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Clinical Features and Rehabilitation Needs in Patients with Neuroinvasive West Nile Virus Infection: A Retrospective Analysis in an Area of High Incidence

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Abstract: Neuroinvasive West Nile Virus disease (WNND) can cause lasting cognitive and motor impairments, impacting autonomy and quality of life. Given the scarcity of research on the rehabilitative needs of patients with WNV infection, this study aims to fill a critical gap by assessing the rehabilitation needs of a real-world cohort of WNND patients. We retrospectively analyzed WNND patients who received early Physical Medicine and Rehabilitation (PMR) evaluations during the 2022 outbreak in Veneto, Italy. Data included demographics, comorbidities, length of hospital stay, days at PMR evaluation, and rehabilitation duration until discharge or death, alongside objective examination findings and Barthel Index scores. Among 29 confirmed WNND patients, the median hospital stay was 20 days, with rehabilitation starting after a median of 7 days. Motor weakness affected 48.28% of patients, swallowing issues 6.90%, and respiratory issues 24.13%. A tailored rehabilitation protocol was designed for 96.55% of patients to address functional concerns and prevent complications. Barthel Index scores showed no significant change. Discharge settings were home (58.34%), other departments (25%), and rehabilitation facilities (16.67%). This study highlights the rehabilitation needs of WNND patients, particularly regarding neuromuscular deficits, swallowing, and respiratory issues, stressing the importance of a comprehensive rehabilitation strategy for improved outcomes.

Keywords: rehabilitation; paralysis; meningitis; encephalitis; respiratory

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1. Introduction

West Nile Virus (WNV) is an arbovirus transmitted via a mosquito vector that replicates in volatiles. Humans and other mammals are accidental hosts of the virus [1,2]. While the majority of individuals infected with WNV show no symptoms, approximately 20% of WNV-infected patients exhibit clinical manifestations of different severity [3]. In most cases, WNV manifests as a flu-like syndrome called West Nile fever, while in less than 1% of infections, it presents as West Nile Neuroinvasive Diseases (WNNDs), the most severe forms including encephalitis, meningitis, acute flaccid paralysis (AFP), or a combination of these manifestations [3–7]. Encephalitis is the most frequent of WNND manifestations and presents in a wide range of severity, from a mild confusional state to the development of coma and eventually death [3,8,9]. Main features include muscle weakness, peripheral nervous system deficit, lethargy, and a reduced level of consciousness [10]. Upper limb tremors and myoclonus may also occur but are less frequent [3]. Meningitis presents with rapid-onset fever, headache, phonophobia, photophobia, meningeal signs, and sometimes nausea and vomiting and is often complicated by disorders of consciousness, cognitive impairment, and epileptic seizures [4,11]. AFP is defined by a rapid onset of asymmetrical muscle weakness of the limbs, mostly without fever. Diaphragm, other respiratory muscles, and head muscles may be involved in the paralysis [12,13]. The diagnosis of infection is obtained through a serology test or genome identification on blood, cerebrospinal fluid, and plasma [6].

WNV is an emerging pathogen that has become a significant public health concern in Europe, where its incidence has increased over the past decade. WNV remains a global public health issue, causing potentially life-altering consequences, especially when considering the neuroinvasive form. Current management for WNV is mainly supportive, although many treatments are currently being studied in clinical trials. With such limited options for treatment, severe disability and death can occur [3]. Historically, WNV outbreaks in Europe have escalated in frequency and scale, with Italy being heavily affected during the record-setting 2018 outbreak. In 2022, Italy experienced a major outbreak of WNV, reporting the highest number of human cases within Europe. The Veneto Region, in particular, saw a severe impact, with a substantial number of neuroinvasive cases and related fatalities. In 2022, WNV activity in Italy began unusually early, with the first WNV-positive Culex mosquito pool detected on 7 June in the Veneto Region. Whole-genome sequencing identified WNV lineage 2 (WNV-2), triggering donor screening in Veneto. The first human cases followed shortly after: a WNV-positive blood donor and an encephalitis patient were identified in June, and another donor tested positive in July. While WNV-2 was confirmed in the initial donor, WNV lineage 1 (WNV-1) was detected in subsequent cases, demonstrating the co-circulation of both lineages. Concurrent veterinary surveillance revealed WNV-1 and WNV-2 infections in wild birds, highlighting the virus's widespread presence across different species. Compared to previous years, WNV transmission in 2022 expanded geographically and started earlier, likely due to favorable ecological and climatic conditions. The persistence of WNV-2 and the emergence of WNV-1 strains in Italy have been identified as significant factors in this heightened disease burden [14].

