

## Case Reports and Series

## Clinical characteristics and outcomes in hospitalized patients with West Nile neuroinvasive disease: A case-series analysis

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## ABSTRACT

**Background:** West Nile virus (WNV) recently caused recurrent outbreaks in Europe and Italy, and the occurrence of neuroinvasive disease (WNND) was observed in less than 1% of cases, mainly older patients with several comorbidities. Due to the high mortality and post-infectious sequelae, the prognosis of this illness was frequently poor.

**Methods:** In this case-series we reported the clinical outcomes of 7 patients hospitalized for WNND in the summer 2023 in our center of Infectious Disease in Vercelli, Italy.

**Results:** Patients were generally older and affected by several comorbidities; at hospital admission fever and postural instability were most common symptoms; mortality rate observed was 42.8%; presence of neurological sequelae was detected in 28.6%. Diagnostic PCR for WNV was performed on cerebrospinal fluid (CSF) in 42.8% and urine sample in 57.1%. Treatment is supportive or with corticosteroids.

**Conclusion:** WNND is a severe illness that may affect a vulnerable population especially in the summer period and requires a prompt diagnosis and knowledge of clinical characteristics and risk factors. Environmental intervention are required in the control of spread of mosquito vectors.

## Introduction

West Nile virus (WNV) is a Flavivirus transmitted by mosquito bites with an extensive distribution in the world and recent outbreaks in Europe and Italy in the early summer with climate condition favorable for the circulation of the vectors (*Culex* and *Aedes*) (Nikolay, 2015).

A major part of subjects infected by WNV are asymptomatic (80 %); the most frequent clinical syndrome is the “West Nile fever” (WNF), following an incubation period of 2–14 days and characterized by an abrupt onset of fever, myalgias, fatigue, headache and rash (Sejvar, 2014). The presence of morbilliform rash predominant in the thorax and limbs is observed in younger patients with a shorter and better course of illness (Huhn and Dworkin, 2006).

Neuroinvasive disease (WNND) occurs in less than 1 % infected subjects; several risk factors are reported such as older age, diabetes, hematological malignancies, kidney disease, immunosuppression and other (Burton et al., 2004). Mortality rate in WNND is approximately of 10 % and 30–40 % of survivors present significant neurological sequelae such as flaccid paralysis syndrome, ataxia, demyelinating neuropathy, motor axonopathy, weakness, dysarthria, dysphagia, seizure or psychiatric symptoms (Patel et al., 2015). Other systemic manifestations were: hepatitis, rhabdomyolysis, myocarditis, hemorrhagic fever with multi-organ failure (Sejvar, 2014; Mori et al., 2023).

In this case-series analysis we described clinical characteristic and outcomes of hospitalized patients with WNND occurred in the summer of 2022 at our Hospital “Saint Andrea”, Vercelli, Italy.

**Abbreviations:** WNV, West Nile virus; WNND, West Nile Neuro-invasive disease; ICU, intensive care unit; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalography.

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**Table 1**  
Characteristics and outcomes of the study population.

Characteristics	Overall patients (n = 7)
Age (median, IQR)	76 [68–81]
Male sex (n, %)	5 (71.4)
Provenance (n, %)	
-home	6 (85.7)
-long-term care	1 (14.3)
Comorbidity (n, %)	
- Cardiovascular disease	3 (42.8)
- Diabetes	5 (71.4)
- Neurological disease	2 (28.6)
- Respiratory disease	2 (28.6)
- Liver disease	1 (14.3)
- Malignancies	2 (28.6)
Days from the symptoms to hospital admission (median, IQR)	4.5 [4–6]
Symptoms and clinical manifestations at the hospital admission (n, %)	
-fever	3 (42.8)
-photophobia	2 (28.6)
-headache	3 (42.8)
-postural instability/ataxia	5 (71.4)
-extrapyramidal symptoms	3 (42.8)
-seizure	4 (57.1)
-rash	1 (14.3)
-confusion/agitation	6 (85.7)
-rhabdomyolysis	4 (57.1)
-hepatitis	5 (71.4)
Diagnostic PCR WNV (n, %)	
-CSF	3 (42.8)
-urine	4 (57.1)
Characteristics of CSF analysis (median, IQR)	
-WBC (µL)	322 [120.5–717]
-Protein (g/L)	1.7 [1.2–3.5]
EEG with signs of encephalitis (n, %)	5 (71.4)
Days of hospitalization (median, IQR)	14 [7.5–17.5]
ICU admission (n, %)	2 (28.6)
Sepsis (n, %)	3 (42.8)
Discharged without sequelae (n, %)	2 (28.6)
Discharged with neurological sequelae (n, %)	2 (28.6)
Death (n, %)	3 (42.8)

## Patients and methods

We retrospectively included patients affected by WNND and hospitalized at our center of Infectious Diseases at the Hospital “Saint Andrea”, Vercelli, Italy from 15 July and 28 August 2022.

