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PSYCHOLOGICAL AND NEUROPSYCHOLOGICAL ADVANCES IN MOTOR NEURON DISEASES: AMYOTROPHIC LATERAL SCLEROSIS AND X-LINKED SPINAL-BULBAR MUSCULAR ATROPHY

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ABSTRACT

Motor neuron disease (MND) is a heterogeneous family of neurodegenerative diseases, rare, characterized by an early involvement of motor neurons and can be hereditary or sporadic, including Amyotrophic lateral sclerosis (ALS) and X-linked spinal-bulbar muscular atrophy (SBMA).Three studies will be briefly presented below, with the aim of developing an understanding of psychological and neuropsychological aspects in these diseases.

In Chapter 3 is presented a retrospective study with the aim to verify whether the presence of cognitive impairment in ALS patients (according to the classification proposed by Phukan et al., 2012) may have an impact on the degree of disease progression in terms of motor decline. Up to date, in literature the debate about the influence of cognitive impairment on survival in ALS patients is still ongoing and results are conflicting. In summary, after 6 or 12 months follow up we observed the same degree of disease progression both in patients with presence or absence of cognitive impairment. In Chapter 4 it is presented a pilot study with the aim to investigate the applicability and efficacy of a hypnotic treatment on the physical and psychological well-being perceived by ALS patients, considering also the indirect effect on the well-being on caregivers. ALS implies an inevitable and devastating psychological impact and this study represent, even if at a preliminary level, the first application of a protocol of psychological intervention with evidence of efficacy in ALS patients. In Chapter 6, it is presented a study with the aim to investigate the neuropsychological and psychological profile in patients with SBMA, poorly characterized in the recent literature. In summary, in contrast with the previous literature, executive functioning seems to be apparently preserved in patients with SBMA; nevertheless patients seem to have a specific dysfunction on the cognitive component of the Theory of Mind (ToM), while the affective component seems to be preserved.

RIASSUNTO

La Malattia del motoneurone (MND) è una famiglia eterogenea di malattie neurodegenerative, rare, caratterizzate da un precoce coinvolgimento dei motoneuroni e possono essere ereditarie o sporadiche, e includono tra le altre la Sclerosi laterale amiotrofica (SLA) e l'Atrofia muscolare spinobulbare (SBMA). Sono stati condotti tre studi, brevemente presentati di seguito, con l'obiettivo di sviluppare la comprensione degli aspetti psicologici e neuropsicologici nelle suddette malattie.

Nel Capitolo 3 viene presentato uno studio retrospettivo con l'obiettivo di verificare se la presenza di deficit cognitivo in pazienti affetti da SLA (in accordo con la classificazione proposta da Phukan et al., 2012) possa avere un impatto sul grado di progressione di malattia in termini di declino motorio, ambito nel quale i dati presenti in letteratura sono contrastanti. In sintesi, a distanza di 6 o 12 mesi dal baseline si osserva lo stesso grado di progressione di malattia sia in presenza sia in assenza del deficit cognitivo. Nel Capitolo 4 viene presentato uno studio pilota con l'obiettivo di indagare l'applicabilità e l'efficacia di un trattamento ipnotico sul benessere psicologico e fisico percepito dai pazienti, valutando inoltre l'effetto indiretto sul benessere dei familiari. Nonostante la SLA implichi un inevitabile e devastante impatto psicologico il presente studio rappresenterebbe, anche se a un livello preliminare, la prima applicazione di un protocollo di intervento psicologico con prove di efficacia in pazienti affetti da SLA. Nel Capitolo 6 viene presentato uno studio con l'obiettivo di indagare il profilo neuropsicologico e psicologico nei pazienti affetti da SBMA, ad oggi poco investigato con riferimento alla recente letteratura. In sintesi, a differenza degli studi presenti in letteratura, il funzionamento esecutivo sembra essere apparentemente preservato nei pazienti affetti da SBMA; ciononostante i pazienti sembrano avere una specifica disfunzione a carico della componente cognitiva della Teoria della Mente (ToM), mentre risulta preservata la componente affettiva.

"*Let us keep looking, in spite of everything.*
Let us keep searching. It is the best method of finding,
and perhaps thanks to our efforts,
the verdict we will give such a patient tomorrow
will not be the same we must give this man today."
(Charcot, 1889)

1

Motor Neuron Disease

1.1 Introduction: definition of Motor Neuron Disease

"Motor neuron disease" is usually used as an umbrella term for all those disorders involving selective loss of function of upper and/or lower motor neurons innervating the voluntary muscles of the limbs and bulbar regions [1].

The term motor neuron disease encompasses:

- combined upper and lower motor neuron disorders (as Amyotrophic lateral sclerosis),
- pure lower motor neuron disorders (e.g. Hereditary bulbar palsy),
- pure upper motor neuron disorders (e.g. Primary lateral sclerosis).

A clinical classification of the different motor neuron disorders is represented in Table 1.1.

In the following chapters we will focus our interest on two diseases: Amyotrophic lateral sclerosis and X-linked spinal and bulbar muscular atrophy.

Amyotrophic lateral sclerosis (ALS), the most common presentation of Motor neuron disease, is a progressive disorder of unknown aetiology, that leads ultimately to death due to respiratory failure. There are other syndromes related to this spectrum of disorders including Progressive bulbar palsy (PBP), Progressive muscular atrophy (PMA), Primary lateral sclerosis (PLS), Flail arm syndrome (Vulpian-Bernhard syndrome), Flail leg syndrome (Pseudopolyneuritic form) and ALS with multi-system involvement (e.g., ALS-Dementia) [2].

Spinal and Bulbar Muscular Atrophy (also known as Kennedy's syndrome) is a recessive adult-onset spinal muscular atrophy which, whilst involving anterior horn cells of the spinal cord and/or brainstem, has a more benign disease course than ALS [3-4]. It is an X-linked disorder due to a CAG trinucleotide repeat expansion in the androgen receptor gene (AR). As patients are frequently misdiagnosed, genetic testing is diagnostic for SBMA.

Table 1.1 Classification of Motor neuron disease (adapted from Donaghy, 1999) [1]
Combined upper and lower motor neuron involvement
Amyotrophic lateral sclerosis (Sporadic and familial forms)
Pure lower motor neuron involvement
Proximal hereditary motor neuronopathy
X-linked spinal and bulbar muscular atrophy (Kennedy's disease)
Hexosaminidase deficiency
Multifocal motor neuropathies
Post polio syndrome
Post-irradiation syndrome
Monomelic, focal or segmental spinal muscular atrophy
Pure upper motor neuron involvement
Primary lateral sclerosis
Hereditary spastic paraplegia
Neurolathyrism
Konzo

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2

Amyotrophic Lateral Sclerosis

2.1 Definition

Amyotrophic Lateral Sclerosis (ALS) is a disease known in the world by different terminologies: *Charcot's disease* (named after the French neurologist who first described it in the 19th century); *Lou Gehrig's disease* (preferred in the United States), eponym for ALS used after the baseball player that in 1939 raised public attention on the disease; *Motor neuron disease* (MND - used in the U.K.); *SLA-sclérose latérale amyotrophique* (term Charcot gave the disease, is used in France).

Amyotrophic Lateral Sclerosis is a progressive neurodegenerative disorder involving primarily motor neurons in the cerebral cortex, brainstem and spinal cord [1]. Moreover, about half patients show cognitive and behavioural impairments in addition to motor decline; while a subgroup of patients develop a frontotemporal dementia [2].

Specifically, the term "Amyotrophy" means the atrophy of muscle fibres, which are denervated as their corresponding anterior horn cells degenerate, leading to weakness of affected muscles and visible fasciculations. "Lateral sclerosis" describes the hardening of the anterior and lateral corticospinal tracts as motor neurons in these areas degenerate and are replaced by gliosis [3].

