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SYSTEMATIC REVIEW

Rehabilitation approaches in West Nile Virus survivors: a systematic review

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ABSTRACT

INTRODUCTION: Periodic increases in West Nile virus (WNV) infections have been documented. Proper rehabilitative management is essential for these patients, who may experience limitations in daily activities even after the resolution of the acute infection. Since there are currently no globally accepted guidelines, our aim is to conduct a best-evidence synthesis on rehabilitative management for patients with neuroinvasive WNV.

EVIDENCE ACQUISITION: We screened the literature with two independent researchers conducting searches on PubMed, Embase, SCOPUS, and Google Scholar databases for WNV-related studies in the field of rehabilitation. Suitable studies were identified and selected through a rigorous process. The review includes original research articles published up to August 15, 2023.

EVIDENCE SYNTHESIS: Despite the potential for bias in the studies, the literature suggests that a comprehensive and interdisciplinary rehabilitation program, which includes physical therapy with neuromotor and respiratory interventions, occupational therapy, neurocognitive interventions, and speech therapy for dysphagia and communication issues, can lead to functional improvement in WNV patients. This program should be tailored to address each patient's specific challenges, and the duration of the rehabilitation program may vary depending on the individual patient's needs.

CONCLUSIONS: Even if additional research with larger cohorts and higher evidence levels is needed for a comprehensive understanding of WNV patient rehabilitation, an early and comprehensive rehabilitation approach addressing respiratory, neuromuscular, and cognitive aspects appears effective for WNV patient recovery.

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KEY WORDS: Encephalitis; Rehabilitation; Activities of daily living; Recovery of function.

Introduction

The West Nile virus (WNV) is a single-stranded RNA virus with an envelope, belonging to the Flaviviridae family, that infects people when bitten by a specific type of mosquito capable of transmitting the infection. Although most infected people are asymptomatic or develop a self-limited flu-like illness, it is estimated that 10% of patients infected with WNV are symptomatic, and 10% of this subgroup develop neuroinvasive disease, presenting encepha-

litis (50%), meningitis (37%), acute flaccid paralysis (6%), or a combination of these symptoms. Risk factors for acquiring WNV meningoencephalitis include age (>50 years old), diabetes, and immunosuppression.[1]

The number of WNV cases had remained relatively stable since 2012, with a reported increase in 2017-2018 (2544 in 2018; 2097 in 2017) in the USA.[2] Emerging concerns related to WNV include the potential for increased transmission due to climate change and the long-term health effects experienced by survivors, highlighting the ongoing need for surveillance, prevention, and effective rehabilitation strategies.[3-6]

Italy has recently faced a rapid increase in the incidence of cases of WNV infection. While from 2008 to 2018, 475 confirmed human cases of autochthonous WNV neuroinvasive disease and seven imported cases were reported in Italy, in 2018, there was a significant increase in the circulation of WNV with a total of 606 confirmed human cases reported. Of these, 239 occurred in the neuroinvasive form involving 6 Italian regions (Emilia-Romagna, Friuli Venezia Giulia, Lombardy, Piedmont, Sardinia, and Veneto), while 299 cases were characterized by fever and 68 were identified in asymptomatic blood donors.[7] Since the beginning of June 2022, there has been another significant increase in the incidence of WNV infection in Italy, with 301 confirmed cases reported. Among these cases, a substantial percentage corresponds to patients who developed the neuroinvasive form, including 19 cases in Piedmont Region, 85 in Veneto Region, 37 in Emilia-Romagna Region, and 8 in Lombardy Region.[8]

Literature suggests different ways of entrance into the central nervous system, including direct entry through the blood-brain barrier, infection of endothelial cells and leukocytes, and peripheral nervous fibers axonal retrograde transport from the injected sites (Figure 1).[9] Clinically, the diagnosis of WNV is based on serology, specifically IgM testing, and cerebrospinal fluid polymerase chain reaction. To determine the phenotype and severity of the disease, patients should undergo magnetic resonance imaging (MRI), electroencephalogram, and electromyography (EMG) evaluations.[10]

Morbidity and mortality of patients with WNV are high, particularly in those who require intensive care for neuroinvasive forms of infection.[11] For individuals in these conditions, prioritizing rehabilitative interventions is essential.

