. Rehabilitation for a child with recalcitrant anti-N-methyl-d-aspartate receptor encephalitis: case report and literature review. Neuropsychiatr Dis Treat. 2014 Nov 24;10:2263-7.

Haberlandt E, Ensslen M, Gruber-Sedlmayr U, Plecko B, Brunner-Krainz M, Schimmel M, Schubert-Bast S, Neirich U, Philippi H, Kurleman G, Tardieu M, Wohlrab G, Borggraefe I, Rostásy K. Epileptic phenotypes, electroclinical features and clinical characteristics in 17 children with anti-NMDAR encephalitis. Eur J Paediatr Neurol. 2017 May;21(3):457-464.

Hacohen Y, Absoud M, Hemingway C, Jacobson L, Lin JP, Pike M, Pullaperuma S, Siddiqui A, Wassmer E, Waters P, Irani SR, Buckley C, Vincent A, Lim M. NMDA receptor antibodies associated with distinct white matter syndromes. Neurol Neuroimmunol Neuroinflamm. 2014 Apr 24;1(1):e2.

Hacohen Y, Deiva K, Pettingill P, Waters P, Siddiqui A, Chretien P, Menson E, Lin JP, Tardieu M, Vincent A, Lim MJ. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. Mov Disord. 2014 Jan;29(1):90-6.

Hacohen Y, Wright S, Gadian J, Vincent A, Lim M, Wassmer E, Lin JP. N-methyl-d-aspartate (NMDA) receptor antibodies encephalitis mimicking an autistic regression. Dev Med Child Neurol. 2016 Oct;58(10):1092-4.

Hinkle CD, Porter JN, Waldron EJ, Klein H, Tranel D, Heffelfinger A. Neuropsychological characterization of three adolescent females with anti-NMDA receptor encephalitis in the acute, post-acute, and chronic phases: an inter-institutional case series. Clin Neuropsychol. 2017 Jan;31(1):268-288.

Iizuka T, Kaneko J, Tominaga N, Someko H, Nakamura M, Ishima D, Kitamura E, Masuda R, Oguni E, Yanagisawa T, Kanazawa N, Dalmau J, Nishiyama K. Association of Progressive Cerebellar Atrophy With Long-term Outcome in Patients With Anti-N-Methyl-d-Aspartate Receptor Encephalitis. JAMA Neurol. 2016 Jun 1;73(6):706-13.

Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain. 2010;133:1655–1667.

Jones HF, Mohammad SS, Reed PW, Dunn PPJ, Steele RH, Dale RC, Sharpe C. Anti-N-methyl-d-aspartate receptor encephalitis in Māori and Pacific Island children in New Zealand. Dev Med Child Neurol. 2017 Jul;59(7):719-724.

Kahn I, Helman G, Vanderver A, Wells E. Anti- N-Methyl-d-Aspartate (NMDA) Receptor Encephalitis. J Child Neurol. 2017 Feb;32(2):243-245.

Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti–N-methyl-d-aspartate receptor encephalitis. JAMA Neurol. 2013 Sep 1;70(9):1133-9.

Kothur K, Gill D, Wong M, Mohammad SS, Bandodkar S, Arbunckle S, Wienholt L, Dale RC. Cerebrospinal fluid cyto-/chemokine profile during acute herpes simplex virus induced anti-N-methyl-d-aspartate receptor encephalitis and in chronic neurological sequelae. Dev Med Child Neurol. 2017 Aug;59(8):806-814.

Kothur K, Wienholt L, Mohammad SS, Tantsis EM, Pillai S, Britton PN, Jones CA, Angiti RR, Barnes EH, Schlub T, Bandodkar S, Brilot F, Dale RC. Utility of CSF Cytokine/Chemokines as Markers of Active Intrathecal Inflammation: Comparison of Demyelinating, Anti-NMDAR and Enteroviral Encephalitis. PLoS One. 2016 Aug 30;11(8):e0161656.

Kruer MC, Koch TK, Bourdette DN, Chabas D, Waubant E, Mueller S, Moscarello MA, Dalmau J, Woltjer RL, Adamus G. NMDA receptor encephalitis mimicking seronegative neuromyelitis optica. Neurology. 2010 May 4;74(18):1473-5.

Lancaster E. The Diagnosis and Treatment of Autoimmune Encephalitis. J Clin Neurol. 2016 Jan;12(1):1-13.

Liba Z, Kayserova J, Elisak M, Marusic P, Nohejlova H, Hanzalova J, Komarek V, Sediva A. Anti-N-methyl-D-aspartate receptor encephalitis: the clinical course in light of the chemokine and cytokine levels in cerebrospinal fluid. J Neuroinflammation. 2016 Mar 3;13(1):55.

Lu T, Cai W, Qiu W, Sun X, Lu Z. Brainstem and vestibulocochlear nerve involvement in relapsing-remitting anti-NMDAR encephalitis. Neurol Sci. 2016 Jan;37(1):149-51.

Mariotto S, Andreetta F, Farinazzo A, Monaco S, Ferrari S. Persistence of anti-NMDAR antibodies in CSF after recovery from autoimmune encephalitis. Neurol Sci. 2017 Aug;38(8):1523-1524.

Matoq AA, Rappoport AS, Yang Y, O'Babatunde J, Bakerywala R, Sheth RD. Anti-NMDA-receptor antibody encephalitis in infants. Epilepsy Behav Case Rep. 2015 Nov 4;4:99-101.

Matricardi S, Patrini M, Freri E, Ragona F, Zibordi F, Andreetta F, Nardocci N, Granata T. Cognitive and neuropsychological evolution in children with anti-NMDAR encephalitis. J Neurol. 2016 Apr;263(4):765-71.

McKeon A. Paraneoplastic and other autoimmune disorders of the central nervous system. Neurohospitalist. 2013 Apr;3(2):53-64.

Mohammad SS, Jones H, Hong M, Nosadini M, Sharpe C, Pillai SC, Brilot F, Dale RC. Symptomatic treatment of children with anti-NMDAR encephalitis. Dev Med Child Neurol. 2015 Aug 28.

Nosadini M, Boniver C, Zuliani L, de Palma L, Cainelli E, Battistella PA, Toldo I, Suppiej A, Sartori S. Longitudinal electroencephalographic (EEG) findings in pediatric anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis: the Padua experience. J Child Neurol. 2015 Feb;30(2):238-45.

Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother. 2015;15(12):1391-419.

Nosadini M, Mohammad SS, Suppiej A, et al: Intravenous immunoglobulin in paediatric neurology: safety, adherence to guidelines, and long-term outcome. Dev Med Child Neurol 58: 1180-1192; 2016.

Nosadini, Sharma, Sartori, Dale, Seminars in Pediatric Neurology 2017

Salvucci A, Devine IM, Hammond D, Sheth RD. Pediatric anti-NMDA (N-methyl D-aspartate) receptor encephalitis. Pediatr Neurol. 2014 May;50(5):507-10.

Sartori S, Nosadini M, Cesaroni E, Falsaperla R, Capovilla G, Beccaria F, Mancardi MM, Santangelo G, Giunta L, Boniver C, Cantalupo G, Cappellari A, Costa P, Dalla Bernardina B, Dilena R, Natali Sora

MG, Pelizza MF, Pruna D, Serino D, Vanadia F, Vigevano F, Zamponi N, Zanus C, Toldo I, Suppiej A. Paediatric anti-N-methyl-D-aspartate receptor encephalitis: The first Italian multicenter case series. Eur J Paediatr Neurol. 2015 Jul;19(4):453-63.

Shah R, Veerapandiyan A, Winchester S, Gallentine W, Mikati MA. Two patients with an anti-N-methyl-D-aspartate receptor antibody syndrome-like presentation and negative results of testing for autoantibodies. Pediatr Neurol. 2011 Dec;45(6):412-6.

Shin Y-W, Lee S-T, Park K-I, Jung K-H, Jung K-Y, Lee SK, Chu K. Treatment strategies for autoimmune encephalitis. Ther Adv Neurol Disord 2017. 1-19.

Sommeling C, Santens P. Anti-N-methyl-D-aspartate (anti-NMDA) receptor antibody encephalitis in a male adolescent with a large mediastinal teratoma. J Child Neurol. 2014 May;29(5):688-90.

Suleiman J, Brilot F, Lang B, Vincent A, Dale RC. Autoimmune epilepsy in children: case series and proposed guidelines for identification. Epilepsia. 2013 Jun;54(6):1036-45.

Suppiej A, Nosadini M, Zuliani L, Pelizza MF, Toldo I, Bertossi C, Tison T, Zoccarato M, Marson P, Giometto B, Dale RC, Sartori S. Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review. Brain Dev. 2016 Aug;38(7):613-22.

Suthar R, Saini AG, Sankhyan N, Sahu JK, Singhi P. Childhood Anti-NMDA Receptor Encephalitis. Indian J Pediatr. 2016 Jul;83(7):628-33.

Tatencloux S, Chretien P, Rogemond V, Honnorat J, Tardieu M, Deiva K. Intrathecal treatment of anti-N-Methyl-D-aspartate receptor encephalitis in children. Dev Med Child Neurol. 2015 Jan;57(1):95-9.

Titulaer MJ, Höftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, Benson LA, Shu H, Irioka T, Hirano M, Singh G, Cobo Calvo A, Kaida K, Morales PS, Wirtz PW, Yamamoto T, Reindl M, Rosenfeld MR, Graus F, Saiz A, Dalmau J. Overlapping demyelinating syndromes and anti–N-methyl-D-aspartate receptor encephalitis. Ann Neurol. 2014 Mar;75(3):411-28.

Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12:157–165.

van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988; 19: 604-7.

Wright S, Hacohen Y, Jacobson L, Agrawal S, Gupta R, Philip S, Smith M, Lim M, Wassmer E, Vincent A. N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. Arch Dis Child. 2015 Jun;100(6):521-6.

Zekeridou A, Karantoni E, Viaccoz A, Ducray F, Gitiaux C, Villega F, Deiva K, Rogemond V, Mathias E, Picard G, Tardieu M, Antoine JC, Delattre JY, Honnorat J. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. J Neurol. 2015 Aug;262(8):1859-66.

Zhang W, Yan L, Jiao J. Repeated misdiagnosis of a relapsed atypical anti-NMDA receptor encephalitis without an associated ovarian teratoma. Neurosci Lett. 2017 Jan 18;638:135-138.

Zuliani L, Graus F, Giometto B, Bien C, Vincent A. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. J Neurol Neurosurg Psychiatry. 2012 Jun;83(6):638-45.

3.3.6 Mycophenolate mofetil in paediatric CNS autoimmune or immune-mediated inflammatory diseases

In progress

Mycophenolate mofetil in paediatric CNS autoimmune or immune-mediated inflammatory diseases

Authors

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Key words

Mycophenolate mofetil; autoimmune; immune-mediated; central nervous system; children; paediatric; safety; efficacy.