The loss of upper (UMN) and lower (LMN) motor neurons contribute in a different measure for each individual to the patient's symptoms and signs.

The cause of ALS is unknown although some genetic risk factors have been identified. The etiology is sporadic (sALS) in the majority of cases, although familial forms (fALS) account for about 10% and are mainly transmitted by an autosomal dominant inheritance [4]. Sporadic ALS is thought to have both genetic and environmental influences, but the main causes have yet to be discovered [5].

To the present day, Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) share common genetic, pathological, and clinical features. It suggests that ALS and FTD are two ends of a possible spectrum of one disease [6] (Figure 2.1).

Genetic variants in the ALS/FTD spectrum including *C9orf72* repeat expansions, *SOD1*, *TDP-43*, and *FUS* mutations are found in familial as well as sporadic patients diagnosed with either of these neurological disorders [7].

Figure 2.1. ALS/FTD spectrum (adapted by Robberecht and Philips, 2013 [6])

2.2 Epidemiology

Amyotrophic lateral sclerosis is a rare disease. In a recent study [8] has been reported a mean incidence of disease range from 1.8 to 2.8/100,000 (respectively in North America and in Europe), while the mean prevalence range goes from 3.40 to 5.40/100,000 (in North America and in Europe).

In the last 25 years there has been an increased incidence which could be partly explained by the constant increase in the average lifespan of Italian population and its aging as much as by an improved diagnostic assessment [9], especially in women and the elderly who nowadays resort to medical attention much more often than in the past [10].

In Europe, ALS is more common in men than in women by a ratio of 1.2-1.5:1, which may be due to protective-hormones in women [11]. This disparity is largely attributable to the increased frequency of spinal-onset ALS in men and bulbar onset is more common in women and in older adults [12].

Median survival is of 3-5 years from first symptom and generally death overcomes with a respiratory failure; only 5-10% of patients survive beyond 10 years [13-14]. Age onset in sporadic ALS (about 90% of ALS patients) is between 58-63 years, while in familial ALS (about 5-10% of ALS patients) is between 47-52 years [15].

2.3 Clinical features: symptomatology, diagnosis, phenotypes, therapy and multidisciplinary care

The clinical feature of ALS is the simultaneous presence of clinical signs of involvement of the upper (UMN) and lower motor neuron (LMN), although the practice has revealed the existence of a large diversity of presentation of the disease.

Symptomatology

Loss of LMNs causes fasciculation, cramps, muscle atrophy and marked weakness, which is often more disabling for patients than the spasticity, hyperreflexia and modest weakness associated with UMN disease.

Babinski and Hoffman signs along with emotional lability are also characteristic findings of UMN degeneration.

In particular, emotional lability occurs at least in 50% of patients with ALS irrespective of the presence or absence of bulbar motor signs [16] and it does not correlate with cognitive impairment [17]. Extraocular movements, bladder and bowel function and sensation are spared.

In two-third of patients ALS begins in the limbs, more often in the arms. Initial symptoms are usually unilateral and focal. Patients may incur in loss of hand dexterity, weakness when lifting the arms or difficulty in walking.

If ALS begins with a bulbar-onset instead, tongue atrophies and fasciculates. The first symptom is more often dysarthria (a motor speech disorder), which may further degenerate into sialorrhea (excessive salivation), malnutrition and anarthria (loss of articulate speech)

Disease progression in ALS patients differs considerably between individuals [18-20], but progressive functional decline ultimately leads to a complete loss of independence.

Cognitive impairment in patients with ALS was first described in the 19th century. Consensus criteria have been proposed to categorize various forms of cognitive and

behavioural impairment [2]. Moreover, depression and anxiety may occur during any stage of the disease. When patients feel this emotional symptoms they perceive a poorer quality of life because of a loss of sleep and appetite [21]. Neuropsychological and psychological aspects will be discussed in detail in the next chapters.

Diagnosis

Despite the advances of investigative medicine over the past century, there is no definitive test for ALS diagnosis, but it is established excluding other causes of progressive upper motor neuron and/or lower motor neuron dysfunction.

To aid in diagnosis and classify patients for research studies, experts (WFN, World Federation of Neurology Research Group on Motor Neuron Diseases) developed in 1994 the "El Escorial" diagnostic criteria and in 2000 the revised "Airlie House" criteria [1], shown in Table 2.1.

Using these criteria patients can be classified into four categories: 'Clinically definite', 'Clinically probable', 'Clinically probable-Laboratory supported' and 'Clinically possible' [22].

Table 2.1 Revised El Escorial Research Diagnostic Criteria for ALS proposed by Brooks et al., 2000 [1] (adapted by Wijesekera & Leigh,2009 [20])

The diagnosis of ALS requires:

1. Evidence of LMN degeneration by clinical, electrophysiological or neuropathological examination;
2. Evidence of UMN degeneration by clinical examination, and
3. Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination,

Together with the absence of:

[1] Electrophysiological and pathological evidence of other disease that might explain the signs of LMN and/or UMN degeneration, and

[2] Neuroimaging evidence of other disease processes that might expalin the observed and electrophysiological signs

Categories of clinical diagnostic certainty on clinical criteria alone

Definite ALS

- ✓ UMN signs and LMN signs in 3 regions

Probable ALS

- ✓ UMN signs and LMN signs in 2 regions with at least some UMN signs rostral to LMN signs

Probable ALS – Laboratory supported

- ✓ UMN signs in 1 or more regions and LMN signs defined by EMG in at least 2 regions

Possible ALS

- ✓ UMN signs and LMN signs in 1 region (together), or
- ✓ UMN signs in 2 or more regions
- ✓ UMN signs and LMN signs in 2 regions with no UMN signs rostral to LMN signs

UMN signs	LMN signs
Clonus Babinski sign Absent abdominal skin reflexes Hypertonia Loss of dexterity	Atrophy Weakness If only fasciculation: search with EMG for active denervation

Regions reflect neuronal pools: bulbar, cervical, thoracic and lumbosacral.

Phenotypes

Disease phenotype is generally classified by the onset disease (spinal or bulbar), but further phenotypic subclassification is based on the degree of upper and lower motor neuron involvement (Figure 2.2). ALS occurs with the simultaneous involvement of the upper and lower motor neuron. Other forms include the involvement of a single motor neuron (upper or lower); while progressive bulbar palsy is characterized by the degeneration of the lower portion of the brain stem. Description of ALS phenotypes will be better illustrated in Table 2.2: primary lateral sclerosis (PLS), progressive muscular atrophy (PMA) and progressive bulbar palsy (PBP) [4].

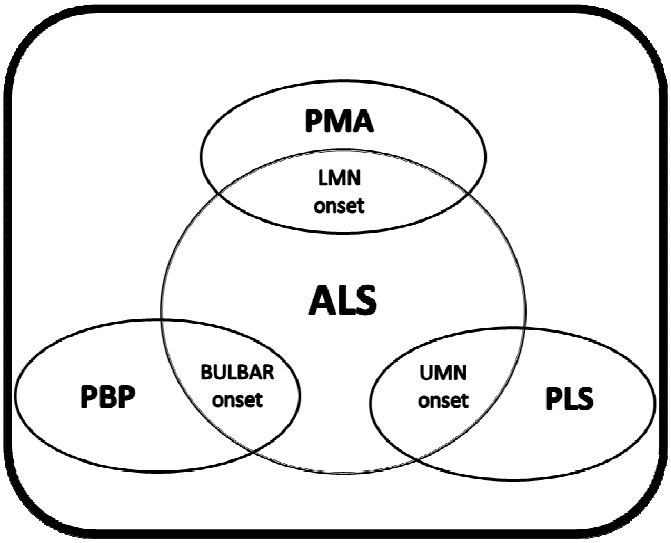

Figure 2.2. Types of onset in Amyotrophic lateral sclerosis (ALS)