In particular, depending on the symptoms presented during the infection and the type of sequelae reported, patients can be classified into three categories of neuroinvasive disease:[12]

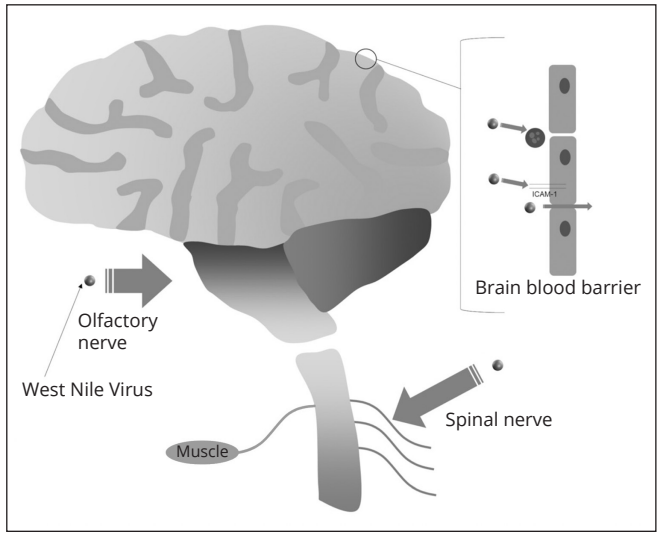

Figure 1.—Different WNV ways of entrance in the central nervous system.

• a first subgroup of patients presents meningoencephalitis, complicated by disorders of consciousness, cognitive impairment, epileptics seizures, and dyskinesias related to deep nuclei involvement highlighted on MRI evaluations. Dyskinesia symptoms may include tremors, myoclonus, and parkinsonism. The tremor can be either static or kinetic, but it is not noticeable at rest.[13] Parkinsonism includes rigidity and bradykinesia. These patients have generally good cognitive recovery with only residual parkinsonism on examination.[3] Therefore, it can be suggested that prognosis depends on the involvement of the basal ganglia and the consequent motor impairments (Figure 2).

• In the second subgroup, encephalitis is complicated by acute flaccid paralysis, respiratory failure and dyspha-

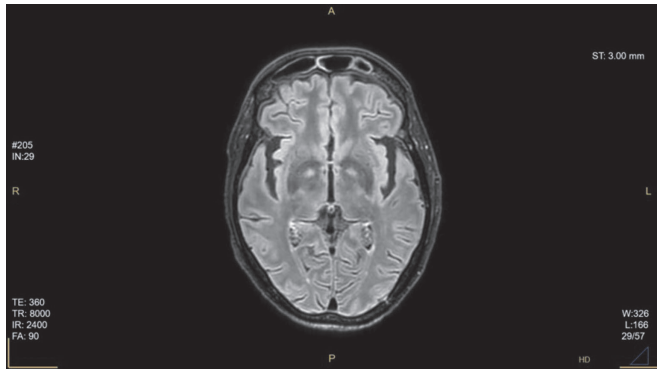

Figure 2.—Involvement of the basal ganglia in brain MRI (T2-Flair sequence) in a patient with neuroinvasive WNV.

gia. Consequently, a prolonged course of rehabilitation is necessary for this form of WNV disease. Patients with asymmetrical limb involvement typically exhibit axonal motor neuropathy without signs of demyelination and with preserved sensory responses, resembling poliomyelitis-like conditions at the EMG evaluations. Conversely, in some patients, neurophysiological evaluation reveals a spectrum similar to Guillain-Barré syndrome, characterized by signs of myelin damage and symmetrical muscle weakness.[13, 14] Cauda equina arachnoiditis is a rare, but possible neuroradiological feature in the acute flaccid paresis form of WNV disease.[15]

• The third subgroup of patients present with meningitis, often complicated by bilateral chorioretinitis, and had generally a good recovery in a few weeks.[16]

Given the limited literature in this area, our aim is to conduct a comprehensive best-evidence synthesis to identify and assess all published manuscripts within the WNV rehabilitation field, describe their quality, and summarize and compare their conclusions, in order to consolidate existing knowledge regarding the rehabilitation of patients with WNV.

Evidence acquisition

Literature search and selection

We performed a systematic review with best-evidence synthesis. The search encompassed the following databases: PubMed, Embase, SCOPUS, and Google Scholar. The initial search was conducted in January 2022 and repeated in August 2023. Database-specific MeSH terms were employed in the initial search, such as "West Nile Virus Infection," "WNV Infection," "West Nile Fever Meningoencephalitis," "West Nile Fever," "West Nile Fever Encephalitis" and "West Nile Fever Meningitis." The search terms were adjusted to align with the vocabulary mapping of each individual database and Boolean operators were employed.