Abstract

Background. Recommendations and data on mycophenolate mofetil (MMF) use, safety and efficacy in paediatric neuroimmunology are limited, and information is mostly derived from other fields of paediatrics.

Methods. Retrospective, international study on children treated with MMF for autoimmune or immune-mediated CNS conditions, with focus on MMF modes of use, efficacy and safety.

Results. 44 children were included (30/44, 68.2% females). 43.2% (19/44) had proven or suspected autoimmune encephalitis, 31.8% (14/44) autoimmune inflammatory demyelinating CNS diseases, and 25% (11/44) other autoimmune/immune-mediated CNS conditions. Worst mRS was median 4 (range 2-6). Disease course was relapsing in 52.3% (23/44), monophasic in 38.6% (17/44), and chronic/chronic-progressive in 9.1% (4/44). Before MMF, all patients received first-line (steroids: 44/44, 100%; intravenous immunoglobulin: 23/44, 52.3%; plasma exchange: 14/44, 31.8%) and 38.6% (17/44) second-line immune therapies (cyclophosphamide: 12/44, 27.3%; rituximab: 6/44, 13.6%). Median age at MMF commencement was 9.3 years (range 1.4-16.4). MMF was started at median 9.5 months from onset (range 1-127; ≤6 months in 31.8%, 14/44). In 55% (22/40) of patients, MMF was started only after ≥2 events had occurred. Median duration of MMF treatment was 18 months (mean 23.2, range 0.3-73). Median annualised relapse rate (excluding patients with chronic/chronic-progressive disease) was 0.52 (mean 0.86, range 0-3) before MMF (excluding first events), and 0 (mean 0.36, range 0-4.64) during MMF. 20.5% (8/39) patients relapsed during MMF; compared to patients who did not relapse (31/49, 79.5%), these patients were younger (median age at onset 4.2 years versus 7.6), were more frequently females (8/8, 100% versus 21/31, 67.7%), had lower rate of second-line treatments before MMF (1/8, 12.5% versus 15/31, 48.4%), a later commencement of MMF (>6 months after onset in 7/8, 87.5% versus 22/35, 58.1%), and more frequently they were started on MMF only after ≥2 events had occurred (7/8, 87.5% versus 14/35, 45.2%). Adverse reactions to MMF occurred in 18.2% (8/44) of cases (6/8: grade 2, 2/8: grade 3 CTCAE v4.0).

Significance. MMF modes of use in paediatric neuroimmunology are heterogenous, although relatively safe. Second-line treatments before MMF and early MMF commencement after onset seem to associate with lower probability of relapsing during MMF. Larger studies on MMF efficacy and safety should be warranted.

Introduction

Mycophenolate mofetil (MMF) is an immunosuppressive agent approved for transplant rejection prophylaxis in the United States and Europe in the mid-1990s. MMF is a prodrug of mycophenolic acid, an inhibitor of the rate-limiting enzyme in de novo synthesis of purine nucleotides. [Nosadini, 2017; Filler, 2017], and it exerts a specific and potent cytostatic effect on T and B lymphocytes, blocking their proliferative response [Filler, 2017]. Beside its wide use as a maintenance anti-rejection drug in transplants, MMF is also largely used as a steroid-sparing agent for chronic immunosuppression in rheumatology and in neurologic autoimmune and immune-mediated conditions. MMF has been used for nearly two decades in myasthenia gravis [Gotterer, 2016], and has been reported to reduce disease in dermatomyositis and polymyositis [Marie, 2011; Johnson, 2015], while its utility in multifocal motor neuropathy and chronic inflammatory demyelinating polyneuropathy is still to be clarified [Umapathi, 2015; Cocito, 2011]. In central nervous system (CNS) autoimmune and immune-mediated conditions, MMF has been increasingly used in relapsing demyelinating diseases such as neuromyelitis optica [Chen, 2017; Xu, 2016; Montcuquet, 2017] and MOG-associated disease [Montcuquet, 2017], while its role in multiple sclerosis has not been completely clarified yet [Frohman, 2010; Etemadifar; 2011; Pandit, 2014; Xiao, 2014]. Other uses in CNS disease include autoimmune/immune-mediated encephalitis [Nosadini, 2015; Titulaer, 2013] and cerebral vasculitis [Pagnoux, 2016; Rosati, 2017]; on the other hand, a limited utility of MMF has been reported in opsoclonus myoclonus ataxia syndrome [Pranzatelli, 2009].

Most of available data on MMF efficacy and tolerability in neurology are derived from adult studies, as information in children is limited. In this context, we carried out a retrospective study on paediatric patients treated with MMF for autoimmune or immune-mediated CNS conditions, in order to gather data on safety and efficacy of MMF in this clinical context.

Methods

Study design and setting. Retrospective, multicenter study based on four paediatric neurology centers: The Children's Hospital at Westmead in Sydney (Australia) (RCD, MN), KK Women's & Children's

Hospital in Singapore (Singapore) (TT), Evelina London Children's Hospital in London (England) (ML, JG) and Department of Women's and Children's Health in Padua (Italy) (MN, SS).

Inclusion criteria. Paediatric patients (<18 years) treated with MMF for autoimmune or immune-mediated CNS conditions in one of the four centers participating to the study. Both monophasic/relapsing and chronic/chronic-progressive diseases were included.

Data collection. Data collection was carried out between April 2016 and September 2017 via an ad hoc questionnaire created for the present study (RCD, MN) (Supplementary material). The questionnaire was filled in by the treating physician (RCD, MN, ML, JG, TT), and subsequently discussed on the phone when clarifications were necessary. The clinical indications for MMF administration were grouped into encephalitis, inflammatory demyelinating CNS diseases, epilepsies, and other autoimmune/immune-mediated CNS conditions (Table 1). Other therapies received beside MMF were categorised into first-line (corticosteroids, intravenous immunoglobulin, plasma exchange), second-line (cyclophosphamide, rituximab) and maintenance treatments (azathioprine, methotrexate). The modified Rankin Scale (mRS) [van Swieten, 1988] was scored by the treating physician to measure disease severity in the acute phase and neurological outcome at last follow-up. Patients with chronic/chronic-progressive disease course were excluded from calculation of number of disease events, proportion of patients who relapsed during and after MMF treatment, and annualised relapse rate (ARR). ARR was calculated as the number of disease events multiplied by 12 (months), divided by the number of months during which the events occurred (calculated only for time intervals ≥6 months). ARR was calculated before (excluding first events), during and after treatment with MMF. Adverse reactions to MMF were classified using the Common Terminology Criteria for Adverse Events (CTCAE v4.0), into grade 1 (mild), 2 (moderate), 3 (severe or medically significant but not immediately life-threatening), 4 (life-threatening consequences) and 5 (death) [ref]. Data collection was subject to data availability, therefore in the results section of this work denominators may differ.

Results

Demographics, clinical characteristics, disease course and outcome. 44 patients treated with MMF for autoimmune or immune-mediated CNS conditions were included (30/44, 68.2% females) (Table 1). The

most frequent diagnosis was proven or suspected autoimmune encephalitis (19/44, 43.2%), followed by autoimmune inflammatory demyelinating CNS diseases (14/44, 31.8%) and other autoimmune or immune-mediated CNS conditions (11/44, 25%). Worst mRS at any stage of disease was median 4 (mean 4.1, range 2-6; data available in 44/44 patients). Overall, 52.3% of the patients had a relapsing disease course (23/44), 38.6% (17/44) had monophasic disease, and 9.1% (4/44) had a chronic/chronic-progressive course (Table 1). Relapsing disease course was more frequent in patients with inflammatory demyelinating CNS diseases (11/14, 78.6%) than in patients with encephalitis (8/19, 42.1%) and other autoimmune or immune-mediated CNS conditions 36.4% (4/11). A total 130 disease events occurred in 40 patients (40 first events and 90 subsequent relapses) (Supplementary Table 1): 113 events in 23 patients with relapsing disease (including first events) (median 4 events per patient, mean 4.9, range 2-25), and 17 events in 17 patients with monophasic disease. Disease severity was worse at first events (median mRS 4, mean 4, range 2-5; data available in 36/40 first events) as compared to subsequent events (median mRS 3, mean 2.9, range 1-5; data available in 58/90 subsequent events). At a median follow-up of 3.8 years (mean 4.8, range 1-14.3; data available in 44/46 patients), median mRS was 1 (mean 1.5, range 0-6; data available in 44/44 patients).

Data on treatment and MMF use. As per inclusion criteria, all children in the study population received MMF. All patients received other immune therapies before MMF (44/44, 100%); second-line immune treatments (cyclophosphamide and/or rituximab) were used in 38.6% of patients before MMF (17/44), and in 47.7% (21/44) during the whole disease course (Table 2). Median time from onset to first immune therapy was 24 days (mean 107, range 3-2190; data available in 37/44 patients). Median age at MMF commencement was 9.3 years (mean 9.4, range 1.4-16.4); 68.2% of patients were ≤12 years old when started on MMF (30/44). MMF was started at median 9.5 months from disease onset (mean 21.4, range 1-127; data in 44/44 patients); only in 31.8% was MMF started within 6 months from onset (14/44). In 55% of patients, MMF was started only after ≥2 events had occurred (22/40) (excluding patients with chronic/chronic-progressive disease). Duration of MMF treatment was median 18 months (mean 23.2, range 0.3-73; ≥6 months in 40/43, 93%; data available in 43/44 patients). 50% (22/44) of the patients discontinued MMF: of these, 66.7% (14/21) discontinued it due to absence of relapses, 23.8% (5/21) for possible inefficacy, and 9.5% (2/21) due to side effects.