Table 2.2. ALS and related phenotypes

Disease	Clinical features	Comments	Median survival
ALS	Multiple spinal segments affected with both upper and lower motor neuron signs	Most common adult-onset form of motor neuron disease	3-5 years
Primary lateral sclerosis	Upper motor neuron signs only	Many patients eventully develop clinical or electrophysiological signs of lower motor neuron involvment: ALS develops in up to 77% of patients within 3-4 years	≥20 years for patients who do not progress to ALS
Progressive muscular atrophy	Lower motor neuron signs only	Variable evolution in ALS	Typically 5 years, but a subset survive for ≥20 years
Progressive bulbar palsy	Speech and swallowing initially affected, owing to lower motor neuron involvment of cranial nerves IX, X and XII	Symptoms include dysarthria, dysphagia and dysphonia; aspiration pneumonia is usually the cause of death	2-3 years

Abbrevation: ALS, Amyotrophic lateral sclerosis
(Table adapted by Hardiman et al., 2011 [4])

However, these three phenotypic categories do not fully capture the spectrum of clinical heterogeneity in ALS. Since the late 19th and early 20th centuries two other forms have been recognized: the flail arm (FA) and flail leg (FL) syndromes. The FA syndrome is a LMN disorder of upper limbs and it is characterized predominantly by progressive proximal weakness and wasting: it may remain relatively confined for a prolonged period, resulting in a man-in-the-barrel appearance. The FL syndrome is a LMN disorder of lower limbs characterized by progressive distal onset weakness and wasting. It presents a slower disease progression [23].

The variability of phenotypes and overall rapid progression of the disease make difficult to predict survival time or timing of interventions. Generally, longer survival is associated with limb-onset, younger age, better motor function, higher breathing capacity, stable weight, and longer interval between symptom onset and diagnosis [24].

The 'flail arm' and 'flail leg' syndromes have a significantly better survival than Amyotrophic lateral sclerosis (ALS) or progressive muscular atrophy (PMA) cases that are not classified as FA or FL [23].

Therapy and multidisciplinary care

Following diagnosis, management of patients with ALS is centred on a combination of neuroprotective medication, multidisciplinary clinics to reduce symptoms (sialorrhoea, emotional lability, cramps, spasticity and pain) and aids for improving personal autonomy, movement and communication. Up to date there is no therapy able to cure ALS, but Riluzole (licensed in 1996) is the only drug approved which can slow the progression of the disease and prolong survival for approximately three months [25]. In advances stage of ALS inadequate nutrition becomes common and when respiratory muscle becomes weak it develops symptoms of dyspnea, daytime fatigue and morning headaches. Recent guidelines highlight that percutaneous endoscopic gastrostomy feeding improves nutrition and quality of life, and gastrostomy tubes should be placed before the development of respiratory

insufficiency. Non-invasive positive-pressure ventilation also improves survival and quality of life. However, advance directives for palliative end-of-life care should be discussed early with the patient and carers, respecting the patients social and cultural background. The purpose of palliative care is to maximize the quality of life of patients and families by relieving symptoms, providing emotional, psychological and spiritual support as needed, removing obstacles to a peaceful death and supporting the family in bereavement [26]. Attendance at multidisciplinary clinics may extend survival, decrease medical complications and improve quality of life [16].

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3

May cognitive impairment in patients with ALS have an impact on disease progression?

3.1 Cognitive functioning, progression disease and survival: an overview

Cognitive functioning

Although motor system deficits are prominent in Amyotrophic lateral sclerosis (ALS), this multisystem disorder is also accompanied by cognitive changes, more or less subtle.

Cognitive deficits might initially have a subtle appearance and are often overlooked, but thanks to an appropriate neuropsychological assessment it has been estimated that cognitive impairment may occur in more than 40% of incident patients with ALS and 10-15% may meet criteria for diagnosis of frontotemporal dementia-FTDL [1-2]. The three variants of FTDL are defined by consensus criteria proposed in 1998 by Neary and colleagues [3] (Table 3.1).

Table 3.1 Variant of frontotemporal lobar dementia
(proposed by Neary et al., 1998; adapted by Phukan et al., 2007) [3-4]

	Neuropathological topografy	**Cognitive symptoms**	**Behavioural changes**	**Neurological findings**
Frontal variant frontotemporal dementia	Frontal atrophy more severe than temporal atrophy. Particularly affected right dorsolateral and prefrontal cortex, and left premotor cortex	Executive dysfunction (eg., verbal fluency and attention)	Distractibility, disinhibition, decline in personal hygiene, hyperorality, compulsions, perseveration, apathy and submissiveness	Frontal release signs and primitive reflexes, motor neuron disease, and possible extrapyramidal features (Progressive Supranuclear Palsy or Corticobasal Degeneration)
Non-fluent progressive aphasia	Asymmetric atrophy of left hemisphere. Particularly affected: left frontal, insular, anterior parietal, superior temporal, and perisylvian cortex	A disorder of expressive language. Non-fluent spotaneous speech with agrammatism, phonemic paraphasias, and anomia. Impaired executive function and working memory	Behavioural changes are typically seen late in the course of this illness. Possible social withdrawal and depression	Supranuclear gaze disturbance, axial rigidity, alien limb, and focal dystonias
Semantic dementia	Temporal atrophy more severe than frontal atrophy. Particularly affected: insula, amygdala, and anterior hippocampus	Impaired understanding of word meaning and object identity, fluent but empty spontaneous speech, semantic paraphasias, long-term memory loss, and perceptual disorder (eg. prosopagnosia, associative agnosia or both)	Emotional withdrawal, depression, mental rigidity, and compulsions	Neurological findings emerge late in the course of this illness

The variant most frequently described in ALS-patients is frontal variant frontotemporal dementia (fvFTD); the other two variants are non-fluent progressive aphasia which is characterized by language impairment and semantic dementia, which is characterized by a loss of conceptual knowledge [4].

Strong and colleagues in 2009 [5] proposed the following classification system (see Table 3.2 for much details) for the frontotemporal syndromes in ALS: cognitively impaired (ALSci), behaviourally impaired (ALSbi), ALS-Frontotemporal dementia (ALS-FTD) in which Neary criteria for FTD are met, FTD-MND like in which patients clinically had FTD and pathologically have motor neuron loss but did not manifest signs of motor neuron disease during life and ALS-Dementia in which patients have Alzheimer's or vascular dementia [6].

Table 3.2 Classification system for the frontotemporal syndromes in ALS
(adapted by Strong et al., 2009) [5]

Axis II. Cognitive/behavioural characterization - Frontotemporal lobar degeneration with ALS

Heading	Subheading	Existing, synonymous term in the literature	Characteristics
ALS-FTD	ALS-bvFTD ALS-PNFA ALS-SD	ALS-Dementia (ALS-D), FTD-MND	ALS patient meeting Neary criteria for FTD ALS patient meeting Neary criteria for PNFA ALS patient meeting Neary criteria for SD
ALSbi			ALS patient meeting at least 2 non-overlapping supportive diagnostic features from Neary criteria for FTD
ALSci			Evidence of cognitive impairment at or below the 5° percentile on at least 2 distinctive tests of cognition that are sensitive for executive functioning
FTD-MND-like			A neuropathological diagnosis in which FTLD is the primary diagnosis but in which there is neuropathological evidence of motor neuron degeneration, but insufficient to be classified as ALS
ALS-dementia	ALS-AD ALS-vascular dementia ALS-mixed dementia	ALS-dementia (ALS-D)	ALS with dementia, not typical of FTLD ALS in association with AD ALS in association with vascular dementia ALS in association with a mixed dementia (eg. AD-vascular dementia)
ALS-Parkinsonism-dementia complex		Western Pacific variant of ALS	ALS concurrent with dementia and/or Parkinsonism occurring in hyperendemic foci of the western Pacific

In non-demented ALS patients cognitive functioning is not an universal feature, while executive dysfunction is predominant. Executive functions, traditionally thought of as higher-level mental processes that control and organise other cognitive

processes [7], are a heterogeneous set of skills that facilitate problem solving and responses to novelty. They are also implicated in behavioural regulation, response initiation, motivation and elements of memory functioning [8].