Two authors (MCM and DC) independently reviewed the titles and abstracts. Original research articles published up to August 15, 2023, were considered for inclusion. We included randomized controlled trials, cohort studies, and case-control studies published in English for quality appraisal. Studies in which the outcome was unclear or did not address rehabilitative management were excluded. Manuscripts were selected based on the following criteria, following the PICO framework: the population included adult subjects (≥18 years) who had experienced WNV infection; the intervention focused on the effects of single or combined rehabilitative interventions; the comparison involved various types of interventions or no comparison. All rehabilitative outcome measures were taken into account. Duplicate records and papers that did not meet the inclusion criteria were excluded. Studies selected for the review needed to have the abstract and the full text available. Articles written in languages other than English were excluded. The title and abstract of each result were assessed to identify articles relevant to the research question. Subsequently, the full-text versions of the manuscripts were obtained and re-evaluated against the criteria described above.

Data extraction

Data were extracted and meticulously organized in a comprehensive table using a customized data extraction model in Microsoft Excel. The table included essential details such as authors' names, year of publication, sample size, subjects' age, outcomes, and discharge location.

Quality assessment

The quality of the studies was independently assessed by two authors (M.C.M. and D.C.). Any discrepancies were discussed until a consensus was reached with the involvement of a third reviewer (S.M.).

Since the majority of the studies found were case reports or case series, the methodological quality and risk of bias in the included manuscripts were assessed using the tool for evaluating the methodological quality of case reports and case series proposed by Murad *et al.*[17] This tool consists of eight items that fall into four domains: selection, ascertainment, causality, and reporting. Each item is accompanied by explanatory questions to aid in its assessment. While one possibility is to calculate an aggregate score by summing the binary responses for the eight items, it is recommended to refrain from using an aggregate score. Instead, it is preferable to conduct an overall assessment of methodological quality based on the questions considered most critical in the specific clinical context for the systematic review.[17] On the other side, the Newcastle-Ottawa Scale was used to evaluate the quality of the remaining studies. The scale utilizes a "star system" to assess studies based on three main perspectives: selection of study groups, comparability of groups, and ascertainment of exposure or outcome for case-control or cohort studies, respectively. During the quality assessment of each article, a maximum score of 9 stars can be achieved, indicating higher quality, while studies of lower quality receive fewer stars.[18]

Evidence synthesis

Studies selection

The initial search strategies yielded 4855 articles for potential inclusion after duplicates had been removed. Of these, 82 full-text articles were assessed for eligibility. After title and abstract screening, we evaluated 41 studies and included nine in the systematic analysis.

Studies characteristics

Seven papers presented case reports,[19-25] while two papers were retrospective studies.[26] All the participants were WNV survivors. Five studies used the Functional Independence Measure (FIM) as an outcome measure.[19-21, 26, 27] Seven papers reported patients being discharged at home,[19, 21-23, 25-27] while in three studies patients were discharged to a nursing facility.[21, 26, 27]

Risk of bias within studies

Quality appraisal revealed the most frequent risks of bias for case reports and case series concerned weaknesses in patients' selection, short periods for follow-up evaluations, and the lack of details in cases and intervention reporting (Table I, III).[19-25] In particular, in the papers considered the rehabilitative protocols were not described in detail, except for the manuscripts by Miller *et al.* and Unger *et al.*[23, 25]

The methodological quality of the retrospective studies varied between scores of 5 to 6. Scores >6 identified studies as of high quality,[27] while the lower score was associated with issues such as lack of a prolonged follow-up and a control group.[26] Nevertheless, the retrospective study conducted by Hoffman and Paschal considered the highest number of WNV patients.[26]

The best-evidence synthesis is presented in Table II,[19-25] where we have synthesized the characteristics of the selected studies, the assessed rehabilitative outcomes, and the discharge settings (Table II).[19-25] We will provide a brief description of our findings below.

Case reports and case series

Ohry *et al.* documented a case of a healthy young woman who developed encephalo-myelitis after contracting WNV during the 2000 epidemic. Encephalitis and tetraparesis evolved into an incomplete upper limb paresis after a multidisciplinary rehabilitation period.[19] Similarly, Marciniak

TABLE I.—*Evaluation of the methodological quality of case reports and case series and risk of bias assessment.*[19-25]

Domains	Leading explanatory questions	Ohry *et al.*[19]	Marciniak *et al.*[20]	Rao *et al.*[21]	VanDemark[22]	Miller *et al.*[23]	Zafar and Ubogu[24]	Unger *et al.*[25]
Selection	1. Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	?	?	?	?	?	?	?
Ascertainment	2. Was the exposure adequately ascertained? 3. Was the outcome adequately ascertained?	+	+	+	–	+	+	+
Causality	4. Were other alternative causes that may explain the observation ruled out? 5. Was there a challenge/rechallenge phenomenon? 6. Was there a dose–response effect? 7. Was follow-up long enough for outcomes to occur?	–	+	–	+	–	+	+
Reporting	8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	–	–	–	–	+	–	+

The symbols "+," "-," and "?" indicate low, high, and unclear risk of bias, respectively.