Table 1

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS IN THE TOTAL COHORT (n=44)	
Demographics	
Age at disease onset (years)	Median 7, mean 7.7, range 0.9-15.7 (data available in 44/44)
Gender	30/44 (68.2%) females
Referring Center	17/44 (38.6%) Sydney; 10/44 (22.7%) Padova; 9/44 (20.4%) London; 8/44 (18.2%) Singapore
Diagnosis	
Encephalitis	19/44 (43.2%)
Anti-NMDAR encephalitis	12/44 (27.3%)
Seronegative suspected autoimmune encephalitis	5/44 (11.4%)
Anti-D2R encephalitis	1/44 (2.3%)
Anti-GAD encephalitis	1/44 (2.3%)
Inflammatory demyelinating CNS diseases	14/44 (31.8%)
MOG-associated demyelinating disease	9/44 (20.4%)*
Neuromyelitis optica spectrum disorders (NMOSD)	3/44 (6.8%) (3/3 NMO-IgG or anti-AQP4 antibody positive)
Multiple sclerosis	1/44 (2.3%)
Chronic relapsing inflammatory optic neuropathy (CRION)	1/44 (2.3%)
Other autoimmune/immune-mediated CNS conditions	11/44 (25%)
Neuropsychiatric systemic lupus erythematosus	3/44 (6.8%)
Cerebral vasculitis	3/44 (6.8%)
Paediatric acute-onset neuropsychiatric syndrome (PANS/PANDAS)	2/44 (4.5%)
Relapsing autoimmune chorea	1/44 (2.3%)
Opsoclonus myoclonus ataxia syndrome (OMAS)	1/44 (2.3%)
Genetic autoinflammation	1/44 (2.3%)
Disease course	
Multiphasic (relapsing)	23/44 (52.3%) (total events/patient: median 4, mean 4.9 events, range 2-25; data available in 23/23)
Monophasic	17/44 (38.6%)
Chronic/chronic-progressive	4/44 (9.1%)**
Disease severity	
Worst mRS during the disease course	Median 4, mean 4.1, range 2-6 (data available in 44/44)#
Admission to paediatric intensive care unit in the acute phase	14/43 (32.5%) (data available in 43/44)
Outcome	
Length of follow-up (years)	Median 3.8, mean 4.8, range 1-14.3 (data available in 44/44)
mRS at last follow-up	Median 1, mean 1.5, range 0-6 (data available in 44/44)#
No ongoing problems	10/43 (23.2%)
Ongoing cognitive or learning problems	21/43 (48.8%)
Ongoing behavioural problems	11/43 (25.6%)
Ongoing motor problems	6/43 (13.9%)
Ongoing visual impairment	5/43 (11.6%)
Ongoing epilepsy	7/43 (16.3%)
Other ongoing problem	8/43 (18.6%)
Ongoing immune therapy at last follow-up	30/43 (69.8%)
MMF	14/30 (46.7%)
MMF + Oral steroids	6/30 (20%) (prednisone 5/6, dexamethasone 1/6)
Intravenous immunoglobulin + Oral steroids	2/30 (6.7%) (hydrocortisone 1/2, prednisone 1/2)
Other	8/30 (26.7%): IVIG 1/30 (3.3%); Oral steroids 1/30 (3.3%); MMF + RTX 1/30 (3.3%); MMF + Hydroxychloroquine 1/30 (3.3%); Sirolimus + Oral steroids 1/30 (3.3%); MMF + Tacrolimus + Oral steroids 1/30 (3.3%); MMF + Intravenous and oral steroids 1/30 (3.3%); MMF + IVIG + Oral steroids 1/30 (3.3%)

Table 1. Demographics and clinical characteristics of 44 paediatric patients with central nervous system autoimmune or immune-mediated inflammatory diseases treated with mycophenolate mofetil.
Legend: Anti-NMDAR: anti-N-methyl-D-Aspartate; AQP4: aquaporin-4; CNS: central nervous system; CRION: chronic relapsing inflammatory optic neuropathy; D2R: dopamine 2 receptor; GAD: glutamate decarboxylase; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; MOG: myelin oligodendrocyte glycoprotein; mRS: modified Rankin Scale; NMOSD: neuromyelitis optica spectrum disorder; OMAS: opsoclonus myoclonus ataxia syndrome; RTX: rituximab.
*Phenotype in the 9 MOG positive patients: 2/9 multiphasic ADEM, 2/9 NMOSD, 2/9 CRION, 2/9 other relapsing MOG-associated demyelinating disease, 1/9 other monophasic MOG-associated demyelinating disease.
**The 4 patients with chronic/chronic-progressive disease course were: 1 boy with seronegative suspected autoimmune encephalitis with onset at 3.3 years; 1 boy with neuropsychiatric systemic lupus erythematosus with onset at 9.1 years; 1 boy with paediatric acute-onset neuropsychiatric syndrome with onset at 7 years; 1 boy with suspected genetic autoinflammatory disease with onset at 11 months, who died at 7.7 years.
#1 patient with genetic autoinflammation and chronic-progressive disease course died 7.7 years from onset.

Table 2

DATA ON TREATMENT, MMF USE AND EFFICACY ACCORDING TO DIAGNOSIS	All patients (n=44)		Encephalitis (n=19)		Inflammatory demyelinating CNS diseases (n=14)		Other autoimmune/immune-mediated CNS conditions (n=11)	
Treatments other than MMF	*Before MMF*	*During the whole disease course*	*Before MMF*	*During the whole disease course*	*Before MMF*	*During the whole disease course*	*Before MMF*	*During the whole disease course*
Any steroids	44/44 (100%)	44/44 (100%)	19/19 (100%)	19/19 (100%)	14/14 (100%)	14/14 (100%)	11/11 (100%)	11/11 (100%)
Intravenous steroids	39/44 (88.6 %)	41/44 (93.2%)*	18/19 (94.7%)	19/19 (100%)	13/14 (93.8%)	13/14 (93.8%)	8/11 (72.7%)	9/11 (81.8%)
Oral steroids	44/44 (100%)	44/44 (100%)	19/19 (100%)	19/19 (100%)	14/14 (100%)	14/14 (100%)	11/11 (100%)	11/11 (100%)
Intravenous immunoglobulin	23/44 (52.3%)	28/44 (63.6%)	14/19 (73.7%)	14/19 (73.7%)	5/14 (35.7%)	8/14 (57.1%)	4/11 (36.4%)	6/11 (54.5%)
Plasma exchange	14/44 (31.8%)	14/44 (31.8%)	11/19 (57.9%)	11/19 (57.9%)	3/14 (21.4%)	3/14 (21.4%)	0/11 (0%)	0/11 (0%)
Second-line therapy (Cyclophosphamide and/or Rituximab)	17/44 (38.6%)	21/44 (47.7%)	10/19 (52.6%)	13/19 (68.4%)	2/14 (14.3%)	2/14 (14.3%)	5/11 (45.4%)	6/11 (54.5%)
Cyclophosphamide	12/44 (27.3%)	14/44 (31.8%)	7/19 (36.8%)	7/19 (36.8%)	1/14 (7.1%)	1/14 (7.1%)	4/11 (36.4%)	6/11 (54.5%)
Rituximab	6/44 (13.6%)	9/44 (20.4%)	3/19 (15.8%)	6/19 (31.6%)	1/14 (7.1%)	1/14 (7.1%)	2/11 (18.2%)	2/11 (18.2%)
Azathioprine	4/44 (9.1%)	4/44 (9.1%)	1/19 (5.3%)	1/19 (5.3%)	0/14 (0%)	0/14 (0%)	3/11 (27.3%)	3/11 (27.3%)
Other	1/44 (2.3%)	3/44 (6.8%)**	0/19 (0%)	0/19 (0%)	0/14 (0%)	0/14 (0%)	1/11 (9.1%)	3/11 (27.3%)
Time from disease onset to first immune therapy (any)								
Days from disease onset to first immune therapy	Median 24, mean 107, range 3-2190 (data available in 37/44)		Median 25, mean 52.5, range 6-365 (data available in 18/19)		Median 15, mean 55.6, range 3-221 (data available in 11/14)		Median 19, mean 300.4, range 4-2190 (data available in 8/11)	
First immune therapy ≤30 days from onset	28/40 (70%) (data available in 40/44)		14/19 (73.7%) (data available in 19/19)		8/12 (66.7%) (data available in 12/14)		6/9 (66.7%) (data available in 9/11)	
Age at MMF commencement (years)	Median 9.3, mean 9.4, range 1.4-16.4 (data available in 44/44)		Median 8.8, mean 8.3, range 1.9-16.4 (data available in 19/19)		Median 8.7, mean 9.7, range 3.6-15.6 (data available in 14/14)		Median 12.8, mean 10.9, range 1.4-16 (data available in 11/11)	
≤6 years	14/44 (31.8%)		7/19 (36.8%)		4/14 (28.6%)		3/11 (27.3%)	
7-12 years	16/44 (36.4%)		7/19 (36.8%)		6/14 (42.8%)		3/11 (27.3%)	
≥13 years	14/44 (31.8%)		5/19 (26.3%)		4/14 (28.6%)		5/11 (45.4%)	
Time from disease onset to MMF (months)	Median 9.5, mean 21.4, range 1-127 (data in 44/44)		Median 8, mean 17.3, range 2-117 (data available in 19/119)		Median 12.7, mean 28, range 1-127 (data available in 14/14)		Median 11, mean 20.1, range 2-96 (data available in 11/11)	
≤6 months	14/44 (31.8%)		5/19 (26.3%)		5/14 (35.7%)		4/11 (36.4%)	
7-12 months	13/44 (29.5%)		8/19 (42.1%)		2/14 (14.3%)		3/11 (27.3%)	
≥13 months	17/44 (38.6%)		6/19 (31.6%)		7/14 (50%)		4/11 (36.4%)	
Number of events before MMF commencement (including first events)#	Median 2, mean 2.2, range 1-6 (data available in 40/44)		Median 1, mean 1.9, range 1-5 (data available in 18/19)		Median 3, mean 2.8, range 1-6 (data available in 14/14)		Median 1, mean 1.9, range 1-4 (data available in 8/11)	
1 event	18/40 (45%)		10/19 (52.6%)		3/14 (21.4%)		5/8 (62.5%)	
2 events	7/40 (17.5%)		5/19 (26.3%)		2/14 (14.3%)		0/8 (0%)	
≥3 events	15/40 (37.5 %)		3/19 (15.8%)		9/14 (64.3%)		3/8 (37.5%)	
Time on MMF (months)	Median 18, mean 23.2, range 0.3-73 (data available in 43/44)		Median 16, mean 22.7, range 7-62 (data available in 19/19)		Median 17.5, mean 20.1, range 0.3-40 (data available in 14/14)		Median 25, mean 25.5, range 1-73 (data available in 10/11)	
≤6 months	3/43 (7%)		0/19 (0%)		1/14 (7.1%)		2/10 (20%)	
7-12 months	10/43 (23.2%)		6/19 (31.6%)		3/14 (21.4%)		1/10 (10%)	
13-24 months	12/43 (27.9%)		6/19 (31.6%)		5/14 (35.7%)		1/10 (10%)	
≥25 months	18/43 (41.9%)		7/19 (36.8%)		5/14 (35.7%)		6/10 (60%)	
Number of patients who relapsed during MMF#	8/39 (20.5%)		4/18 (22.2%)		3/14 (21.4%)		1/7 (14.3%)	
Proportion of patients who discontinued MMF at any time during disease course	23/44 (52.3%) (4/23 subsequently were restarted on MMF)		10/19 (52.6%)		8/14 (57.1%)		5/11 (45.4%)	
Time after MMF discontinuation	Median 12, mean 16.2, range 0-46 (data available in 22/23 patients)		Median 19, mean 19.3, range 0-38 (data available in 10/10 patients)		Median 9, mean 12.4, range 0-46 (data available in 8/8)		Median 15.5, mean 15.7, range 2-30 (data available in 4/5)	
≤6 months	7/22 (31.8%)		2/10 (20%)		3/8 (37.5%)		2/4 (50%)	
7-12 months	4/22 (18.2%)		1/10 (10%)		3/8 (37.5%)		0/4 (0%)	
≥13 months	11/22 (50%)		7/10 (70%)		2/8 (25%)		2/4 (50%)	
Number of patients who relapsed after MMF discontinuation#	4/21 (19%) (3/4 had also relapsed whilst on MMF)		1/10 (10%)		2/8 (25%)		1/3 (33.3%)	
Efficacy								
ARR before MMF (excluding first events)#	Median 0.52, mean 0.86, range 0-3 (data available in 29/44)		Median 0.45, mean 0.78, range 0-3 (data available in 14/19)		Median 0.52, mean 0.86, range 0-2.18 (data available in 9/14)		Median 1, mean 1.05, range 0-2.18 (data available in 6/11)	
ARR during MMF#	Median 0, mean 0.36, range 0-4.64 (data available in 37/44)		Median 0, mean 0.43, range 0-4.6 (data available in 18/19)		Median 0, mean 0.42, range 0-3 (data available in 13/14)		Median 0, mean 0.06, range 0-0.37 (data available in 6/11)	
ARR after MMF discontinuation#	Median 0, mean 0.15, range 0-1.5 (data available in 13/19)		Median 0, mean 0, range 0-0 (data available in 6/9)		Median 0, mean 0.3, range 0-1.5 (data available in 5/7)		Median 0.21, mean 0.21, range 0-0.43 (data available in 2/11)	