Recently a three domain-based classification was proposed suggesting that ALS with cognitive impairment is a heterogenous disease [2]: 1. Impairment in executive dysfunction (ALS-Ex); 2. Non-executive cognitive impairment (ALS-NECI); 3. No cognitive impairment. The criteria used by Phukan and colleagues (2012) [2] to define dysfunction in each cognitive domain is shown in Table 3.3.

Table 3.3 Cognitive domain-based categorization for non-demented ALS patients proposed by Phukan et al., 2012 [2]

COGNITIVE GROUPS	COGNITIVE DOMAIN
1. ALS-Ex	Impairment in executive dysfunction (ALS-Ex) single domain or in association with impairment in other cognitive domains (multidomain)
2. ALS-NECI	Non-executive cognitive impairment (ALS-NECI), single domain (eg. Language only) or multidomain dysfunction (eg. Language and memory)
3. No cognitive impairment	

A similar approach has been adopted in a recent study conducted in Italy [9], where a different degree of cognitive impairment has been observed in about 50% of ALS patients. The authors suggested a possible role of cognitive reserve in ALS-related cognitive impairment, corroborated by some studies showing that a lower educational level and bulbar onset associate with cognitive involvement [10].

Cognitive decline appears to be influenced by cognition at baseline, in particular ALS patients with normal cognition at baseline showed a tendency to remain cognitively intact with a slower motor and cognitive progression, while ALS patients with cognitive impairment have been associated with a more rapid cognitive decline [11].

Rate of disease progression

Phenotypic variability in ALS complicates measurements of disease progression that differs considerably between individuals [12-14]. In an individual with ALS, disease advances at a relatively constant rate, although progression may be influenced by clinical, demographic and genetic features [12].
Ultimately, progressive functional decline leads to a complete loss of independence.
In literature the debate about the influence of cognitive impairment on survival in ALS patients is still ongoing and results are conflicting.
Some authors suggest that cognitive performance was not related to survival [15] or that demented and non-demented ALS patients did not differ in disease duration [16], while some others reply that faster rates of motor functional decline have been observed in ALS patients with cognitive impairment in executive function at baseline [11].

Survival

In ALS patients the time to death or tracheostomy, in clinical trials, is generally used to define survival. Median survival is of 3-5 years from first symptom and generally death overcomes with a respiratory failure; only 5-10% of patients survive beyond 10 years [17-18]. Previous studies of ALS populations identified several negative prognostic factors, including older age at onset and bulbar onset [17-19]. Furthermore, Elamin and colleagues (2011) [20] suggested that executive dysfunction is a negative prognostic indicator. In particular, ALS-FTD patients and patients with executive dysfunction have shorter survival time than any other cognitive group [9,20], regardless of the limb or bulbar onset [4,21].

3.1 Aim of study

Recent studies have shown that ALS patients with cognitive impairment in executive functioning have a shorter survival than patients with cognitive impairment in other domains or the ones cognitively intact: hence the need to identify whether cognitive impairment may have a different impact on degree of disease progression or if a shorter survival can be associated to poor compliance with medical intervention [21]. The study aims to determine if the presence of cognitive impairments has an impact on disease progression, in terms of motor decline. Disease progression was assessed using the ALS-MITOS system (ALS Milano-Torino Staging) [22], a new tool that captures the loss of functions based on subscores of the ALSFRS-R (revised ALS Functional Rating Scale) [23].

3.2 Methods: participants and measures

ALS patients recruitment has been based on the patients group who has participated in a previous retrospective study [24], as shown in Figure 3.1. Cognitive profile has been assessed with an extensive neuropsychological battery, at the first visit after diagnosis. Performance of these 165 sporadic ALS patients, without diagnosis of FTD or other frank dementia, was compared with the one obtained by 134 healthy volunteers (HCs). HCs was matched with patients group regarding age, sex and educational level.

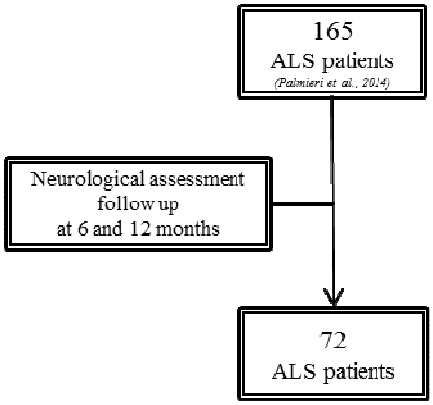


Figure 3.1 Flow chart of patients included in analysis. ALS. Amyotrophic lateral sclerosis

Palmieri and colleagues (2014) [24] categorised all 165 patients into three cognitive subgroups, according to the recent classification suggested by Phukan and colleagues (2012) [2]:

- *Impairment in executive dysfunction (ALS-Ex)*: patients (n=47; 28.5% of total) with executive impairment in single domain of executive functioning or in association with impairment in other cognitive domain.
- *Non-executive cognitive impairment (ALS-NECI)*: patients (n=30; 18.2% of total) with non-executive cognitive impairment, but impairment in other single or multiple cognitive domains (e.g. memory and language functioning, visuospatial abilities, nonlogic reasoning).
- *ALS-No cognitive impairment*: patients (n=88; the remaining 53.3%) without apparent cognitive impairment.

Participants: Demographic and clinical characteristics

ALS patients referred to Motor Neuron Disease Centre of Padua University Hospital from 2006 to 2010 with a diagnosis of possible, probable or definite ALS according to Revised El Escorial Criteria [25].

Exclusion criteria include diagnosis of FTD or other kinds of dementia, history of previous neurological conditions that could affect cognition (e.g. brain stroke or traumatic brain injury), permanent active ventilation, psychiatric diseases (such as depression or alcoholism) and the use of high-dose of psychoactive medications.

Cognitive profile has been defined by performance to tests of a comprehensive neuropsychological battery, which it has been administered to patients at the time of the first visit after diagnosis.

Degree of disease was assessed at baseline (T0) and then at 6-month intervals (T1 and T2) only for 72 of 165 sporadic ALS patients (37 males and 35 females). These participants have a mean age of 63.06 years (SD = 7.87; age range = 45-81). To

study the effect of cognitive status on disease progression, we operationally classified the participants into three cognitive subgroups (ALS-Ex, ALS-NECI and ALS-No cognitive impairment, Figure 3.2).

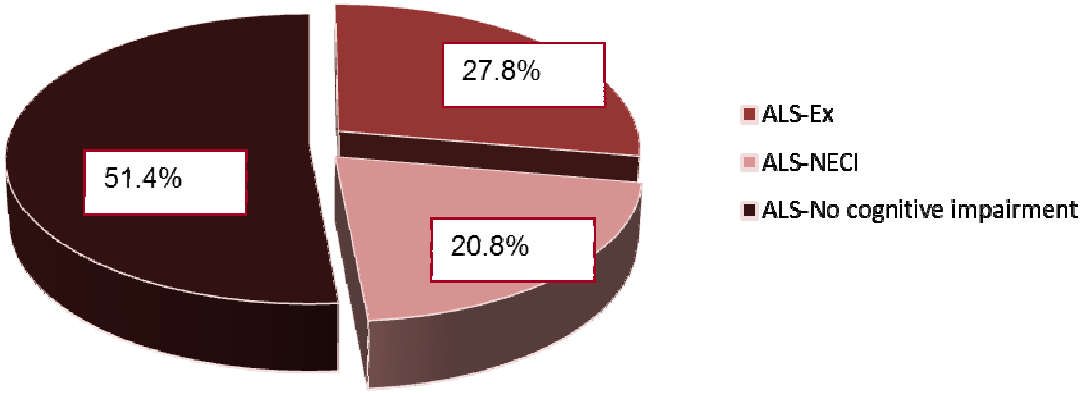


Figure 3.2. Percent of ALS patients into the three cognitive subgroups.