TABLE II.—*Summary of the studies considered.*[19-27]

Authors	Article type	Population (N.)	Age	Length of stay	Outcomes	Discharge setting
Care reports and case series						
Ohry *et al.*[19]	Case report	1	33	1 month	FIM variation: admission 81, discharge 91	Home
Marciniak *et al.*[20]	Case series	4	29-72 years	From 37 days to 106 days	Modest improvements in upper and lower strength (Motor Scores) and function (FIM variation)	NA
Rao *et al.*[21]	Case series	5	35-70 years	From 10 to 71 days (mean 32 days)	FIM variation (discharge *vs.* admission) statistically significant (P<0.002)	1 patient: subacute nursing facility 4 patients: home
VanDemark[22]	Case report	1	55	30 days	Improvement in strength and independence	Home
Miller *et al.*[23]	Case report	1	55	17 days	Gait progression: from 4-wheeled walker to wide-based quad cane (week 13) and single-point cane (week 18); ambulation without any assistive device part-time at home (week 21), ambulation in the community with no assistive device (week 34) Progression in manual muscle testing	Home
Zafar and Ubogu[24]	Case report	1	48	NA	Improvements in upper extremity strength, more pronounced distally	NA
Unger *et al.*[25]	Case report	1	67	5 months	Improvements in Berg Balance Score, 10meter Walking Test, and 6 Minutes Walking Test maintained after 3 months Visual Analog Fatigue Scale declined throughout training, but increased at the 3-month follow-up Improvement in Balance/Trunk Scale	Home
Retrospective studies						
Hoffman and Paschal[26]	Retrospective chart review	48	Mean age 67.75 (24 - 91 years)	From 1 to 62 days	FIM variation (discharge *vs.* admission) statistically significant (P <.001)	
Patel *et al.*[27]	Case series	5	Mean age 64.8 (43-78 years)	From 14-21 days) (mean 17.8)	Mean total FIM gain 37 points (range 24-60 points)	3 patients: home 1 patient: skilled nursing facility 1 patient: assisted living facility

FIM: Functional Independence Measure. NA: not available.

TABLE III.—*Evaluation of the methodological quality of retrospective studies and risk of bias assessment.*[26, 27]

Study, year	Number of stars		
	Selection	Comparability	Outcome
Hoffman and Paschal[26]	3	0	2
Patel *et al.*[27]	3	0	3

et al. discussed the improvement in motor and FIM instrument scores in four patients with severe flaccid weakness caused by WNV infection from the time of admission to an acute inpatient rehabilitation hospital, up to the six-month follow-up. Participation in an acute inpatient rehabilitation program resulted in modest gains in motor and FIM scores for these patients, but significant deficits continued despite the intervention: after six months from the onset of WNV disease, none of the patients fully regained their strength or became capable of walking independently.[20]

Rao *et al.* considered five patients who presented with severe neurological symptoms and meningoencephalitis. These patients were admitted to an acute inpatient rehabilitation center between September 2002 and January 2003 to address their functional deficits. Among the patients, three exhibited quadriparesis, while the other two had profound and generalized muscle weakness. Electrodiagnostic evaluations revealed axonal neuropathy in the latter two cases, which was associated with poorer func-

tional outcomes. Additionally, all five patients displayed cognitive deficits and dysphagia, and one patient experienced acute respiratory failure during the infection, requiring tracheostomy and ventilator support. Following a multidisciplinary rehabilitation program involving physical therapy, occupational therapy, and speech therapy, all patients demonstrated significant functional improvement. One patient was discharged to a subacute nursing facility, while the remaining patients were discharged home.[21]

VanDemark documented a case with a four-month follow-up, involving a 55-year-old construction worker who presented with progressive numbness, lower extremity weakness, and swallowing difficulties. The presence of WNV was confirmed through serum and cerebrospinal tests. During the patient's hospitalization, physical and occupational therapy were administered. Initially, passive range-of-motion exercises were performed while in the intensive care unit, and later, a strengthening program was implemented.[22] Miller *et al.* discussed the physical therapist management and outcomes of a female patient with WNV disease. The patient in this case report showed significant progress by combining intensive strengthening exercises with fatigue monitoring. Over the course of treatment, the patient transitioned from a nonambulatory state to walking with a single-point cane at week 18 after symptom onset. By week 20, the patient no longer required an assistive device for walking. Additionally, she returned to full-time work by week 43.[23] Zafar and Ubogu presented a case of a 48-year-old man who experienced severe painless bilateral weakness in his upper extremities caused by WNV myelitis. Upon discharge, the patient underwent physical and occupational therapy. Three months after treatment, the patient reported no changes in shoulder flexion or elbow extension strength but showed a slight improvement in distal upper extremity strength.[24]