Table 2. Data on mycophenolate mofetil use, efficacy and safety in 44 paediatric patients with central nervous system autoimmune or immune-mediated inflammatory diseases treated with mycophenolate mofetil, according to diagnosis.
Legend: ARR: annualized relapse rate; CNS: central nervous system; CTCAE: common terminology criteria for adverse events; MMF: mycophenolate mofetil.
*Intravenous steroids were: intravenous methylprednisolone in 40/41; intravenous dexamethasone in 1/41
**Other immune therapies received in 3/44 patients were: cyclosporine and rapamycin in 1/3; hydroxychloroquine in 1/3; tacrolimus in 1/3
#Excluding 4 patients with chronic/chronic-progressive disease course.

MMF efficacy. Median ARR (excluding patients with chronic/chronic-progressive disease) was 0.52 (mean 0.86, range 0-3; data available in 29/44) before MMF (excluding first events), and 0 (mean 0.36, range 0-4.64; data available in 37/44) during MMF (Table 2). After MMF, median ARR was 0 (mean 0.15, range 0-1.5; data available in 13/19 patients who discontinued MMF).

20.5% patients relapsed during treatment with MMF (8/39), and 19% after MMF discontinuation (4/21; 3/4 of these had also relapsed whilst on MMF) (excluding patients with chronic/chronic-progressive disease). In the 8 patients who relapsed whilst on MMF, a total of 34 events occurred on MMF (median 1.5, mean 4.2, range 1-23) (Table 3). Time from MMF commencement to the clinical event was median 6 months (mean 12.8, range 2-49; data available in 11/34 events). 72.7% (8/11) of the events occurred whilst on MMF and with available information were during tapering or within 2 months from cessation of immune therapy: 4/8 occurred during tapering of oral steroids, 2/8 within 2 months after cessation of oral steroids, and 2/7 during MMF weaning. The remaining 3/11 events on MMF, that did not occur whilst tapering immune therapy, occurred in 2 patients: 2 events in a 2 year-old girl with highly relapsing MOG-associated demyelinating disease (7 total events), respectively at 5 and 13 months after MMF initiation (this patient also had a further event 4 months after discontinuation of MMF); and 1 event in a 14.1 year old girl with cerebral vasculitis, 24 months after MMF commencement (total disease events: 4).

Table 3

STUDY OF 34 DISEASE EVENTS OCCURRED IN 8 PATIENTS WHILST ON MMF					
Gender, age at onset (diagnosis)	**Event number (including 1st event)**	**Time from MMF commencement to the event**	**MMF dose at the event**	**Other immune therapy at the event**	**Medication weaning**
F, 3.2 y (MOG-associated demyelinating disease: ADEM)	4	8 mo	20 mg/kg/day (200 mg BD; bw 20 kg)	No	No, but OP stopped 2 mo prior to the event
F, 5.2 y (MOG-associated demyelinating disease: CRION)	4	2 mo	22 mg/kg/day (500 mg BD, bw 45 kg)	OP 5 mg OD	OP tapering
	5	5.5 mo	22 mg/kg/day (500 mg BD, bw 45 kg)	OP 15 mg alt. days	OP tapering (last dose lowering: 2 weeks prior to the event)
***F, 14.1 y (Cerebral vasculitis)**	3	24 mo	48 mg/kg/day (1000 mg BD; bw 42 kg)	No	No
	4	49 mo	18.9 mg/kg/day (500 mg BD, bw 53 kg)	No	MMF tapering (started 5 mo prior to the event; last dose lowering: 1 month prior to the event)
~F, 1.6 y (Seronegative suspected autoimmune encephalitis)	3	20 mo	16 mg/kg/day (150 mg BD; bw 19 kg)	No	MMF tapering (started 1 mo prior to the event)
F, 9.7 y (anti-NMDAR encephalitis)	3	6 mo	Dose/kg/day n.a. (600 mg/m2; bw 48 kg)	OP 5 mg alternate days	OP tapering (started 9 mo prior to the event; last dose lowering: 1 wk prior to the event)
#F, 2 y (MOG-associated demyelinating disease)	4	n.a.	55 mg/kg/day (400 mg BD; bw 14.5 kg)	No	OP stopped <1 mo prior to the event
	5	n.a.	55 mg/kg/day (400 mg BD; bw 14.5 kg)	No	No
	6	13 mo	Dose/kg/day n.a. (400 mg BD; bw n.a)	No	No
F, 2.2 y (seronegative suspected autoimmune encephalitis)	3	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	4	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	5	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	6	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	7	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	8	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	9	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	10	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	11	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	12	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	13	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	14	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	15	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	16	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	17	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	18	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	19	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	20	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	21	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	22	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	23	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	24	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
	25	n.a.	Dose/kg/day n.a. (500 mg BD; bw n.a.)	OP, IVIG	n.a.
F, 8 y (seronegative suspected autoimmune encephalitis)	5	4 mo	31 mg/kg/day (750 mg BD; bw 48 kg)	Oral DEX; IVIG	DEX tapering
STUDY OF 3 DISEASE EVENTS OCCURRED IN 3 PATIENTS AFTER DISCONTINUATION OF MMF					
Gender, age at onset (diagnosis)	**Event number (including first event)**	**Time from MMF discontinuation to the event**		**Immune therapy at the event**	**Medication weaning**
F, 5.2 y (MOG-associated demyelinating disease: CRION)	7	5 d		OP 25 mg OD	OP tapering (started <1 month prior to the event)
~F, 1.6 y (Seronegative suspected autoimmune encephalitis)	4	8 mo		Pulsed DEX	No
#F, 2 y (MOG-associated demyelinating disease)	4	4 mo		No	No
***F, 14.1 y (Cerebral vasculitis)**	2	4 mo		No	No (OP stopped 8 months prior to the event)

Table 3. Study of the disease events occurred during and after treatment with MMF.
Legend: BD: bis in die; bw: body weight; d: day; DEX: dexamethasone; F: female; IVIG: intravenous immunoglobulin; mo: month; n.a.: not available; OD: once per day; OP: oral prednisone; wk: week; y: year. ~The two cases with this symbol were the same patient. #The two cases with this symbol were the same patient. *The two cases with this symbol were the same patient.

A comparison between demographics, clinical characteristics and treatment data in the subgroups of patients who relapsed and who did not relapse during/after treatment with MMF is presented in Table 4. Diagnosis distribution and disease severity were similar in the two subgroups. Patients who relapsed during MMF (8/39, 20.5%), compared to patients who did not relapse (31/39, 79.5%), were younger (median age 4.2 years, mean 5.7, range 1.6-14.1; data in 8/8; versus median 7.6, mean 8.3, range 1.2-15.7; data in 31/31 patients), had higher proportion of females (8/8, 100% versus 21/31, 67.7%), had lower rate of treatment with second-line therapies (cyclophosphamide and/or rituximab) before MMF (1/8, 12.5% versus 15/31, 48.4%), a later commencement of MMF (>6 months after disease onset in 7/8, 87.5% versus 18/31, 58.1%), and more frequently they were started on MMF only after ≥2 events had occurred (7/8, 87.5% versus 14/31, 45.2%).

Safety. Adverse reactions to MMF occurred in 18.2% of cases (8/44) (Table 5): gastrointestinal adverse reactions included abdominal pain in 2 patients, not requiring medications, and appetite suppression in 1 (grade 2 CTCAE v4.0); infectious adverse reactions occurred in 2 patients: 1 patient had herpes zoster (2.75 years after commencement of MMF), and another one required admission for pneumonia (1.4 years after commencement of MMF) (grade 3 CTCAE v4.0); 1 patient had a maculopapular rash 7 days after commencement of MMF (grade 2 CTCAE v4.0); 2 patients had movement disorders: 1 had tremor, and 1 developed jerking and stiffness of legs on MMF dose escalation (grade 2 CTCAE v4.0). Time from MMF commencement to adverse reaction was median 1 month (mean 9.2, range 0.25-33; data available in 7/8 patients). 42.8% (3/7) patients were on other medications at the time of the adverse event. In 37.5% (3/8) cases was MMF discontinued due to side effects: one 5.2 year old girl with MOG-associated CRION discontinued MMF 3 weeks after commencement (at the dose of 55 mg/kg/day) due to crampy abdominal pain (she relapsed 5 days after discontinuation, and MMF was resumed 1.5 months after the relapse, still ongoing at last follow-up); one 14.7 year old girl with MOG-associated NMOSD discontinued MMF 10 days after commencement (at the dose of 13 mg/kg/day) due to tremor; one 2 year old girl with MOG-associated demyelinating disease discontinued MMF 17 months after commencement (at the dose of 13 mg/kg/day) due to inefficacy and appetite suppression. An additional 4 year old girl with MOG-associated demyelinating disease developed jerking and stiffness of legs on dose escalation, 1 month after MMF commencement, and benefitted from dose reduction (dose was increased again later in the absence of adverse reactions).