To check whether there were statistically significant differences between cognitive groups in age, educational level (years), time since ALS onset (months), site of onset and ALSFRS-R score the Kruskal-Wallis test was performed. The result of the nonparametric test indicates that the differences are statistically significant in gender ($X^2_{(2)}$=8.31,p=0.02), age ($X^2_{(2)}$=16.23,p≤0.001) and educational level ($X_{(2)}$=16.23, p=0.002), but there were no statistically differences in time since ALS onset, site of onset and ALSFRS-R score at baseline. Demographic and clinical details are shown in Table 3.4.

Table 3.4 Baseline characteristics					
N tot = 72	ALS-Ex N=20	ALS-NECI N=15	ALS-No Cogn. Imp. N=37	Statistic (df)	p Value
DEMOGRAPHIC CHARACTERISTICS					
Female, n (%)	14 (70%)	9 (60%)	12 (32.4%)	X^2 (2)=8.31	**0.02**
Age, years					
Mean±SD	65.35±6.19	68.33±6.95	59.68±7.53	X^2 (2) =16.23	**0.001**
Median (range)	66 (53-78)	68 (60-81)	60 (45-79)		
Educational level, years					
Mean±SD	6.55±2.44	6.71±2.55	9.57±3.86	X^2 (2) =12.62	**0.002**
Median (range)	5 (5-13)	5 (4-13)	8 (5-18)		
CLINICAL CHARACTERISTICS					
Time since onset, months					
Mean±SD	44.95±47.38	41.20±43.01	28.97±31.96	X^2 (2) =0.68	0.71
Median (range)	25.50 (7-180)	24 (4-145)	19 (2-169)		
Onset type, n (%)					
Spinal	16 (80%)	12 (80%)	27 (73%)	X^2 (2)=0.49	0.78
Bulbar	4 (20%)	3 (20%)	10 (27%)		
ALSFRS-R (score at baseline)					
Mean±SD	38.95 (4.64)	37.47±5.25	38.30±6.10	X^2 (2) =10.54	0.76
Median (range)	38 (30-48)	38 (28-45)	39 (24-48)		

Measures: neuropsychological assessment

Neuropsychological assessment, lasting approximately an hour, consisted in standardized neuropsychological instruments and it encompassed mainly executive function and also non-executive cognitive domains such as memory and language functions. The available literature suggests early involvement of frontally-mediated executive functions in ALS patients and verbal fluency is a sensitive and reliable test of executive functioning.

The majority of tests were not timed, and when it was expected, the score was corrected considering bulbar and/or motor patient's disability in time-dependent tasks.

The neuropsychological battery [24] included tests to evaluate:

a. executive functions

   - the Phonemic Verbal Fluency Test (PVFT), in accordance to Abrahams' protocol [26] has been considered *F index* (a measure of the average time taken to think of each word) to control individual variations as consequence of dysarthria,

   - the Abrahams M and C Written Verbal Fluency Tests (AWVFT), *M and C indexes* have been used to control motor impairment,

   - the Modified Wisconsin Cards Sorting Test (M-WCST),

   - the Trial Making Test (TMT) A e B direct score, number of error and the TMT B-A derived score, in accordance with Reitan's protocol [27].

b. long-term and short-term memories

   - the Prose Memory Test (PMT), considering recency and latency effects.

   - the Digit Span Forward (DSFT) and the Backward (DSBT),

   - the Dysillabic Word Test (DWT).

c. language

   - the Semantic Verbal Fluency Test (SVFT), in accordance to Abrahams' protocol [26] has been considered *S index*,

   - the Boston Naming Tests (BNT), considering total number of errors, semantic and phonemic cues.

   - the Token Test (TT).

d. non-verbal logic reasoning

   - the Raven's Coloured Progressive Matrices (RsCPM).

e. visuospatial abilities

   - the Rey-Osterrieth Complex Figure Test (ROCFT), considering copy and recall performance.

Healthy controls underwent the same neuropsychological battery.

Abnormal performance on any test was defined as a score that is 2 SD below the mean for HCs. Executive dysfunction was defined as abnormal performance on at least two executive tests. Non-executive cognitive impairment was defined by

abnormal performance on at least four parameters in memory, language or visuo-spatial functions. Further, mood tone was assessed using the Beck Depression Inventory [28].

Measures: neurological assessment

Neurologist with extensive clinical experience about the disease assessed motor functional decline using the following tool: the revised ALS Functional Rating Scale (ALSFRS-R, Panel 3.1): a scale that measures fine and gross motor tasks, bulbar functions and respiratory functions in ALS patients [23]. It is composed by 12 items and the maximum score is 48.

The ALSFRS-R is a useful outcome measure in therapeutic trials [23] and it is a known predictor of progression and survival in ALS patients [29]. Recently Chiò and colleagues (2015) [22] proposed an ALS staging system (ALS Milano-Torino Staging, MITOS) to measure the progression of ALS and to overcome the intrinsic limitations of the ALSFRS-R including: (a) non-linear, thus prone to biases; (b) multidimensional, thus unfit as single score and unable to satisfy rigorous measurement standards; (c) floor-effect, thus unable to capture late-stage clinical changes.

This ALS staging system was also recently validated [30] and it can reliably predict the course of ALS up to 18 months.

Specifically, the ALS-MITOS system [22] is based on four functional domains of the ALSFRS-R: movement (walking or self-care), swallowing, communicating (speech and handwriting) and breathing (dyspnoea or respiratory insufficiency), as shown in Table 3.5. Each domain has a threshold focusing on loss of function in the specific ALSFRS-R subscores. Values of 0 or 1 (respectively below or above threshold) were assigned and the stages were determined by the sum of functional score of 1 for each domain. Stage 0 correspond with none loss of function, while Stage 5 coincide with loss of five functional domains (death). For ALS-MITOS the cut-off to predict survival at 12 and 18 months correspond to 1 (loss of at least one function).

Panel 3.1 Amyotrophic lateral sclerosis functional rating scale - revised [23]

1. Speech

4 Normal speech

3 Detectable disturbance

2 Intelligible without repeating

1 Speech with non-verbal communication

0 Loss of useful speech

2. Salivation

4 Normal

3 Slight, but definite excess of saliva

2 Moderate excessive of saliva, minimum drooling

1 Marked excessive of saliva, some drooling

0 Marked drooling, needs constant tissue

3. Swallowing

4 Normal eating habits

3 Early eating problems, occasional choking

2 Dietary consistency changes

1 Needs supplemental tube feeding

0 Nil orally

4. Handwriting

4 Normal

3 Slow or sloppy, all words legible

2 Not all word legible

1 Able to grip pen, but cannot write

0 Unable to grip pen

5. Cutting food and handling utensils

4 Normal

3 Slow and clumsy, but no help needed

2 Can cut most food, although clumsy and needs some help

1 Food must be cut by someone else

0 Needs to be fed

6. Dressing and hygiene

4 Normal

3 Independent, but decreased efficiency

2 Some help with closures and fasteners

1 Provides minimum assistance to caregiver

0 Unable to perform any task

7. Turning in bed

4 Normal

3 Slow and clumsy

2 Can turn alone with difficulty

1 Can initiate but cannot turn or adjust sheets

0 Total dependence

8. Walking

4 Normal

3 Early ambulation difficulties

2 Walks with assistance

1 Non-ambulatory, functional movement

0 No purposeful leg movement

9. Climbing stairs

4 Normal

3 Slow

2 Mild unsteadiness or fatigue

1 Needs assistance

0 Cannot do

10. Dyspnoea

4 None

3 Occurs when walking

2 Occurs when eating, bathing, or dressing

1 Occurs at rest

0 Considerable difficulty

11. Orthopnoea

4 None

3 Some difficulty, does not routinely use more than two pillows

2 Needs extra pillows to sleep

1 Only sleeps sitting up

0 Unable to sleep

12. Respiratory isufficiency

4 None

3 Intermittent use of non-invasive ventilation

2 Continuous use of non-invasive ventilation at night

1 Continuous use of non-invasive ventilation, day and night

0 Mechanical ventilation via tracheostomy

Table 3.5 ALS-MITOS Functional domains and stages [22]