There is a general agreement that the WNNV sequelae require personalized rehabilitation protocols [5,11]. Some patients may experience physical and cognitive impairments even 18 months after the initial infection [4,15].

Given the scarcity of research on the rehabilitative needs of patients with WNV infection, this study aims to fill a critical gap by assessing the rehabilitation needs of a real-world cohort of patients who were hospitalized following WNND. Additionally, considering the limited research data regarding the prevalent discharge setting in these patients, this paper focuses on the post-hospital discharge location in the analyzed population.

2. Materials and Methods

2.1. Study Design

This retrospective, observational, and single-center study involved retrieving data from the digitalized medical records of patients hospitalized at the University Hospital of Padua, and it was conducted following the approval of the local ethical committee (436n/AO/23).

2.2. Study Population

Subjects for the study were selected from the pool of WNV cases who were hospitalized at the University Hospital of Padua (79 patients). Patients with an unconfirmed diagnosis of WNV were excluded, and only those who received a Physical Medicine and Rehabilitation (PMR) evaluation by the staff of the Neurorehabilitation Unit at the University Hospital of Padua were included in the analysis (Figure 1).

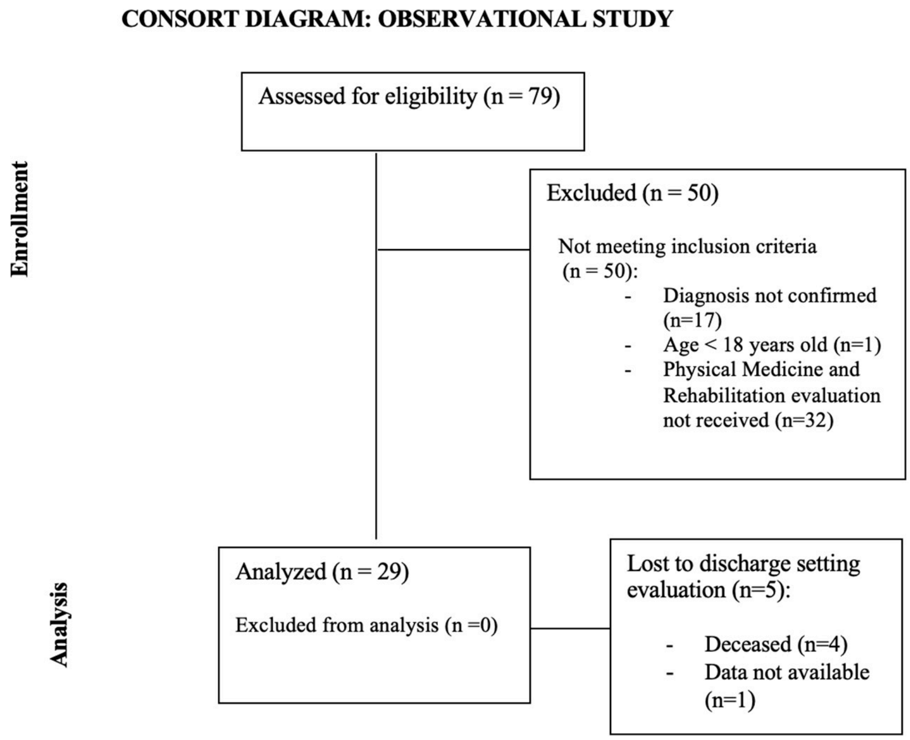

Figure 1. The diagram illustrates the process of patient selection and participation in the study.

Inclusion criteria were as follows: subjects with a confirmed diagnosis of WNV infection who were hospitalized at the University Hospital of Padua between June 2022 and November 2022, aged between 18 and 90 years, and who underwent at least one PMR assessment during hospitalization. Patients under 18 years of age, with an unconfirmed WNV diagnosis, or lacking hospitalization and PMR assessment were excluded from the study.

2.3. Outcome Evaluation

Through the analysis of patients' computerized medical records, demographic data were collected, including information on gender and age at the time of admission, pre-hospitalization living situation, degree of autonomy in walking and activities of daily living (ADL) before the acute event, total hospitalization days, days of hospitalization at the time of PMR evaluation, and rehabilitation days until patient discharge or death. Data on the subjects' remote medical history were also extracted from medical records, with a focus on cardiovascular, respiratory, diabetic, neoplastic, vascular, and neurological comorbidities. In addition, cumulative scores obtained from the Barthel Index administered at admission and discharge were extracted.