Table 4

COMPARISON BETWEEN PATIENTS WHO DID AND DID NOT RELAPSE DURING TREATMENT WITH MMF (excluding 4 patients with chronic/chronic-progressive course)	Patients who relapsed during MMF (n=8)		Patients who did not relapse during MMF (n=31)	
Demographics				
Age at disease onset (years)	Median 4.2, mean 5.7, range 1.6-14.1 (data available in 8/8 patients)		Median 7.6, mean 8.3, range 1.2-15.7 (data available in 31/31 patients)	
Gender	8/8 (100%) females		21/31 (67.7%) females	
Diagnosis				
Encephalitis	4/8 (50%)		14/31 (45.2%)	
Anti-NMDAR encephalitis	1/8 (12.5%)		11/31 (35.5%)	
Seronegative suspected autoimmune encephalitis	3/8 (37.5%)		1/31 (3.2%)	
Anti-D2R encephalitis	0/8 (0%)		1/31 (3.2%)	
Anti-GAD encephalitis	0/8 (0%)		1/31 (3.2%)	
Inflammatory demyelinating CNS diseases	3/8 (37.5%)		11/31 (35.5%)	
MOG-associated demyelinating disease	3/8 (37.5%)		6/31 (19.3%)	
Neuromyelitis optica spectrum disorders (NMOSD)	0/8 (0%)		3/31 (9.7%)	
Multiple sclerosis	0/8 (0%)		1/31 (3.2%)	
Chronic relapsing inflammatory optic neuropathy (CRION)	0/8 (0%)		1/31 (3.2%)	
Other	1/8 (12.5%)		6/31 (19.3%)	
Neuropsychiatric systemic lupus erythematosus	1/8 (12.5%)		1/31 (3.2%)	
Cerebral vasculitis	0/8 (0%)		2/31 (6.4%)	
Pediatric acute-onset neuropsychiatric syndrome (PANS/PANDAS)	0/8 (0%)		1/31 (3.2%)	
Relapsing autoimmune chorea	0/8 (0%)		1/31 (3.2%)	
Opsoclonus myoclonus ataxia syndrome (OMAS)	0/8 (0%)		1/31 (3.2%)	
Genetic autoinflammation	0/8 (0%)		0/31 (0%)	
Disease course				
Multiphasic (relapsing)	8/8 (100%)		17/31 (54.8%)	
Monophasic	0/8 (0%)		14/31 (45.2%)	
Disease severity				
Worst mRS during the disease course	Median 4, mean 4.1, range 3-5 (data available in 8/8)		Median 4, mean 4.1, range 2-5 (data available in 31/31)	
Admission to paediatric intensive care unit	2/7 (87.5%)		11/31 (35.5%)	
Treatments other than MMF	*Before MMF*	*During the whole disease course*	*Before MMF*	*During the whole disease course*
Any steroids	8/8 (100%)	8/8 (100%)	31/31 (100%)	31/31 (100%)
Intravenous steroids	7/8 (87.5%)	8/8 (100%)	29/31 (93.5%)	29/31 (93.5%)
Oral steroids	8/8 (100%)	8/8 (100%)	31/31 (100%)	31/31 (100%)
Intravenous immunoglobulin	5/8 (62.5%)	6/8 (75%)	15/31 (48.4%)	17/31 (54.8%)
Plasma exchange	2/8 (25%)	2/8 (25%)	12/31 (38.7%)	12/31 (38.7%)
Any second-line treatment (Cyclophosphamide and/or Rituximab)	1/8 (12.5%)	3/8 (37.5%)	15/31 (48.4%)	15/31 (48.4%)
Cyclophosphamide	1/8 (12.5%)	1/8 (12.5%)	11/31 (35.5%)	11/31 (35.5%)
Rituximab	0/8 (0%)	2/8 (25%)	5/31 (16.1%)	5/31 (16.1%)
Azathioprine	1/8 (12.5%)	1/8 (12.5%)	1/31 (3.2%)	1/31 (3.2%)
Other	0/8 (0%)	0/8 (0%)	1/31 (3.2%)	2/31 (6.4%)
Time from disease onset to first immune therapy (any)				
Days from disease onset to first immune therapy	Median 26, mean 82, range 5-221 (data available in 5/8)		Median 22, mean 42.3, range 3-365 (data available in 30/31)	
First immune therapy ≤30 days from onset	5/7 (71.4%)		22/30 (73.3%)	
Time from disease onset to MMF (months)	Median 14.2, mean 16.8, range 6-46.2 (data available in 8/8)		Median 7, mean 20.4, range 1-127 (data available in 31/31)	
≤6 months	1/8 (12.5%)		13/31 (41.9%)	
7-12 months	2/8 (25%)		9/31 (29%)	
≥13 months	5/8 (62.5%)		9/31 (29%)	
Age at MMF commencement (years)	Median 6.4, mean 7.2, range 2.2-14.7 (data available in 8/8)		Median 9.5, mean 9.8, range 1.4-16.4 (data available in 31/31)	
≤6 years	4/8 (50%)		8/31 (25.8%)	
7-12 years	3/8 (37.5%)		12/31 (38.7%)	
≥13 years	1/8 (12.5%)		11/31 (35.5%)	
Number of events before MMF commencement	Median 2.5, mean 2.5, range 1-4 (data available in 8/8)		Median 1, mean 2.1, range 1-6 (data available in 31/31)	
1 event	1/8 (12.5%)		17/31 (54.8%)	
2 events	3/8 (37.5%)		4/31 (12.9%)	
≥3 events	4/8 (50%)		10/31 (32.2%)	
Time on MMF (months)	Median 21.5, mean 29, range 7-64 (data available in 8/8)		Median 18, mean 20.8, range 0.3-55 (data available in 31/31)	
Outcome				
Length of follow-up (years)	Median 4.3, mean 4.4, range 1.6-6.4 (data available in 8/8)		Median 3.2, mean 4.2, range 1-14.3 (data available in 31/31)	
mRS at last follow-up	Median 2.5, mean 2, range 0-4 (data available in 8/8)		Median 1, mean 1.1, range 0-3 (data available in 31/31)	
No ongoing problems	2/8 (25%)		8/31 (23.5%)	
Ongoing cognitive or learning problems	6/8 (75%)		13/31 (41.9%)	
Ongoing behavioural problems	4/8 (50%)		6/31 (19.3%)	
Ongoing motor problems	1/8 (12.5%)		3/31 (9.7%)	
Ongoing visual impairment	1/8 (12.5%)		4/31 (12.9%)	
Ongoing epilepsy	1/8 (12.5%)		45/31 (16.1%)	
Other ongoing problem	1/8 (12.5%)		4/31 (12.9%)	
Ongoing immune therapy at last follow-up	7/8 (87.5%)		18/31 (58.1%)	

Table 4. Comparison between demographics, clinical characteristics and treatment data in the subgroups of patients who relapsed and who did not relapse during treatment with mycophenolate mofetil, after exclusion of patients with chronic/cronic-progressive disease course.
Legend: Anti-NMDAR: anti-N-methyl-D-Aspartate; AQP4: aquaporin-4; CNS: central nervous system; CRION: chronic relapsing inflammatory optic neuropathy; D2R: dopamine 2 receptor; GAD: glutamate decarboxylase; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; MOG: myelin oligodendrocyte glycoprotein; mRS: modified Rankin Scale; NMOSD: neuromyelitis optica spectrum disorder; OMAS: opsoclonus myoclonus ataxia syndrome; RTX: rituximab.

Table 5

ADVERSE REACTIONS TO MMF OCCURRED IN 8 PATIENTS						
Gender, age at onset (diagnosis)	**Adverse reaction**	**Severity (CTCAE v4.0)**	**Time from MMF commencement to adverse reaction**	**MMF dose at the time of adverse reaction**	**Intervention required**	**Other concomitant medications**
F, 5.2 yr (MOG-associated demyelinating disease: CRION)	Gastrointestinal: crampy abdominal pain	Grade 2	3 weeks	55 mg/kg/day (1000 mg + 500 mg/day; bw 27 kg)	MMF discontinuation 3 weeks after commencement (5 days after discontinuation she relapsed; MMF was resumed 1.5 months after the relapse and was still ongoing at last follow-up)	OP 25 mg OD; Omeprazole (IVMP 3 weeks before MMF adverse reaction)
F, 9.7 y (anti-NMDAR encephalitis)	Gastrointestinal: mild abdominal pain	Grade 2	n.a.	600 mg/m2 (bw 40 kg)	None (MMF discontinued due to inefficacy, not due to side effects)	n.a.
F, 2 y (MOG-associated demyelinating disease)	Gastrointestinal: appetite suppression	Grade 2	12 months	53 mg/kg/day (400 mg BD; bw 15 kg)	MMF discontinuation 17 months after commencement (due to inefficacy and appetite suppression)	None
F, 14.7 y (MOG-associated demyelinating disease: NMOSD)	Movement disorder: tremor	Grade 2	10 days	13 mg/kg/day (500 mg BD; bw 78 kg)	MMF discontinuation 10 days after commencement (not subsequently resumed)	OP 50 mg OD (IVMP 2 weeks before MMF adverse reaction)
F, 4 y (MOG-associated demyelinating disease)	Movement disorder: jerking and stiffness of legs	Grade 2	1 month	500mg/m2 BD (bw n.a.) [on dose escalation: after 2 weeks from 300mg/m2 BD to 500mg/m2 BD]	MMF dose reduction, with good tolerability (subsequently dose was increased without adverse events to 500mg/m2 BD; MMF still ongoing at last follow-up)	OP tapering
M, 4.3 y (anti-NMDAR encephalitis)	Dermatologic: maculopapular rash	Grade 2	7 days	600 mg/m2/dose BD (bw 18 kg)	None (MMF not discontinued, still ongoing at last follow-up)	None (Steroids, IVIG, RTX 1 month prior to MMF adverse reaction)
F, 14.1 y (Cerebral vasculitis)	Infectious: herpes zoster	Grade 3	33 months	48 mg/kg/day (1000 mg BD; bw 42 kg)	None (MMF not discontinued, still ongoing at last follow-up)	None (CYC up to 2.5 years and IVMP up to 1.5 prior to adverse reaction)
F; 2.2 y (anti-NMDAR encephalitis)	Infectious: pneumonia; recurrent infections	Grade 3	17 months	600 mg/m2/dose BD (bw n.a.)	Required admission for pneumonuia (no PICU, no ventilation) (MMF discontinued 25 months after commencement due to absence of relapses)	None

Table 5. Adverse reactions to MMF occurred in 8 patients.
Legend: BD: bis in die; bw: body weight; CTCAE v4.0: Common Terminology Criteria for Adverse Events; CYC: cyclophosphamide; F: female; IVIG: intravenous immunoglobulin; IVMP: intravenous methylprednisolone; M: male; MMF: mycophenolate mofetil; n.a.: not available; OD: once per day; OP: oral prednisone; PICU: paediatric intentive care unit; RTX: rituximab; wk: week; y: year.