ALSFRS-R domain		Functional score
Movement	Walking **or**	**0/1**
	Self-care	**0/1**
Swallowing	Swallowing	**0/1**
Communicating	Speech **and**	**0/1**
	Handwriting	**0/1**
Breathing	Dispnea **or**	**0/1**
	Respiratory insufficiency	**0/1**

ALS-MITOS

Stage	Functional domains lost
0	None
1	1 domain
2	2 domains
3	3 domains
4	4 domains
5	Death

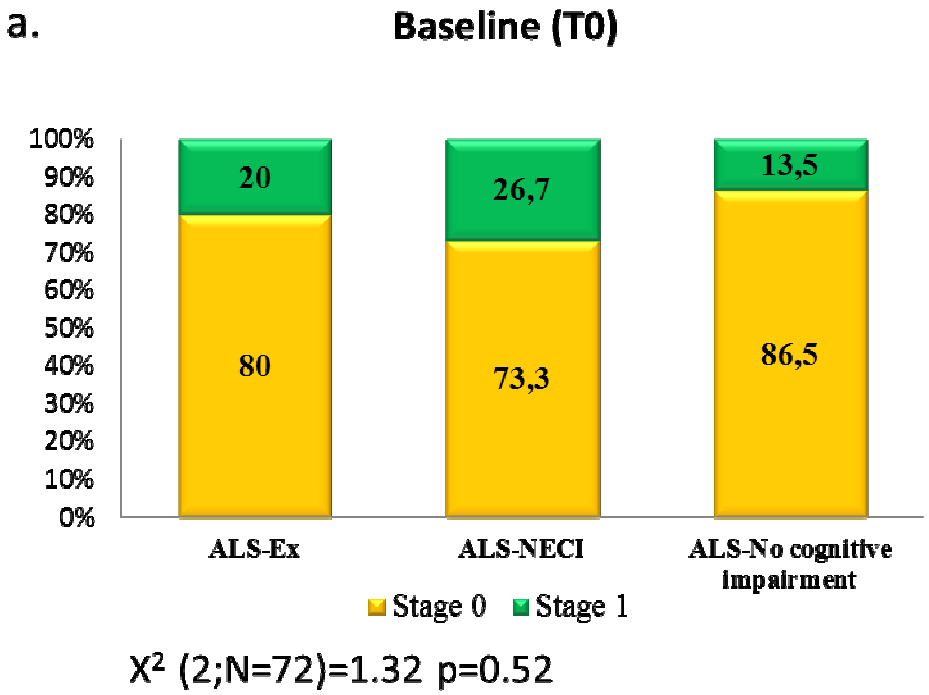
3.4 Statistical analyses

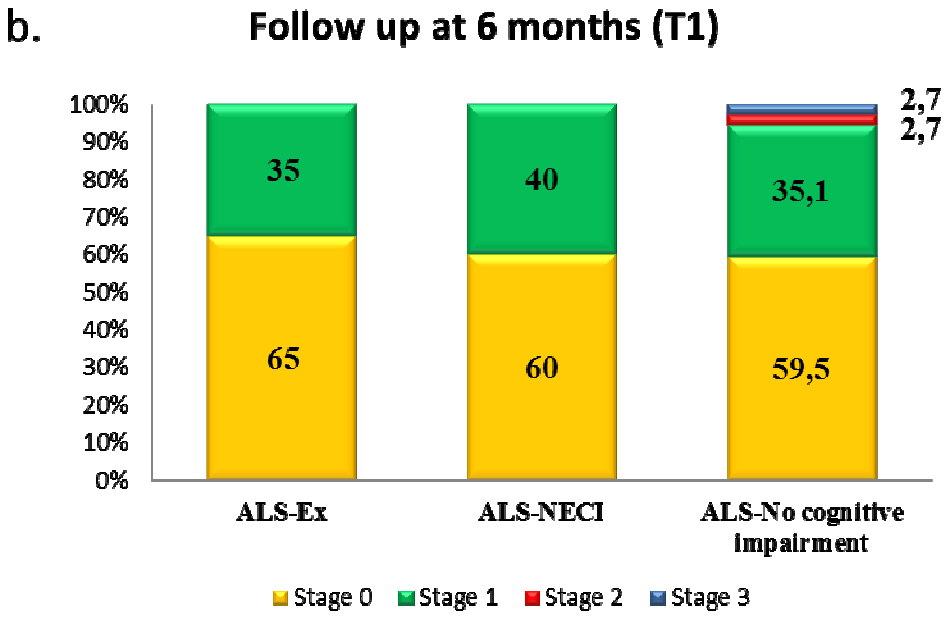
Data analysis were carried out using SPSS (Chicago, IL). The Kruskal-Wallis test was performed to check whether there were statistically significant differences between cognitive subgroups in age, educational level (years), time since ALS onset (months), site of onset and ALSFRS-R score, as detailed above (pgg. 27-28).
The ALS-MITOS system was calculated for each patient at baseline and then at 6-month intervals (T1 and T2). The distribution of ALS stage was examined using descriptive statistics. The X^2 test was performed to verify the presence of significant differences in ALS-MITOS stages between the three cognitive subgroups.

3.5 Results

The analysis of progression based on the ALS-MITOS system was performed between the three cognitive subgroups. At baseline, among the ALS-Ex group 16 patients (80%) were in Stage 0 and 4 patients (20%) were in Stage 1 and none in other Stages.
In ALS-NECI group 11 patients (73.3%) were in Stage 0 and 4 patients (26.7%) were in Stage 1. In ALS-No cognitive impairment group 32 patients (86.5%) were in Stage 0 and the remaining 5 patients (13.5%) were in Stage 1. In the three cognitive subgroups, all patients in Stage 1 had lost function in movement (walking/self-care) and details are shown in Figure 3.3a.
At 6-month follow up, patients that remained in Stage 0 were 13 (65%) of ALS-Ex, 9 (60%) of ALS-NECI and 22 patients (59.5%) cognitively intact. The other patients were in Stage 1 and only 2 patients cognitively intact progressed to advances stages of disease (Stage 2 and Stage 3).
At 12 months, only 1 ALS-Ex patient (5%) progressed to Stage 2.
In ALS-NECI group 2 patients (13.3%) were in Stage 2 and 1 patient was in Stage 4.
Among the ALS patients cognitively intact, 5 patients (13.5%) were in Stage 2, 4 patients (10.8%) were in Stage 3 and 2 patients (5.4%) progressed to Stage 4.

The results of the X^2 test do not reveal significant differences in the progression of disease between the cognitive subgroups at baseline and at 6-12 months (Figure 3.3).