Unger *et al.* examined the effects of an intensive locomotor training program on a patient with chronic paraplegia resulting from a previous WNV infection. Following rehabilitation, the patient became a wheelchair user and began locomotor training three years after the infection. The training program consisted of 55 sessions, including overground training that involved walking, balance, and strengthening exercises, as well as bodyweight-supported treadmill training. The patient received three sessions per week, progressing to four sessions per week. After five months of training, the patient was able to walk independently again.[25]

Retrospective studies

Hoffman and Paschal conducted a retrospective review of 48 patients who were admitted to an inpatient rehabilitation service with a WNV diagnosis between January 1, 2002, and December 31, 2009 and were discharged within that same period. The patients were assigned to one of three levels of care – acute rehabilitation, sub-acute rehabilitation, or the long-term acute care hospital unit – depending on their medical and physical condition. Patients who were in good health and could participate in three hours of therapy (physical therapy, occupational therapy, and/or speech therapy) were accepted to acute rehabilitation, while patients who needed urgent medical attention were admitted to the long-term acute care hospital unit. Medically stable patients who were not able to undergo three hours of rehabilitation sessions were placed in the subacute unit. Among the patients considered, 37.5% developed acute respiratory failure, and 33% were mechanically ventilated and/or had a tracheostomy tube. After treatment, there was a statistically significant change in FIM scores. While most patients experienced statistically significant improvements in their FIM scores, none of the patients in this study fully regained their pre-illness functional status, and only three out of 48 patients did not require follow-up physical therapy services. Older patients required a longer length of stay due to the medical complexity and higher rehabilitation needs.[26]

Patel *et al.* conducted a retrospective chart review of five subjects diagnosed with neuroinvasive WNV disease who were admitted to a single acute inpatient brain injury rehabilitation facility between June and December 2012. Brain MRI findings were positive for only two of the five subjects evaluated: one subject demonstrated mild bilateral subcortical white matter occipital lobe hyperintensities, while the other displayed bilateral thalamic, peri-aqueduct gray matter, dorsal pons, cerebellar peduncle, and dentate nuclei plaques with no acute demyelination. The mean admission FIM score was 45.2 points (range 14-63 points) while the mean discharge FIM score was 82.2 points (range 61-100). The mean total FIM gain was 37 points (range 24-60 points) with an improvement in all three FIM subcategories. Four of the five subjects were discharged to the community.[27]

Discussion

The WNV disease, especially in its neuroinvasive form, can have a profound impact on patients, resulting in neurological symptoms, functional limitations, and a significant

reduction in their overall quality of life. Given the global recurrence of WNV infections, patients affected by WNV often require rehabilitation. Nonetheless, there is still an absence of worldwide guidelines for the rehabilitation of WNV patients. Our systematic review and best-evidence synthesis represent the first attempt to summarize the existing evidence in the literature regarding rehabilitative approaches for WNV patients.

Our literature search has identified low-quality studies, primarily consisting of case reports and case series. Nevertheless, these studies have still highlighted motor and functional improvements following acute customized rehabilitation programs, as well as the possibility for home discharge,[21, 26-28] although some enduring deficits may persist.[20, 24] Indeed, in particular in patients suffering from encephalitis complicated by acute flaccid paralysis only a reduced percentage seems to be able to regain their previous functional level after 6-8 months of rehabilitation. Sometimes full recovery is achieved at 12 months from diagnosis.[29] For these patients, late mortality is described up to three years after the onset of symptoms, with one-year mortality of 4% and four-year mortality of 12%.[30]

Nevertheless, subjects with WNV-related limb weakness can exhibit strength recovery, with the majority of improvement occurring within the initial 6-8 months following symptom onset.[31] In the case series and case reports we reviewed, only Marciniak *et al.* conducted a six-month follow-up evaluation,[20] whereas VanDemark *et al.* performed a four-month follow-up,[22] and Zafar and Obugo and Unger *et al.* conducted a three-month follow-up.[24, 25] Interestingly, from the literature we analyzed, it has been observed that following acute rehabilitation, patients affected by WNV tetraparesis have transitioned into incomplete upper limb paresis.[19] Consequently, the early initiation of rehabilitative interventions should be generally favored. During the early stage of disease, collaboration between physiatrists and healthcare professionals should contribute to prevent musculoskeletal complications associated with prolonged bed rest[32, 33] and to consider patients' overall clinical condition and nutritional status.[12]