Discussion

Our retrospective study on paediatric patients treated with MMF for autoimmune or immune-mediated CNS disorders disclosed a great heterogeneity in MMF use, reflecting the lack of definite recommendations and the limited availability of literature data. While all patients received other immune therapies before MMF, second-line treatments (cyclophosphamide and/or rituximab) were administered only in 38.6% (17/44) before MMF (Table 2). Recent surveys on treatment of autoimmune encephalitis have documented the persistence of a vast heterogeneity in the use of second-line immune therapy and, even more, of maintenance immune suppression [Bartolini, 2017; Kahn, 2017]. Moreover, in our population MMF administration was delayed >6 months from onset in 68.2% (30/44), and in 55% (22/40) MMF was administered only after relapses had occurred. The duration of treatment with MMF was also highly heterogeneous, ranging between 0.3 and 73 months. Indeed, for many of the clinical conditions included in our population, it is unclear how long the inflammatory component of disease lasts for. In this respect, there is some correlation of CXCL13 and disease severity and relapse [Kothur, 2016; Kothur, 2017] that may be useful in guiding treatment.

In our population, the main indications for MMF use were encephalitis and inflammatory demyelinating CNS diseases, while a smaller, more heterogeneous group included other autoimmune/immune-mediated CNS conditions (Table 1). MMF role in autoimmune or immune-mediated encephalitis, and its efficacy compared to other steroid sparers, has not been thoroughly explored yet [Nosadini and Dale, in progress], while its use is more consolidated in some inflammatory demyelinating CNS diseases. In recent studies on adults with neuromyelitis optica spectrum disorders, MMF was shown to be effective [Montcuquet, 2017], and both MMF and azathioprine significantly reduced relapse rate and disability scores [Chen, 2017; Xu, 2016]. During treatment with MMF, ARR was reduced in all diagnosis groups in our population (Table 2), although definite comparisons are hindered by the limited number of cases.

While a comparison of patients who did and did not receive MMF was not possible in our population in view of the inclusion criteria, we tried to identify factors associated with lack of efficacy of MMF. In our population, the subgroup of patients who relapsed during MMF, compared to patients who did not relapse, were younger and more frequently females, had lower rate of second-line therapies before MMF, a later commencement of MMF, and more frequently they were started on MMF only after ≥2

events had occurred. These results seem to be in agreement with other data in the literature, supporting the role of early and aggressive immune therapy [Nosadini, 2015].

Adverse reactions to MMF occurred in 18.2% (8/44) of cases in our population, mostly of moderate severity, although two patients had severe infections. While studies focused on MMF safety in paediatric neurology are not available, data derived from MMF use in subsets of children with neurologic conditions and other paediatric diosorders [Rosati, 2017; Hassan, 2013], seem to disclose a favorable safety profile. In a recent study on adults with neuromyelitis optica specturm disorders, MMF had a significantly better tolerability profile than azathioprine [Chen, 2017].

Our study is primarily limited by the retrospective design and the restricted number of patients. Severity of disease was estimated via the mRS score, although this scale was not designed to detect and render the vast array of disturbances that occur in some of the disorders included in the study. Similarly, the utility of ARR in this setting may be limited in some diagnosis group, such as anti N-methyl-D-aspartate encephalitis. In view of the inclusion criteria, efficacy of MMF could not be studied with comparison to patients who did not receive MMF, which would be of utmost clinical interest and warrants further studies. Similarly, the efficacy of steroid sparers for sustained remission and relapse prevention should be explored further in comparison to other approaches proposed in the literature, such as monthly rituximab, IVIG or plasma exchange, or sustained use of oral corticosteroids [Shin, 2017; Dale, 2017].

Despite these limitations, our study contributes to addressing the lack of literature data on the use, efficacy and safety of MMF in paediatric autoimmune or immune-mediated CNS disorders. The utility of MMF as compared to other agents could not be investigated in our study, and remains to be clarified. Although, when MMF is used, our results seem to point to a better efficacy when MMF is preceded by second-line immune therapies, and MMF is given early in the disease course. Even if MMF safety profile appears relatively good, the possibility of adverse reactions, also severe, should not be overlooked, and weighted in a ‘risk versus benefit’ approach.

References

Bartolini L, Muscal E. Differences in treatment of anti-NMDA receptor encephalitis: results of a worldwide survey. J Neurol. 2017 Apr;264(4):647-653.

Chen H, Qiu W, Zhang Q, Wang J, Shi Z, Liu J, Lian Z, Feng H, Miao X, Zhou H. Comparisons of the efficacy and tolerability of mycophenolate mofetil and azathioprine as treatments for neuromyelitis optica and neuromyelitis optica spectrum disorder. Eur J Neurol. 2017 Jan;24(1):219-226.

Cocito D, Grimaldi S, Paolasso I, Falcone Y, Antonini G, Benedetti L, Briani C, Fazio R, Jann S, Matà S, Sabatelli M, Nobile-Orazio E; Italian Network for CIDP Register. Immunosuppressive treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy. A nationwide retrospective analysis. Eur J Neurol. 2011 Dec;18(12):1417-21.

Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 (accessed on 25.09.2017)

Etemadifar M, Kazemi M, Chitsaz A, Hekmatnia A, Tayari N, Ghazavi A, Maghzi AH. Mycophenolate mofetil in combination with interferon beta-1a in the treatment of relapsing-remitting multiple sclerosis: A preliminary study. J Res Med Sci. 2011 Jan;16(1):1-5.

Filler G, Alvarez-Elías AC, McIntyre C, Medeiros M. The compelling case for therapeutic drug monitoring of mycophenolate mofetil therapy. Pediatr Nephrol. 2017 Jan;32(1):21-29.

Frohman EM, Cutter G, Remington G, Gao H, Rossman H, Weinstock-Guttman B, Durfee JE, Conger A, Carl E, Treadaway K, Lindzen E, Salter A, Frohman TC, Shah A, Bates A, Cox JL, Dwyer MG, Stüve O, Greenberg BM, Racke MK, Zivadinov R. A randomized, blinded, parallel-group, pilot trial of mycophenolate mofetil (CellCept) compared with interferon beta-1a (Avonex) in patients with relapsing-remitting multiplesclerosis. Ther Adv Neurol Disord. 2010 Jan;3(1):15-28.

Gotterer L, Li Y. Maintenance immunosuppression in myasthenia gravis. J Neurol Sci. 2016 Oct 15;369:294-302.

Hassan AV, Sinha MD, Waller S. A single-centre retrospective study of the safety and efficacy of mycophenolate mofetil in childrenand adolescents with nephrotic syndrome. Clin Kidney J. 2013 Aug;6(4):384-9.

Jinka M, Chaudhry V. Treatment of multifocal motor neuropathy. Curr Treat Options Neurol. 2014 Feb;16(2):269.

Johnson NE, Arnold WD, Hebert D, Gwathmey K, Dimachkie MM, Barohn RJ, McVey AL, Pasnoor M, Amato AA, McDermott MP, Kissel J, Heatwole CR. Disease course and therapeutic approach in

dermatomyositis: A four-center retrospective study of 100 patients. Neuromuscul Disord. 2015 Aug;25(8):625-31.

Kahn I, Helman G, Vanderver A, Wells E. Anti- N-Methyl-d-Aspartate (NMDA) Receptor Encephalitis. J Child Neurol. 2017 Feb;32(2):243-245.

Marie I, Mouthon L. Therapy of polymyositis and dermatomyositis. Autoimmun Rev. 2011 Nov;11(1):6-13.

Montcuquet A, Collongues N, Papeix C, Zephir H, Audoin B, Laplaud D, Bourre B, Brochet B, Camdessanche JP, Labauge P, Moreau T, Brassat D, Stankoff B, de Seze J, Vukusic S, Marignier R; NOMADMUS study group and the Observatoire Français de la Sclérose en Plaques (OFSEP). Effectiveness of mycophenolate mofetil as first-line therapy in AQP4-IgG, MOG-IgG, and seronegative neuromyelitis optica spectrum disorders. Mult Scler. 2017 Sep;23(10):1377-1384.

Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother. 2015;15(12):1391-419.

Nosadini M, Sartori S, Sharma S, Dale RC. Immunotherapeutics in Pediatric Autoimmune Central Nervous System Disease: Agents and Mechanisms. Semin Pediatr Neurol. 2017 Aug;24(3):214-228.

Pagnoux C, Hajj-Ali RA. Pharmacological approaches to CNS vasculitis: where are we at now? Expert Rev Clin Pharmacol. 2016;9(1):109-16.

Pandit L, Mustafa S, Malli C, D'Cunha A. Mycophenolate mofetil in the treatment of multiple sclerosis: a preliminary report. Neurol India. 2014 Nov-Dec;62(6):646-8.

Pranzatelli MR, Tate ED, Travelstead AL, Baumgardner CA, Gowda NV, Halthore SN, Kerstan P, Kossak BD, Mitchell WG, Taub JW. Insights on chronic-relapsing opsoclonus-myoclonus from a pilot study of mycophenolate mofetil. J Child Neurol. 2009 Mar;24(3):316-22

Rosati A, Cosi A, Basile M, Brambilla A, Guerrini R, Cimaz R, Simonini G. Mycophenolate mofetil as induction and long-term maintaining treatment in childhood: Primary angiitis of the central nervous system. Joint Bone Spine. 2017 May;84(3):353-356.

Umapathi T, Hughes RA, Nobile-Orazio E, Léger JM. Immunosuppressant and immunomodulatory treatments for multifocal motor neuropathy. Cochrane Database Syst Rev. 2015 Mar 4;(3):CD003217

Xiao Y, Huang J, Luo H, Wang J. Mycophenolate mofetil for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2014 Feb 7;(2):CD010242.

Xiao Y, Huang J, Luo H, Wang J. Mycophenolate mofetil for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2014 Feb 7;(2):CD010242.

Xu Y, Wang Q, Ren HT, Qiao L, Zhang Y, Fei YY, Zhao Y, Cui LY. Comparison of efficacy and tolerability of azathioprine, mycophenolate mofetil, and cyclophosphamide among patients with neuromyelitis optica spectrum disorder: A prospective cohort study. J Neurol Sci. 2016 Nov 15;370:224-228.

Zizzo G, De Santis M, Ferraccioli GF: Mycophenolic acid in rheumatology: mechanisms of action and severe adverse events. Reumatismo 62: 91-100; 2010.