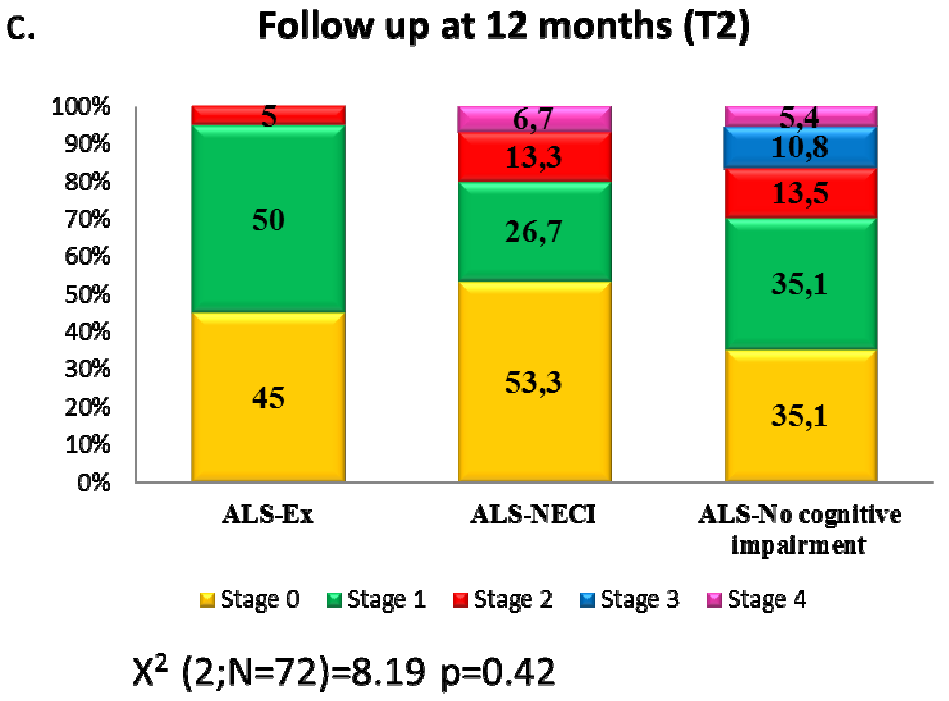


Figure 3.3. ALS stage at baseline (a), at 6 months (b) and at 12 months (c) in the three cognitive subgroups.

3.6 Discussion

In literature the debate of the effect of cognitive impairment on survival in ALS patients is still ongoing and results are conflicting. The present study aimed to reveal whether cognitive impairment may have a different impact on degree of disease progression or if a shorter survival can be associated to poor compliance with medical intervention [21].

We examined disease progression, in term of motor decline, using ALS-MITOS system, a novel tool that was recently validated [30] and overcomes limitations of ALSFRS-R.

This stage system is based on the unidirectional progression of function in four key domains (movement, swallowing, communicating and breathing), the attainment of which means their loss without any possibility to recover.

Our findings have demonstrated that cognitive impairment does not have any influence on disease progression, because at 6-12 month intervals the rate of progression was similar between the three cognitive subgroups. Specifically, patients lost the same functions (walking/self-care) at baseline and showed a similar progression in reaching the following stages.

This results corroborates the recent studies [20-21] which don't rule out the chance that survival rate of ALS affected patient with a cognitive impairments resulting statistically lower is not related to a more aggressive form of disease as much as their poor compliance with medical intervention, like not-invasive ventilation (NIV) and/or enteral nutrition (NE, PEG).

The main limitation of our study was the small sample size within the three cognitive subgroups because clinical assessment was not available for all the initial 165 patients at 6-12 months follow up, but this is a natural consequence of a retrospective study design. Despite this, our findings determine that at 6 and 12 months follow-up presence of cognitive impairments does not have an impact on disease progression, in terms of different rate of motor decline, indicating that shorter survival of ALS

patients with executive dysfunction, which is reported in other studies [20-21], is not explained by progression rate of their disease progression (in term of motor decline). Future research in this field should investigate specifically the relationship between the different degrees of cognitive impairment and patient's compliance in the use of medical interventions aids.

Acknowledgement: Dott.ssa Arianna Palmieri e ASLA Onlus.

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4

Efficacy of hypnosis-based treatment in Amyotrophic lateral sclerosis: a pilot study

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4.1 Psychological aspects of ALS patients and caregivers: an overview

People with Amyotrophic Lateral Sclerosis (ALS) experience a huge amount of continuous emotional distress. From breaking the news to the rapid motor decline, which causes physical dependence even in activities of daily living, the patient and his caregiver are exposed to complex emotional reactions.

The Constitution of the World Health Organization (WHO) defines health as "a state of complete physical, mental, and social well-being not merely the absence of disease or infirmity". It follows that the measurement of health and the effects of health care must include not only an indication of changes in the frequency and severity of diseases but also an estimation of well-being and quality of life, regardless of the physical status of person [2].

WHO defines quality of life as "a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment" [3].

Some studies have shown the relative independence of the degree of disability on the quality of life perceived by patients with ALS [4-6]. Psychological well-being seems to be more important in maintaining the perceived quality of life, than the degree of impairment of physical aspects [7]. Impact of disease on emotional well-being differs greatly between individuals, and the psychological reaction of patients to their disease, and their ability to cope with it have an effect on disease's evolution itself [8-10]. Psychological well-being seems to be also crucial in determining a better prognosis in patients with ALS [11]. Disease affects not only the patient, but also his relatives, who face harsh emotional challenges that interact with those of the patient [12-13]: there would seem to be a relationship between well-being perceived by the patient and the one perceived by his relatives [14]. Depression and anxiety typically occurs in response to the disease, especially in the first phase, in which patients experience anger, hopelessness and suicidal ideation [15-16]. The psychological status of patient seems to be directly related to their caregiver's one [13,17-18].

Likewise, the psychological status of the caregiver appears to have a profound impact on the patient [19].

4.2 Aim of study

Psychological issues in the Amyotrophic lateral sclerosis' (ALS) field have been relatively well studied, considering the low prevalence of the illness, but as recently emphasized by Pagnini (2013) [16] there is an absence of research on efficacy of psychological interventions in ALS: hence the need to investigate the effect of hypnosis-based intervention on psychological and perceived physical well-being in patients and the indirect effect on caregivers.

4.3 Methods

For this pilot study were recruited eight (50% females) volunteers patients (mean age=55, SD=7.14) referred to Motor Neuron Disease Clinic in Padua with a diagnosis of possible, probable or definite ALS according to Revised El Escorial Criteria [20] and their respective caregivers. They underwent Neurological and neuropsychological assessment within a week before the first treatment session. ALSFRS-R [21] mean score was 35 (SD=7.1, range: 21-42). Patients' neuropsychological profiles did not reveal any abnormal performance if compared to normative data.

At pre and post treatment phase anxiety and depression levels in patients and their caregivers were measured with the Hospital Anxiety and Depression Scale (HADS) [22]. This questionnaire is composed of an Anxiety subscale and a Depression subscale. Quality of life was assessed with the Amyotrophic Lateral Sclerosis Specific Quality of Life-revised (ALSSQOL-r) [23-24] and the ALS Assessment Questionnaire (ALSAQ-5 derived from the broader ALSAQ-40) [25-26].

However, global satisfaction with hypnotic-based treatment and perceived physical symptoms' changes were qualitatively investigated in patients.

The hypnosis intervention and self-hypnosis training protocol lasted 1 month with domiciliary sessions. The general induction was recorded in a CD audio which was left to each patients to practice at least once a day. This procedure was common for all patient and for all treatment phases and it is inspired by Jensen and colleagues (2009, 2011) [27-28] hypnosis-based protocol, also applied with success on patients with multiple sclerosis.

4.4 Data analysis

All analyses were carried out with R software, version 2.15.1. Non-parametric statistics were preferred because of small samples' size where it is not safe to assume a normal distribution.

4.5 Results

Patients declared to have successfully practiced self-hypnosis at least once every day in the great majority of the days during the treatment. Data analysis revealed the efficacy of the psychological intervention protocol on patients with ALS, both on a psychological and physical level. It was also observed an improvement in caregivers psychological well-being, probably due to the improvement of both psychological (improvement in depression, anxiety and quality of life) and physical (decreases in pain, sleep disturbances, emotional lability and fasciculations) aspects perceived by patients.