In the literature, most studies concerning rehabilitation in WNV patients have considered outcome measures related to motor function, strength, and disability. Particularly, the most frequently reported outcome measure for tracking WNV patient progress in rehabilitation has been found to be the FIM scale, an international standard for measuring disability, with high metric-statistical validity.[19, 21, 26, 27]

However, it is important to recognize that while FIM is a valuable tool, its applicability should be considered in conjunction with other clinical measures tailored to individual patient needs. Presently, there is a lack of studies addressing respiratory outcomes in WNV patients. Nonetheless, during the early phase, primary rehabilitation aims in WNV patients should also include enhancing ventilatory function, preventing atelectasis, and increasing diaphragm and inspiratory muscle strength in individuals with respiratory muscle impairments and diaphragm issues caused by motoneuron involvement or brainstem network failures.[34, 35] Early assessment for signs of dysarthria and dysphagia is also crucial in this phase, as they can be predictive of later respiratory failure.[21, 28]

Rehabilitation has demonstrated also favorable effects on chronic WNV outcomes, contributing to the regaining of independent walking among patients with chronic paraplegia.[25] Nevertheless, the duration of hospital stays for WNV patients, as documented in the literature, can vary widely, ranging from a few days to up to 5 months.[21, 25-27, 36] In particular, elderly patients and those with comorbidities may necessitate extended treatment periods.[26, 29, 37] Consequently, for these individuals, continuing rehabilitation care in outpatient settings after hospitalization is advisable.[38, 39]

In the post-acute phase, rehabilitation should be multidisciplinary, integrating physical therapy, occupational therapy, speech therapy, and psychological support.[21, 23] Respiratory rehabilitation should be particularly important also in this phase, since some patients may require supplementary oxygen for extended periods.[31, 40] Moreover, progressive muscle strengthening exercises, moderate-intensity aerobic exercises, exercises to improve balance and proprioception, and potentially the use of electrotherapeutic methods should be provided to these patients.[22, 23, 41, 42] Exercises sessions should be performed monitoring heart rate, oxygen saturation levels, and fatigue levels.[23]

Preliminary studies have also shown that cognitive symptoms, such as memory and executive function problems, might persist for years after the initial WNV infection.[21, 28, 43] Therefore, assessing cognitive function and offering cognitive rehabilitation, focusing on planning and working memory enhancement, should be considered to mitigate these challenges.[43] Additionally, incorporating occupational therapy into post-acute rehabilitation can contribute to achieving social reintegration and independence.[25]

Taken together, our findings, while they may not lead to definitive conclusions, highlight the importance of initiating early and comprehensive rehabilitation for individuals with neuroinvasive WNV infections. However, our analy-

sis also brings to light the absence of standardized protocols in this context. Due to the epidemic nature and the periodic outbreaks of the infection,[6, 11] conducting higher-quality studies such as randomized controlled trials remains difficult. Nevertheless, it is essential to propose future studies that provide a more detailed description of rehabilitative management and incorporate longer follow-up periods. Furthermore, the outcome measures considered in different studies should be broader, taking into account the respiratory, psychological, and cognitive concerns experienced by WNV patients, and should be more standardized across studies.

Limitations of the study

Our best-evidence synthesis has some limitations. First, the available literature on WNV rehabilitation is largely composed of case reports and small case series, resulting in limited generalizability to a broader population. The absence of large-scale, randomized controlled trials does not allow the possibility to draw definitive conclusions about the efficacy of specific rehabilitation interventions. Second, the variability in the severity and clinical manifestations of WNV infections among patients introduces heterogeneity in the available studies, making it challenging to establish standardized rehabilitation protocols. Moreover, there is a risk of publication bias, as studies with positive findings are more likely to be published. Furthermore, the absence or the relatively short follow-up periods in many studies may not capture long-term outcomes accurately. Lastly, the evolving nature of WNV infection, with occasional outbreaks and changing viral strains, underscores the need for ongoing research to adapt rehabilitation approaches to the latest developments in the field.

Conclusions

In conclusion, our analysis has highlighted that a tailored and comprehensive rehabilitation approach targeting respiratory, neuromuscular, cognitive, and psychosocial aspects seems to be effective for the WNV patients' recovery. Close collaboration with other healthcare professionals, social support systems, and family members is important for effective management. The duration of the rehabilitation program may vary depending on the individual patient's needs.

Although these observations are notable, they may not lead to definitive conclusions. Indeed, while this best-evidence synthesis provides a foundation for guiding the rehabilitation of WNV patients, further studies involving larger patient cohorts and higher levels of evidence are essential to comprehensively address the rehabilitation needs of individuals affected by WNV.