Supplementary Table 1

STUDY OF DISEASE EVENTS (excluding 4 patients with chronic/chronic-progressive disease course)	All events (n=130)	First events (n=40)	Subsequent events (n=90)
Event severity			
Worst mRS during event	Median 3, mean 3.3, range 1-5 (data available in 94/130)	Median 4, mean 4, range 2-5 (data available in 36/40)	Median 3, mean 2.9, range 1-5 (data available in 58/90)
Best mRS after event	Median 1, mean 1.3, range 0-4 (data available in 92/130)	Median 1, mean 1, range 0-4 (data available in 36/40)	Median 1, mean 1.4, range 0-4 (data available in 56/90)
Events occurred whilst on immune therapy	58/130 (44.6%)	1/40* (2.5%)	57/90 (63.3%)
Steroids + Intravenous immunoglobulin + MMF	24/58 (41.4%)	0/40 (0%)	24/57 (42.1%)
Steroids	16/58 (27.6%) (14/16: OP, 1/16 oral DEX, 1/16 IVDEX)	0/40 (0%)	16/57 (28.1%) (14/16: OP, 1/16 oral DEX, 1/16 IVDEX)
MMF	7/58 (12.1%)	0/40 (0%)	7/57 (12.3%)
Steroids + Intravenous immunoglobulin	3/58 (5.2%)	0/40 (0%)	3/57 (5.3%)
Steroids + MMF	3/58 (5.2%)	0/40 (0%)	3/57 (5.3%)
Steroids + Azathioprine + Tacrolimus	3/58 (5.2%)	1/40 (2.5%)	2/57 (3.5%)
Intravenous immunoglobulin	2/58 (3.4%)	0/40 (0%)	2/57 (3.5%)
Events occurred whilst tapering or ≤2 months from discontinuation of immune therapy	31/103 (30.1%)	0/40 (0%)	31/63 (49.2%)
Oral steroids (Prednisone or Dexamethasone)	22/31 (71%)	0/40 (0%)	22/31 (71%)
Oral Prednisone + MMF	5/31 (16.1%)	0/40 (0%)	5/31 (16.1%)
MMF	4/31 (12.9%)	0/40 (0%)	4/31 (12.9%)
Immune therapy received at the event	124/130 (95.4%)	37/40 (92.5%)	87/90 (96.7%)
Time to treatment (days)	Median 10, mean 25.6, range 0-426 (data available in 73/124)	Median 17.5, mean 25.8, range 3-137 (data available in 32/37)	Median 10, mean 25.4, range 0-426 (data available in 41/90)
Any steroids	116/130 (89.2%)	37/40 (92.5%)	79/90 (87.8%)
Intravenous steroids	88/130 (67.7%) (84/88: IVMP; 4/88: IVDEX)	32/40 (80%) (30/32: IVMP; 2/32: IVDEX)	56/90 (62.2%) (54/56: IVMP; 2/56: IVDEX)
Oral steroids	114/130 (87.7%)	37/40 (92.5%)	77/90 (85.5%)
Intravenous immunoglobulin	66/130 (50.7%)	15/40 (37.5%)	51/90 (56.7%)
Plasma exchange	15/130 (11.5%)	11/40 (27.5%)	4/90 (4.4%)
Any second-line treatment (Cyclophosphamide and/or Rituximab)	21/130 (16.1%)	15/40 (37.5%)	6/90 (6.7%)
Cyclophosphamide	12/130 (9.2 %)	11/40 (27.5%)	1/90 (1.1%)
Rituximab	10/130 (7.7%)	5/40 (12.5%)	5/90 (5.5%)
Azathioprine	4/130 (3.1%)	1/40 (2.5%)	3/90 (3.3%)
MMF	79/130 (60.8%)	18/40 (45%)	61/90 (67.8%)
Other	4/130 (3.1%) (3/4 Tacrolimus, 1/4 Hydroxychloroquine)	2/40 (5%) (Hydroxychloroquine, Tacrolimus)	2/90 (2.2%) (Tacrolimus)

Supplementary Table 1. Study of disease events.
A total 130 events occurred in 40 patients (excluding 4 patients with chronic/chronic-progressive disease course): 113 events in 23 patients with multiphasic (relapsing) disease (including first events) (median 4 events per patient, mean 4.9, range 2-25), and 17 events in 17 patients with monophasic disease.
Legend: DEX: dexamethasone; IVDEX: intravenous dexamethasone; IVMP: intravenous methylprednisolone; MMF: mycophenolate mofetil; OP: oral prednisone.
*1 patient was on low dose prednisone, azathioprine and tacrolimus for renal transplant before onset of PANS/PANDAS

4. DISCUSSION

The present thesis is a collection of ten works exploring several aspects of the clinical and therapeutic decision-making in paediatric autoimmune and immune-mediated inflammatory conditions. This field includes a vast array of diseases with variable clinical manifestations and severity, and with a broad differential diagnosis. An additional challenge is represented by the fact that this is a quickly expanding field, thanks to a more and more accurate clinical phenotyping, and neuroradiology and laboratory advances. Therefore, classifications and disease groupings are being rearranged, and new clinical entities introduced. This is the case for the identification of anti-NMDAR antibodies in 2007, leading to the subsequent identification of an array of other antibodies targeting neuronal surface antigens associated to autoimmune encephalitis. Similarly, the identification of MOG antibodies has led to the definition of a group of demyelinating disorders whose clinical features are yet to be fully understood.

Immune therapies, such as corticosteroids, have been used for a long time in neurology and in other fields of paediatrics, although their mechanism of action are not always fully understood, and it is possible that multiple, concomitant actions are responsible for the therapeutic effect [Nosadini, 2017]. With the new diagnostic categories introduced by advances in disease identification, “old” drugs are being used for “new” indications, but also new drugs are becoming more and more available: disease modifying drugs for multiple sclerosis introduced in the last decades have changed the natural history of this condition, and the utility of monoclonal antibodies is currently being broadly investigated. Although, the enthusiasm in the exploration of the effect and safety of immune therapeutic agents, is usually held back by the relative rarity of most autoimmune and inflammatory conditions, which, along with their recent identification in some cases, make for the lack of quality data, such as randomized controlled trials, in most paediatric autoimmune and inflammatory neurological conditions. Moreover, data in children are sometimes derived from adult studies.

In this context, the present thesis aimed at gathering data and shedding more light on the available evidence on the use of immune therapy in the literature, and at investigating this aspect in different clinical situations. One of the main areas of our exploration focused on the category of autoimmune encephalitis with antibodies targeting neuronal surface antibodies [Nosadini, 2015]. This is a fascinating, relatively recent section in neuroimmunology, likely bound to quickly expand further in the

next years possibly leading to further diagnostic definition of some of those entities yet with poor serologic characterization, such as seronegative suspected autoimmune encephalitis [Graus, 2016]. The distinction between the categories of encephalitis with antibodies targeting neuronal surface antibodies and that associated to antibodies targeting intracellular antigens (paraneoplastic syndromes) can be done at different levels, where the relatively good response to immune therapy in the former group is central. Despite data are heterogeneous, there are common therapeutic themes emerging: firstly, patients given immune therapy do better and relapse less than patients given no treatment; secondly, patients given early treatment do better; and thirdly, when patients fail first-line therapy, second-line therapy improves outcomes and reduces relapses. This literature trend was confirmed also in out Italian cohort of paediatric anti-NMDAR encephalitis [Sartori, 2015], with a better neurological outcome in patients treated early. Still within the theme of autoimmune encephalitis, we explored the particular circumstance of anti-NMDAR encephalitis occurring after herpes simplex virus CNS infection [Nosadini, 2017]. The description of this phenomenon in 2012 [Prüss, 2012] gave a further insight on the pathogenesis of anti-NMDAR encephalitis, and it possibly provided arguments in favour of the rationale for the debated use of immune therapy in the acute phase of herpes simplex encephalitis. It is noteworthy that in this literature cohort none of the patients treated with immune therapy for herpes simplex virus-induced anti-NMDAR encephalitis were reported to have recurrence of herpes simplex encephalitis, suggesting immune therapy given for herpes simplex virus-induced anti-NMDAR encephalitis does not predispose to recurrence of herpes simplex encephalitis.

The last part of the work for the present thesis focused on the study of individual immune therapies declined into different clinical situations. Intravenous immunoglobulin was studied through a retrospective cohort of children with a vast array of neuroimmunology conditions, who received intravenous immunoglobulin over the years 2000-2014. The analysis of this cohort of children also included health economics data and comparison with available recommendations on use of intravenous immunoglobulin in paediatric neurology, and results showed that intravenous immunoglobulin is a relatively safe treatment, although very expensive. This work also disclosed discrepancies between guidelines and clinical practice in paediatric neurology, suggesting both the need for greater adherence to current recommendations, and for recommendations to be updated to accommodate emerging indications.

Therapeutic plasma exchange is a procedure relatively frequently used at our University hospital of Padova, Italy, also in children - thanks to the expertise of the apheresis team – while its use in other centres in paediatric neurology is strongly influenced by the individual centres' treating habits. The use of plasma exchange is regulated by the guidelines of the American Society for Apheresis, which include several neurological indications; it is noteworthy that anti-NMDAR encephalitis was included in the latest issue [Schwartz, 2016]. When we reviewed the use of therapeutic plasma exchange in a literature cohort of children with anti-NMDAR encephalitis [Suppiej, 2016], we observed a trend toward a better outcome when therapeutic plasma exchange was coupled with steroids in first-line treatments, possibly benefitting of the association with an agent acting centrally.

One of the project of the present thesis focused on rituximab re-dosing in paediatric neuromyelitis optica spectrum disorder [Nosadini, 2016]. While another large study focused on rituximab safety has recently been published [Dale, 2014], this work aimed at identifying factors related to treatment efficacy or failure. Indeed, relapse prevention in neuromyelitis optica is key to avoid the accumulation of permanent neurological deficits, and the identification of factors able to maximise rituximab efficacy could be of invaluable utility in clinical practice, possibly also in other diseases. The association between B cell repopulation and relapse risk was studied thoroughly, confirming the relationship between CD19 repopulation and increased risk for relapses, and the validity of a previously proposed threshold for B cell repopulation (CD19 $\geq 10 \times 10^6$ cells/L). Therefore, suggestions were formulated on the need for a close CD19 monitoring in order to prevent relapses.

Finally, two of the projects have been focusing on steroid sparing agents in paediatric autoimmune and immune-mediated conditions, disclosing huge heterogeneity in the use of these compounds and the need for quality studies to clarify their risk-benefit profile.

The main limitations of the present work are represented by the retrospective nature of the studies and the limited number of patients. Despite this, the present project may help shed further light on some aspects of treatment in paediatric neurology that are still partly unexplored or incompletely clarified, and contribute to the growth and the shaping of this field. Most importantly, this thesis has helped me grow and gain perspective in the field of decision making in paediatric neuroimmunology, even though there are major areas that warrant further exploration.