The Barthel Scale is one of the most widely used clinical tools to assess an individual's physical functionality. The analyzed items evaluate the ability to perform activities such as eating, dressing, managing personal hygiene, washing, controlling bladder and bowel function, walking on flat ground and climbing stairs, performing bed–chair and chair–bed transfers, and executing bathroom transfers. Assignable scores are 0, 5, 10, or 15, with a higher score indicating greater autonomy in that specific activity. The maximum score of

100 indicates complete independence in all described activities, while the minimum score of 0 identifies a condition of total dependence in managing ADL.

For each patient, the initial PMR assessment during hospitalization was analyzed, collecting data on objective examination findings. Tactile sensitivity, muscle tone, respiratory deficits, and the presence of dysphagia were considered. Segmental muscle strength was assessed using the Medical Research Council (MRC) scale, and the MRC Sum Score was calculated based on the obtained data. The MRC Scale is an extensively employed method for assessing muscle strength. It assigns a numerical grade (ranging from 0 to 5) to the muscle strength of specific muscle groups, with 0 indicating no muscle contraction and 5 indicating normal strength. The MRC Sum Score is a variation on the MRC Scale that considers the measurement of 12 muscle groups, specifically shoulder adductors, elbow flexors, wrist extensors, hip flexors, leg extensors, and dorsiflexors of the foot, for both sides of the body. By assigning the scores described in the MRC Scale and summing each muscle group, an overall score ranging from 0 to 60 is obtained. Cutoffs of <48 and <36 are used to identify significant weakness and severe weakness, respectively.

2.4. Statistical Analysis

In the analysis of the collected data, categorical variables were presented as absolute numbers and percentages, while continuous variables were reported as mean $\pm$ standard deviation, median, and interquartile range (IQR). The data distribution was assessed using the Lilliefors normality test (Kolmogorov–Smirnov) at a significance level of $\alpha = 0.05$.

Based on the data distribution, a Student's *t*-test, a Wilcoxon signed-rank test for dependent samples, or a Mann–Whitney U-test for independent samples was employed to identify differences between the analyzed variables. The *p*-value was considered statistically significant if it was less than 0.05.

3. Results

3.1. Demographic Characteristics

As depicted in Figure 1, 1 subject was excluded due to age criteria, 17 were excluded because they did not have a confirmed diagnosis of WNV, and 32 subjects were excluded due to a lack of PMR evaluation data. In total, 29 patients were included in the study.

The average age of the patients was 75 $\pm$ 9.38 years. Among the subjects, 22 out of 29 participants (75.86%) were male. When comparing the mean age of subjects by gender, a statistically significant difference was observed, with females (68.71 $\pm$ 13.65) having a significantly lower average age than males (77 $\pm$ 6.85).

Regarding medical history and comorbidities, Table 1 outlines the conditions identified in the population and their respective frequencies. Of the 29 patients included, 20 were hospitalized in the Infectious Diseases department (68.96%), while the remaining patients were admitted to the Intensive Care Unit, Internal Medicine, or Neurosurgery departments (31.04%). Concerning the patients' autonomy status prior to hospital admission, all subjects were residing at home. A total of 23 (79.31%) subjects exhibited complete autonomy in walking and full independence in ADL.

Table 1. Comorbidities in WNV population.

Comorbidity	Number of Patients (Percentage of Total Population)
Hypertension	16 (55.17%)
Arteriopathy	8 (27.59%)
Previous cerebral ischemia	3 (10.74%)

Table 1. *Cont.*

Comorbidity	Number of Patients (Percentage of Total Population)
Previous non-cerebral thromboembolic event	2 (6.90%)
Previous ischemic heart disease	5 (17.24%)
Type 2 diabetes	11 (37.93%)
Dyslipidemia	5 (17.24%)
Chronic obstructive pulmonary disease	3 (10.34%)
Active smoking	1 (3.45%)
Previous smoking	4 (13.79%)
Previous neoplastic disorder	2 (6.90%)
Concomitant neoplastic disorder	5 (17.24%)
Non-neoplastic hematologic disorder	2 (6.90%)
Transplant	2 (6.90%)

3.2. Outcome Evaluation

The analysis of hospitalization timelines revealed significant heterogeneity in both total hospitalization days, days at the PMR evaluation, and onset of rehabilitation, and the overall duration of rehabilitation until patient discharge or demise, with medians of 20.7 and 13 days, respectively (Table 2). Four patients (13.79%) died during their hospitalization period.

Table 2. Total hospitalization days, days at the Physical Medicine and Rehabilitation (PMR) evaluation and onset of rehabilitation, and rehabilitation duration at the time of discharge (or death) for the analyzed population.