References

1. Debiasi RL, Tyler KL. West Nile virus meningoencephalitis. Nat Clin Pract Neurol 2006;2:264–75.

2. Krow-Lucal E, Lindsey NP, Lehman J, Fischer M, Staples JE. West Nile Virus and Other Nationally Notifiable Arboviral Diseases - United States, 2015. MMWR Morb Mortal Wkly Rep 2017;66:51–5.

3. Farooq Z, Sjödin H, Semenza JC, Tozan Y, Sewe MO, Wallin J, *et al.* European projections of West Nile virus transmission under climate change scenarios. One Health 2023;16:100509.

4. Barrett AD. West Nile in Europe: an increasing public health problem. J Travel Med 2018;25.

5. Farooq Z, Rocklöv J, Wallin J, Abiri N, Sewe MO, Sjödin H, *et al.* Artificial intelligence to predict West Nile virus outbreaks with eco-climatic drivers. Lancet Reg Health Eur 2022;17:100370.

6. Bai F, Thompson EA, Vig PJ, Leis AA. Current Understanding of West Nile Virus Clinical Manifestations, Immune Responses, Neuroinvasion, and Immunotherapeutic Implications. Pathogens 2019;8:193.

7. Istituto Superiore di Sanità. West Nile Dati epidemiologici in Italia.

8. Istituto Superiore di Sanità Bollettino N. 11 del 31 agosto 2022. Sorveglianza Integrata Del West Nile e Usutu Virus 2.

9. Samuel MA, Diamond MS. Pathogenesis of West Nile Virus infection: a balance between virulence, innate and adaptive immunity, and viral evasion. J Virol 2006;80:9349–60.

10. Barzon L, Pacenti M, Ulbert S, Palù G. Latest developments and challenges in the diagnosis of human West Nile virus infection. Expert Rev Anti Infect Ther 2015;13:327–42.

11. Ouhoumanne N, Lowe AM, Fortin A, Kairy D, Vibien A, K-Lensch J, *et al.* Morbidity, mortality and long-term sequelae of West Nile virus disease in Québec. Epidemiol Infect 2018;146:867–74.

12. Yu A, Ferenczi E, Moussa K, Eliott D, Matiello M. Clinical Spectrum of West Nile Virus Neuroinvasive Disease. Neurohospitalist 2020;10:43–7.

13. Sejvar JJ, Haddad MB, Tierney BC, Campbell GL, Marfin AA, Van Gerpen JA, *et al.* Neurologic manifestations and outcome of West Nile virus infection. JAMA 2003;290:511–5.

14. Leis AA, Stokic DS. Neuromuscular manifestations of west nile virus infection. Front Neurol 2012;3:37.

15. Santini M, Zupetic I, Viskovic K, Krznaric J, Kutlesa M, Krajinovic V, *et al.* Cauda equina arachnoiditis - a rare manifestation of West Nile virus neuroinvasive disease: A case report. World J Clin Cases 2020;8:3797–803.

16. Khairallah M, Ben Yahia S, Ladjimi A, Zeghidi H, Ben Romdhane F, Besbes L, *et al.* Chorioretinal involvement in patients with West Nile virus infection. Ophthalmology 2004;111:2065–70.

17. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 2018;23:60–3.

18. Wells GA, Shea B, O'Connell D, Peterson J, Welch V. M Losos PT. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [cited 2023, Nov 21].

19. Ohry A, Karpin H, Yoeli D, Lazari A, Lerman Y. West Nile Virus Myelitis. Spinal Cord 2001;39:662–3.

20. Marciniak C, Sorosky S, Hynes C. Acute flaccid paralysis associated with West Nile virus: motor and functional improvement in 4 patients. Arch Phys Med Rehabil 2004;85:1933–8.

21. Rao N, Char D, Gnatz S. Rehabilitation outcomes of 5 patients with severe West Nile virus infection: a case series. Arch Phys Med Rehabil 2005;86:449–52.

22. VanDemark MV. West Nile virus—the eye of the storm: a case study. J Neurosci Nurs 2004;36:328–31.

23. Miller NH, Miller DJ, Goldberg JL. Physical therapist examination, evaluation, and intervention for a patient with West Nile virus paralysis. Phys Ther 2006;86:843–56.

24. Zafar SF, Ubogu EE. Subacute brachial diplegia associated with West Nile virus myelitis. Muscle Nerve 2012;45:900–4.

25. Unger J, Jervis Rademeyer H, Furlan JC, Pujol C, Dawe J, Musselman KE. Personalized adapted locomotor training for an individual with sequelae of West Nile virus infection: a mixed-method case report. Physiother Theory Pract 2020;36:844–54.