Shifting the focus from the therapy to the disease, it should not be forgotten that an adequate understanding of the pathophysiology may allow for a more adequate treatment strategy. The blood brain barrier is a dynamic element those modifications, such as changes in permeability due to an inflammatory state, may play a role in the pathophysiology of the disease [Alvarez, 2015] as well as in the penetration of immune therapy to the CNS. Moreover, knowing if neuroinflammation is predominantly driven centrally or peripherally may influence how we choose or direct therapy [Dale, 2016]. For example, in disease with intrathecal inflammation such as anti-NMDAR encephalitis, while immune therapies acting peripherally (i.e. plasma exchange) may help reducing the total circulating antibodies, lymphocytes and other inflammatory molecules, an immune therapeutic agent acting centrally, such as corticosteroids, should be warranted [Dale, 2016].

The theme of clinical and therapeutic decision making in paediatric neurology goes far beyond a thorough knowledge of immune therapeutic agents and their action, modes of use, efficacy and safety profile, notwithstanding this certainly is a key element. Indeed, clinical practice often requires that this theoretical knowledge be declined into a variety of scenarios, and the ability to understand each clinical situation in all its facets. While difficult to be learnt on books, these aspects are mainly derived from each clinician's personal experience, and are beautifully dealt with in a recent discussion paper by Russell Dale [Dale, 2016]. Neuroimmunology conditions in paediatric age represent a spectrum with a broad range of severity and that may include life-threatening situations, such as in anti-NMDAR encephalitis and ADEM. Severe clinical scenarios may justify more aggressive therapies to get past the acute phase, in a balanced approach that takes into consideration potential treatment's side effects. Moreover, the natural history of different conditions may vary hugely, with the potential for relapses in many cases, suggesting the need for a long-term immune suppression. The risk for permanent disability is another pivotal element of discussion in the decision making process, such as in neuromyelitis optica spectrum disorders, where the minimization of neurological injury in the acute phase and the prevention of relapses are exponentially increased, as compared to other situations, in view of the possibility of accumulation of irreversible disability. Although, the recent literature has been pointing to the actual existence of "subtle" sequelae also in situations where overt neurological deficits are typically not observed, such as in anti-NMDAR encephalitis and ADEM [Matricardi, 2016; Suppiej, 2014; Pawela, 2017], adding elements in favour of a more aggressive treatment regimen. Despite the considerable

clinical challenges encountered in the abovementioned situations, an even further level in the complexity of the clinical and decisional decision making process is represented by scenarios such as that of seronegative suspected autoimmune encephalitis [Graus, 2016], where the clinical definition and therefore the potential severity and natural history of the condition are less clear.

In conclusion, a comprehensive understanding of the therapeutic aspects should not go without the ability to understand each clinical situation in all its facets, taking into considerations not only potential effects, adverse reactions and mechanisms of treatment agents, but also the pathophysiology, the severity of the acute disease, the risk of relapses and of permanent disability, in a complex 'risk-versus-benefit' determination and a tailored approach (Figure 1) [Dale, 2016].

Figure 1

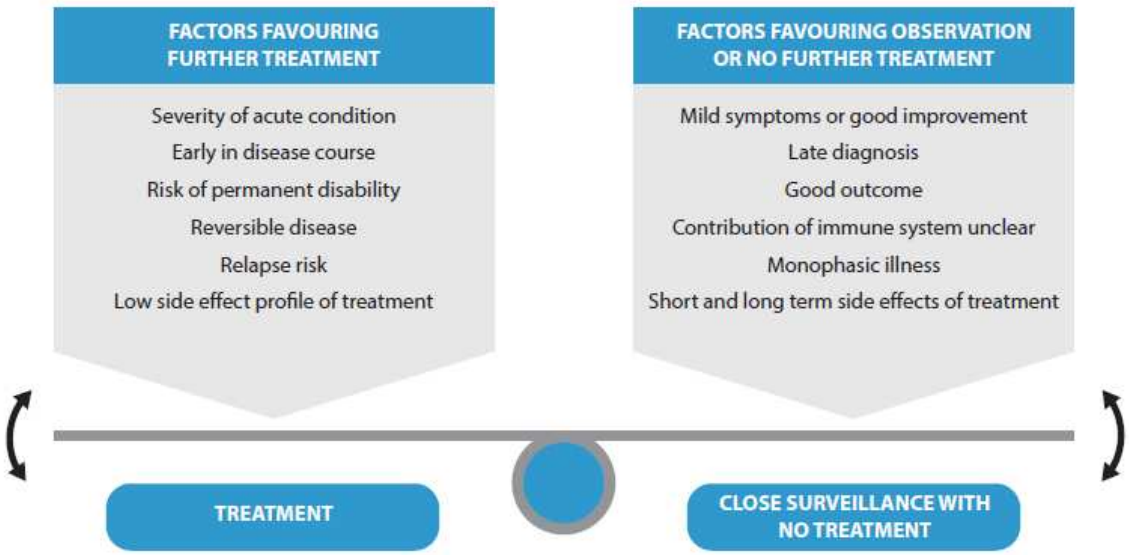

Figure 1 [Dale, 2016]. The complexity of therapeutic decision-making: Balancing the risk of disease with risk of drug side effects. The figure demonstrates some of the variables involved in therapeutic decision-making.

References

Alvarez JI, Saint-Laurent O, Godschalk A, Terouz S, Briels C, Larouche S, Bourbonnière L, Larochelle C, Prat A. Focal disturbances in the blood-brain barrier are associated with formation of neuroinflammatory lesions. Neurobiol Dis. 2015 Feb;74:14-24.

Dale RC, Nosadini M, Lim M. Therapeutic decision making in autoimmune and inflammatory disorders of the central nervous system in children. JICNA. 2016;16:11.

Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, Muscal E, Deiva K, Andersen E, Eyre MR, Eleftheriou D, Brogan PA, Kneen R, Alper G, Anlar B, Wassmer E, Heineman K, Hemingway C, Riney CJ, Kornberg A, Tardieu M, Stocco A, Banwell B, Gorman MP, Benseler SM, Lim M. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease.Neurology. 2014 Jul 8;83(2):142-50.

Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.

Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Höftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Prüss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostásy K, Saiz A, Venkatesan A, Vincent A, Wandinger KP, Waters P, Dalmau J. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016 Apr;15(4):391-404.

Hennes EM, Baumann M, Schanda K, Anlar B, Bajer-Kornek B, Blaschek A, Brantner-Inthaler S, Diepold K, Eisenkölbl A, Gotwald T, Kuchukhidze G, Gruber-Sedlmayr U, Häusler M, Höftberger R, Karenfort M, Klein A, Koch J, Kraus V, Lechner C, Leiz S, Leypoldt F, Mader S, Marquard K, Poggenburg I, Pohl D, Pritsch M, Raucherzauner M, Schimmel M, Thiels C, Tibussek D, Vieker S, Zeches C, Berger T, Reindl M, Rostásy K; BIOMARKER Study Group. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. Neurology. 2017 Aug 29;89(9):900-908.

Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinshenker BG. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 2004 Dec 11-17;364(9451):2106-12.

Matricardi S, Patrini M, Freri E, Ragona F, Zibordi F, Andreetta F, Nardocci N, Granata T. Cognitive and neuropsychological evolution in children with anti-NMDAR encephalitis. J Neurol. 2016 Apr;263(4):765-71.

Mohammad SS, Nosadini M, Grattan-Smith P, Dale RC. Intravenous immunoglobulin in acute Sydenham's chorea: A systematic review. J Paediatr Child Health. 2015 Dec;51(12):1235-8.

Pawela C, Brunsdon RK, Williams TA, Porter M, Dale RC, Mohammad SS. The neuropsychological profile of children with basal ganglia encephalitis: a case series. Dev Med Child Neurol. 2017 Apr;59(4):445-448.

Nosadini M, Alper G, Riney CJ, Benson LA, Mohammad SS, Ramanathan S, Nolan M, Appleton R, Leventer RJ, Deiva K, Brilot F, Gorman MP, Waldman AT, Banwell B, Dale RC. Rituximab monitoring and redosing in pediatric neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm. 2016 Jan 21;3(1):e188.

Nosadini M, Mohammad SS, Corazza F, Ruga EM, Kothur K, Perilongo G, Frigo AC, Toldo I, Dale RC, Sartori S. Herpes simplex virus-induced anti-N-methyl-d-aspartate receptor encephalitis: a systematic literature review with analysis of 43 cases. Dev Med Child Neurol. 2017 Aug;59(8):796-805.

Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother. 2015;15(12):1391-419.

Nosadini M, Mohammad SS, Suppiej A, Sartori S, Dale RC; IVIG in Neurology Study Group. Intravenous immunoglobulin in paediatric neurology: safety, adherence to guidelines, and long-term outcome. Dev Med Child Neurol. 2016 Nov;58(11):1180-1192.

Nosadini M, Sartori S, Sharma S, Dale RC. Immunotherapeutics in pediatric autoimmune CNS disease: agents and mechanisms. Seminars in Pediatric Neurology, 2017 (in press).

Prüss H, Finke C, Höltje M, Hofmann J, Klingbeil C, Probst C, Borowski K, Ahnert-Hilger G, Harms L, Schwab JM, Ploner CJ, Komorowski L, Stoecker W, Dalmau J, Wandinger KP. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol. 2012 Dec;72(6):902-11. doi: 10.1002/ana.23689.

Sartori S, Nosadini M, Cesaroni E, Falsaperla R, Capovilla G, Beccaria F, Mancardi MM, Santangelo G, Giunta L, Boniver C, Cantalupo G, Cappellari A, Costa P, Dalla Bernardina B, Dilena R, Natali Sora MG, Pelizza MF, Pruna D, Serino D, Vanadia F, Vigevano F, Zamponi N, Zanus C, Toldo I, Suppiej A. Paediatric anti-N-methyl-D-aspartate receptor encephalitis: The first Italian multicenter case series. Eur J Paediatr Neurol. 2015 Jul;19(4):453-63.

Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, Dunbar NM, Witt V, Wu Y, Shaz BH. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approachfrom the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J Clin Apher. 2016 Jun;31(3):149-62.

Suppiej A, Cainelli E, Casara G, Cappellari A, Nosadini M, Sartori S. Long-term neurocognitive outcome and quality of life in pediatric acute disseminated encephalomyelitis. Pediatr Neurol. 2014 Apr;50(4):363-7.

Suppiej A, Nosadini M, Zuliani L, Pelizza MF, Toldo I, Bertossi C, Tison T, Zoccarato M, Marson P, Giometto B, Dale RC, Sartori S. Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review. Brain Dev. 2016 Aug;38(7):613-22.