Variable	Median	Min-Max
Total hospitalization days	20	7–168
Days at the PMR evaluation and onset of rehabilitation	7	1–95
Rehabilitation duration at the time of discharge (or death)	13	0–88

During the clinical evaluation, tactile sensitivity was preserved in 20 patients (68.96%). Fifteen patients reported hypotonia (27.58% in the upper limbs and 24.13% in the lower limbs). The median of the total MRC Sum Score was 48. Considering scores < 48 as indicative of significant weakness and scores < 36 as indicative of severe weakness, the corresponding frequencies within the population were calculated. The results showed that 48.28% of subjects (14 patients) exhibited significant weakness, while 41.38% had a condition of severe weakness (12 patients).

Among the observed patients, two presented swallowing issues (6.90%), while respiratory complications were observed in seven cases (24.13%), requiring tracheostomy placement in three cases (10.34%).

3.3. Rehabilitation Protocols and Discharge Settings

Following the PMR assessment, a tailored rehabilitation protocol was established for 28 of the 29 examined patients (96.55%), aiming to address the functional concerns of each patient. In the majority of cases, the prevention of bed-related complications (22 patients, 75.86%) was prescribed. When necessary, interventions to maintain muscle tone, recover postural changes, and improve swallowing and respiratory function were prescribed (Table 3). Rehabilitation interventions were carried out daily, with each session lasting between one and two hours.

Table 3. Rehabilitation protocols prescribed.

Type of Rehabilitation Protocol	Number of Patients (Percentage of Total Population)
Prevention of bed-related complications	22 (75.86%)
Maintenance of muscle tone-trophism and muscle strengthening	4 (13.79%)
Respiratory function recovery	2 (6.90%)
Recovery of postural changes and transfers	3 (10.34%)
Balance and gait training	5 (17.24%)
Interventions for dysphagia (diet modification, compensatory posture, etc.)	2 (6.90%)

The mean Barthel Index scores at admission and discharge were similar, 36.38 ± 30.70 and 35.2 ± 35.69, respectively. The comparison between admission and discharge values did not reveal statistically significant differences ($p > 0.05$).

The analysis of the discharge diagnoses for the 25 patients who survived hospitalization revealed that the majority, 21 patients (84%), were diagnosed with meningitis or encephalitis, while 4 patients (16%) were diagnosed with AFP associated with encephalitis.

Discharge settings could be defined for 24 out of 29 patients (due to 4 deaths and one case of missing data). Among these, 14 subjects (58.34%) were discharged home, 6 (25%) were transferred to other departments or community hospitals, with 2 awaiting potential transfer to a rehabilitation facility, and 4 (16.67%) were transferred to rehabilitation facilities.

4. Discussion

While WNV is often asymptomatic, its neuroinvasive form can lead to severe, long-term cognitive and neuromuscular deficits [3,11,16]. Nevertheless, comprehensive studies on rehabilitation for these patients have been lacking. This study represents the first comprehensive investigation in Italy into the rehabilitation needs of patients affected by WNND. The cohort included 29 subjects, a notable proportion of whom were over 75 years old, presenting a range of comorbidities such as hypertension, type II diabetes, arteriopathies, and concurrent neoplastic conditions. Despite showing significant independence in ambulation and ADL before their acute phase, the combination of advanced age and diverse comorbidities highlighted increased needs for rehabilitation. Advanced age is often associated with reduced physiological reserve and slower recovery rates [17]. Elderly patients generally face a greater decline in muscle mass, strength, and functional capacity, which can be further aggravated by the severity of WNND. Additionally, comorbidities complicate the recovery process by impairing cardiovascular health, diminishing physical endurance, and delaying healing [4].

These factors contribute to the increased rehabilitation needs and longer treatment durations observed in older adults. Effective rehabilitation in this population requires a more intensive and extended approach to address both the direct impact of WNND and the challenges imposed by their pre-existing conditions [4].

The significant variability in hospitalization, ranging from 7 to 168 days with a median of 20 days, and rehabilitation durations observed in this study could not be correlated with factors such as age, severity of WNND, or comorbidities. This suggests that other individual patient factors, such as the heterogeneous progression of WNND, may influence these durations. Similarly, the initiation and duration of rehabilitation varied widely, with rehabilitation commencing as early as 1 day into hospitalization and lasting up to 88 days until discharge or death.

In our cohort, rehabilitation was initiated in the acute setting, with an assessment conducted within the first few days of hospitalization in the majority of cases. In our population, the rehabilitative intervention began on the same day as the PMR evaluation. An early initiation of rehabilitation during acute care should be recommended to prevent complications associated with WNND [4,18,19]. Therapies were adapted according to the ongoing evaluation of the patients' progress, with modifications made to address evolving needs and limitations throughout the hospitalization period.