26. Hoffman JE, Paschal KA. Functional outcomes of adult patients with West Nile virus admitted to a rehabilitation hospital. J Geriatr Phys Ther 2013;36:55–62.

27. Patel K, Greenwald BD, Sabini RC. Rehabilitation Outcomes in Subjects with West Nile Neuro-Invasive Disease. Brain Sci 2021;11:1253.

28. Hawkes MA, Carabenciov ID, Wijdicks EF, Rabinstein AA. Outcomes in Patients With Severe West Nile Neuroinvasive Disease. Crit Care Med 2018;46:e955–8.

29. Klee AL, Maidin B, Edwin B, Poshni I, Mostashari F, Fine A, *et al.* Long-term prognosis for clinical West Nile virus infection. Emerg Infect Dis 2004;10:1405–11.

30. Lindsey NP, Sejvar JJ, Bode AV, Pape WJ, Campbell GL. Delayed mortality in a cohort of persons hospitalized with West Nile virus disease in Colorado in 2003. Vector Borne Zoonotic Dis 2012;12:230–5.

31. Sejvar JJ, Wilson ME, Sejvar JJ. The long-term outcomes of human West Nile virus infection. Clin Infect Dis 2007;44:1617–24.

32. Coletta EM, Murphy JB. The complications of immobility in the elderly stroke patient. J Am Board Fam Pract 1992;5:389–97.

33. Santini M, Haberle S, Židovec-Lepej S, Savić V, Kusulja M, Papić N, *et al.* Severe West Nile Virus Neuroinvasive Disease: Clinical Characteristics, Short- and Long-Term Outcomes. Pathogens 2022;11:52.

34. Morrey JD, Siddharthan V, Wang H, Hall JO, Motter NE, Skinner RD, *et al.* Neurological suppression of diaphragm electromyographs in hamsters infected with West Nile virus. J Neurovirol 2010;16:318–29.

35. Morrey JD, Siddharthan V, Wang H, Hall JO. Respiratory insufficiency correlated strongly with mortality of rodents infected with West Nile virus. PLoS One 2012;7:e38672.

36. Fromm NM, Salisbury DB, Driver SJ, Dahdah MN, Monden KR. Functional recovery from neuroinvasive West Nile Virus: A tale of two courses. Rehabil Psychol 2015;60:383–90.

37. Berner YN, Lang R, Chowers MY. Outcome of West Nile fever in older adults. J Am Geriatr Soc 2002;50:1844–6.

38. Masiero S, Maccarone MC, Agostini F. Health resort medicine can be a suitable setting to recover disabilities in patients tested negative for COVID-19 discharged from hospital? A challenge for the future. Int J Biometeorol 2020;64:1807–9.

39. Masiero S, Maccarone MC. Health resort therapy interventions in the COVID-19 pandemic era: what next? Int J Biometeorol 2021;65:1995–7.

40. Lacasse Y, Guyatt GH, Goldstein RS. The components of a respiratory rehabilitation program: a systematic overview. Chest 1997;111:1077–88.

41. Maccarone MC, Masiero S, Papathanasiou J, Panayotov K, Kashilska Y, Prokopidis K, *et al.* Frailty education: promoting geriatric competencies among Physical Medicine and Rehabilitation residents. Am J Phys Med Rehabil 2023;102:e137–40.

42. Carraro U, Marcante A, Ravara B, Albertin G, Maccarone MC, Piccione F, *et al.* Skeletal muscle weakness in older adults home-restricted due to COVID-19 pandemic: a role for full-body in-bed gym and functional electrical stimulation. Aging Clin Exp Res 2021;33:2053–9.

43. Samaan Z, McDermid Vaz S, Bawor M, Potter TH, Eskandarian S, Loeb M. Neuropsychological Impact of West Nile Virus Infection: An Extensive Neuropsychiatric Assessment of 49 Cases in Canada. PLoS One 2016;11:e0158364.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Conceptualization and methodology: Maria C. Maccarone, Daniele Coraci, Marina Munari, Francesco Piccione and Stefano Masiero; data collection: Maria C. Maccarone, Daniele Coraci, Lisa Ragazzo, and Francesco Piccione; data curation: Maria C. Maccarone, Daniele Coraci, Lisa Ragazzo, Marina Munari and Stefano Masiero; writing—original draft preparation: Maria C. Maccarone, Daniele Coraci, Marina Munari, Francesco Piccione and Stefano Masiero; writing—review and editing: Maria C. Maccarone, Daniele Coraci, Marina Munari, Francesco Piccione, Stefano Masiero; supervision: Francesco Piccione and Stefano Masiero. All the authors have read and approved the final version of the manuscript.

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