4.6 Conclusion

To the best of our knowledge, this is the first report of a psychological intervention protocol on ALS patients.

Even if at a preliminary level, and despite the pilot study limitations, the findings provided an encouraging support for using hypnosis to manage some physical consequences of ALS and mainly to cope with its dramatic psychological implications for the patients and, indirectly, for their caregivers.

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5

X-linked Spinal and Bulbar Muscular Atrophy

5.1 Definition

X-linked Spinal and Bulbar Muscular Atrophy (SBMA), also known as Kennedy's disease (after its initial description as a clinical entity in 1968) [1], is a rare, genetically inherited neuromuscular disorder characterized by dysfunction and loss of lower motor neurons (LMN) in the brainstem and spinal cord [1-2].

The causative mutation in SBMA is the expansion of a CAG trinucleotide repeat, which encodes a polyglutamine (polyQ) tract in the androgen receptor [3].

Androgen receptor (AR) contains three polyQ tracts, of which one is polymorphic in length with an average length of approximately 21-25 residues; the other two are respectively composed of five and six glutamine residues [4].

Expansion of the first polyQ tract to greater than 37 residues causes disease and the longest expansion described to date in patients is 62 residues [5].

Since SBMA is X-chromosomal it affects only adult males. Females only show subclinical symptoms even if they are homozygous for the mutation [6].

5.2 Epidemiology

Among the hereditary motor neuron diseases, Spinal and Bulbar Muscular Atrophy has one of the lowest prevalence, that is estimated to be 3.3/100,000 among male population and the mean annual incidence was 0.19/100,000 among male population [7].

The onset of weakness is usually between 30 and 60 years of age. Postural tremor of the fingers is often observed prior to weakness.

5.3 Clinical features

Phenotypically, patients present amyotrophic, proximal or distal weakness and wasting of the facial, bulbar and limb muscles, occasional sensory disturbances, and

endocrine disturbances, such as androgen resistance, gynecomastia, elevated testosterone or progesterone, and reduced fertility [8].

Nowadays SBMA is described as a multisystem disease because neurologic deficits associated with SBMA are very similar to those of ALS. The main differences are the absence of upper motor neuron involvement in SBMA and the X-linked inheritance pattern. Patients with SBMA typically present progressive neuromuscular weakness that most commonly includes the bulbar muscles. Fasciculations are a prominent feature of both. Previously, distinction between these two disorders was difficult. Up to date, however, with genetic testing these can be distinguished with a certain grade of reliability [9]. The symptoms are slowly progressive in SBMA, and the susceptibility for aspiration pneumonia increases as bulbar paralysis develops. The most common cause of death is pneumonia [10].

SBMA is generally believed to be relatively benign compared to other life-ending and neurologically devastating forms of other motor neuron disorders [9].

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6

Theory of mind, empathy and neuropsychological functioning in X-linked Spinal and Bulbar Muscular Atrophy: a controlled study of 20 patients

[1] Di Rosa, E., Sorarù, G., Kleinbub, J. R., Calvo, V., Vallesi, A., Querin, G., Marcato S., Grasso I. & Palmieri, A. (2015). *Journal of Neurology*, 262(2), 394-401

6.1 Psychological and neuropsychological aspects of SBMA patients: an overview

Spinal and bulbar muscular atrophy (SBMA or Kennedy's disease) is an adult-onset hereditary neurodegenerative disorder, associated predominantly with a lower motor neuron syndrome and eventually endocrine and sensory disturbances. In contrast to other motor neuron diseases such as amyotrophic lateral sclerosis (ALS), the impairment of cognition in SBMA is poorly characterized. Recent studies highlight that fronto-temporal cognitive functions are impaired in SBMA patients, although at a subclinical level and not relevant to the patients' everyday functioning. Thus, functional deficits in SBMA, which could indicate subtle frontal lobe dysfunction, are not confined to motor neurons but also affect extramotor networks [2-3].

From a clinical viewpoint, it is common for patients with SBMA to have particular psychological characteristics such as diffidence, marked emotional sensitivity and concentration problems. These observation generally seems to confirm that higher-order frontotemporal functions could be particularly vulnerable in SBMA, as often see in ALS [1,4].

6.2 Aim of study

The aim of this research was to investigate the not well documented and mostly unknown neuropsychological and psychological profile of SBMA patients, focusing on cognitive functions and on Theory of Mind (ToM) abilities.

The emerging literature suggests that social cognition abilities are subserved by a complex fronto-striatal network, likely with right hemispheric predominance [5]. An integral component of social signal processing is an extensively investigated phenomenon termed Theory of Mind (ToM) or mentalizing.

ToM refers to the ability to attribute independent "mental states", including knowledge, belief and motives to other individuals in order to understand and predict their behaviour [6].

There are two subcomponents of ToM:
- “cognitive ToM” refers to the ability to recognise that another individual may have knowledge and belief which are different from one’s own beliefs. It has been linked to the temporal-parietal junctions and dorsolateral prefrontal cortex [7-8];
- “affective ToM” refers to ability to infer another person’s emotional state or how they are “feeling”. This subcomponents is largely subserved by the ventro-medial prefrontal cortex and the orbitofrontal cortex, particularly in the right emisphere [7-9].
Although it has been shown that cognitive and affective ToM can de dissociated, everyday life social interactions often requires contributions from both subcomponents.

6.3 Methods

For this study were recruited 20 genetically proven SBMA patients (age range 41-74 years) referred to Motor Neuron Disease Centre of Padua University Hospital and 18 age/educational-matched controls (HCs, age range 41-71 years), all healthy males volunteers.
Exclusion criteria for patients and HCs include: diagnosis of any king of dementia, history of previous neurological conditions that could affect cognition, depressive symptoms, psychiatric diseases, ongoing use of high-dose psychoactive medication.
All patients underwent a neurological assessment before the neuropsychological and psychological assessment.
Neuropsychological assessment, in accordance to the recent literature, included tests to evaluate:

a. executive functions and attention
   - the Semantic Fluency Tests by semantic and phonemic categories [10-11],
   - the Trial Making Test (TMT) A e B [12].

b. long-term and short-term memories
   - the Babcock Story immediate and delayed recall test [13].
   - the Digit Span Forward and the Backward [13].

c. ToM tasks
   - the Faux Pas Test [14-15],
   - the Reading the Mind in the Eyes Test [16].

Healthy controls underwent the same neuropsychological battery.

6.4 Data analysis

All analyses were carried out with SPSS rel. 18.0. Non-parametric statistical analysis were preferred because they require few, if any, assumptions about the shapes of the underlying population distributions, and they are more robust for small samples [17-18].

6.5 Results

The results of the neuropsychological assessment for the group of patients showed no significant impairment in executive function, attention or memory by comparison with the control group. However, a clear dissociation emerged between patient's cognitive and affective empathy. Patients had distinctive deficits in mentalizing, as assessed with the Faux Pas Test, whilst affective empathy, assessed with the Reading the Mind in the Eyes test, appeared to be preserved.

6.6 Conclusion

To the best of our knowledge, this is the first study to investigate ToM in connection with neuropsychological functioning in SBMA patients. To sum up, in contrast with the previous literature, executive functioning seems to be apparently preserved in

patients with SBMA. Nevertheless, patients seem to have a specific dysfunction in the ability to interpret social situations by appropriately identifying other people's intentions. The likely implications of subtle frontal lobe impairments and the influence of androgen insensitivity in these SBMA male patients seem to explain these findings. Subtle frontal lobe impairment could explain variable cognitive impairment and the "cognitive" subcomponent of Theory of Mind (ToM) could be compromised because it seems to involve several extra-frontal areas while, on the other hand, insensitivity to androgens could afford a sort of affective empathy advantage for males with SBMA, whose more affective subcomponents of ToM result consequently preserved.

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