Overall, patients in our study showed impairments in muscular strength and hypotonia, which contributed to difficulties in mobility and increased susceptibility to prolonged bed rest and limited mobilization. These factors can exacerbate muscle atrophy, limit joint range of motion, and predispose subjects to complications like pulmonary thromboembolism and skin ulcers [20,21]. Therefore, a key element of the rehabilitation project for these patients was the prevention of bedridden complications and the maintenance of muscle trophism [22–25].

In addition to assessing predominantly motor aspects, attention was directed towards swallowing and respiratory function. Seven subjects exhibited respiratory insufficiency, necessitating tracheostomy in three cases. Currently, studies on respiratory outcomes in WNV patients are lacking [4]. Early-phase rehabilitation should focus on enhancing ventilatory function, preventing atelectasis, and strengthening the diaphragm and inspiratory muscles, particularly in those with respiratory muscle impairments due to motoneuron or brainstem issues [26,27]. Early assessment for dysarthria and dysphagia is also important, as they can predict later respiratory failure [27,28].

The lack of significant improvement in Barthel Index scores during hospitalization reflects the severity and chronicity of impairments in our cohort. Despite early rehabilitation, some patients with severe or long-term impairments may require more time for functional recovery. The low Barthel Scale values at admission and discharge indicated significant deficits in motor function and daily activities due to WNND, which extended beyond hospitalization. This justified the inability of ten patients to return home immediately after discharge. Instead, six were transferred to community hospitals, and four were referred to rehabilitation or long-term care facilities for vegetative states. In a previous study focusing on five subjects with WNND admitted to an acute inpatient brain injury rehabilitation facility in the United States, the efficacy of targeted rehabilitation was evaluated using the Functional Independence Measure (FIM) as a metric. The results indicated significant improvements in functional independence from admission to discharge across several subcategories: cognitive function, mobility, and ADL [29]. These findings underscore the potential benefits of customized rehabilitation programs in enhancing functional outcomes and suggest that some patients may achieve sufficient recovery to be discharged to their homes. However, enduring deficits may persist, particularly in patients with encephalitis complicated by AFP. Indeed, only a small percentage of WNND patients seem to regain their previous functional levels after 6–8 months of rehabilitation [4,12,29,30]. Consequently, continuing rehabilitation care in inpatient or outpatient settings post-hospitalization is advisable for these patients [19]. In another study, the functional impairments and outcomes of 48 adults with WNV admitted to a rehabilitation facility between 2002 and 2009 were assessed. Patients were transferred to the rehabilitation hospital from acute care settings after lengths of stay ranging from 1 to 62 days, with their time in rehabilitation varying from 2 to 304 days. The change in FIM scores during inpatient rehabilitation was statistically significant, highlighting the significant improvements achieved through rehabilitation [31]. In the post-acute phase, a multidisciplinary approach to rehabilitation should be adopted, integrating physical therapy, occupational therapy, speech therapy, and psychological support [22,32]. Indeed, while limiting complications and preventing muscle and movement function loss are essential during hospitalization, post-acute care should focus on promoting autonomy recovery [4,30,33]. The rehabilitation plan should be individualized, considering not only the acute condition but also comorbidities, previous levels of autonomy, and the prognosis of each subject.

The main strength of this study is its comprehensive analysis of the rehabilitation needs, rehabilitation programs, and discharge settings for a real-life cohort of patients with WNND. Unlike previous research, which often focuses on individual cases or small sample sizes, this study assesses a larger and more diverse group of patients [3,28,31,32,34]. While our findings underscore the importance of early and individualized rehabilitation protocols, there are notable limitations that should be addressed in future research. The lack of long-term follow-up data restricts our ability to assess sustained recovery and functional outcomes beyond the acute phase. Furthermore, the absence of cognitive rehabilitation in our study highlights a significant gap, as cognitive impairments are common in WNND and can greatly affect overall recovery and quality of life. Moving forward, incorporating cognitive assessments and extending follow-up periods will be essential to provide a more comprehensive understanding of the long-term rehabilitation needs of WNND patients.

5. Conclusions

WNV infection manifests in its symptomatic form infrequently, but during endemic periods, affected subjects can experience a range of symptoms from mild to severe. Our study has shown that WNND predominantly affects older adults with underlying comorbidities, leading to significant neuromotor impairments that often necessitate increased assistance and rehabilitation even after hospitalization. Effective rehabilitation strategies should therefore be adopted early in the acute setting and continued throughout hospitalization, employing a comprehensive approach that addresses all acquired disabilities, not only motor impairments.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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