Mandatory inclusion criteria was the detection of RT PCR for WNV in the cerebrospinal fluid (CSF) or urine. Patients with clinical syndrome of encephalitis admitted in the same period without PCR detection were excluded. We used the diagnostic RT PCR for WNV by EliTechGoup s.p.a. (Turin, Italy).

For descriptive statistics, continuous variables were reported as median (inter-quartile range [IQR]: 25th to 75th percentile). Categorical variables were described as frequency and percentage. categorical data were compared using the Mann-Whitney or Kruskal-Wallis statistical test rank correlation was utilized to investigate continuous data.

Univariate logistic regression was performed to test the predictive role of single variables for mortality in WNND: only variables with a P value lower than 0.2 have been tested in the multivariate analysis. Statistical analysis were performed through SPSS version 29.

## Results

We reported the data of 7 patients hospitalized with WNND during the observation period. The clinical characteristics and outcomes were reported in the [Table 1](#).

Median age was 76 years; male subjects were 5 (71.4 %); most frequent comorbidities were diabetes (5, 71.4 %) and cardiovascular disease (3, 42.8 %). Median time from the onset of symptoms and hospital admission was 4.5 days. The most common clinical manifestations observed at the admission were: confusion (6, 85.7 %), postural instability/ataxia (5, 71.4 %) and seizure (4, 57.1 %). Rhabdomyolysis and hepatitis were observed in 4 (57.1 %) and 5 (71.4 %) patients respectively. Diagnostic PCR for WNV was detected in 3 patients in the CSF (42.8 %) and in 4 in the urine sample (57.1 %). Electroencephalography (EEG) with evidence of encephalitis was observed in 5 subjects (71.4 %). Median time of hospitalization was 14 days. Admission in the intensive care unit (ICU) was observed in 2 patients (28.6 %). Mortality rate was 42.8 %; 2 patients were transferred in long-term care facilities due to presence of neurological sequelae (28.6 %) and 2 subjects were discharged at home without significant residual symptoms.

In the clinical analysis of these cases, we observed a different presentation at the onset of illness (reported data by anamnestic interview) and the hospital admission ([Fig. 1](#)). At the onset of illness were prevalent: fever (6, 85.7 %), headache, photophobia, confusion (5, 71.4 %), rash (3, 42.8 %). At hospital admission were prevalent neurological symptoms such as postural instability/ataxia, seizure, confusion, agitation/psychosis, and extrapyramidal signs ([Fig. 1](#)).

Clinical course of illness was detailed in the [Fig. 2](#). The most frequent presentation was the abrupt onset of fever followed by confusion or postural instability (even with accidental fall). In 4 cases (57.1 %) the delayed hospital admission was due to antibiotic therapy prescription at home before the appearance of major neurologic symptoms. In 3 patients bacterial superinfection occurred during the clinical worsening and required broad-spectrum antibiotic treatment.

Median time of hospitalization was 9 days [IQR: 6.2–13.5] in survivors, while 17 days [IQR: 14–18.5] in deceased ( $p < 0.001$ ).

Protein level in the CSF (g/L) was significantly higher in deceased patients: 1.7 g/L [IQR: 1.2–2.2] than in alive patients: 0.7 g/L [IQR: 0.6–0.9] ( $p < 0.001$ ) ([Fig. 3](#)).

In univariate analysis we consider the following factor as predictive of WNND mortality: age, sex, comorbidities, presence of neurological signs at hospital admission, EEG abnormalities, proteins in the CSF, rhabdomyolysis, hepatitis, hospitalization time, sepsis. The following factors resulted significantly predictive on the mortality: presence of seizure (OR = 1.7; 95 %CI: 1.5–3.8;  $p = 0.009$ ), time of hospitalization (OR = 1.1; 95 %CI: 1–2.9;  $p = 0.025$ ), CSF protein (OR = 5.1; 95 %CI: 2.8–9.7;  $p < 0.001$ ); sepsis (OR = 2.8; 95 %CI: 1.9–4.1;  $p = 0.020$ ). In multivariate analysis seizure (OR = 1.5; 95 %CI: 1.4–3.7;  $p = 0.007$ ), CSF protein (OR = 5.8; 95 %CI: 2.7–11.4;  $p < 0.001$ ) and sepsis (OR = 2.1; 95 %CI: 1.8–4.4;  $p = 0.005$ ) were predictive factor on in-hospital mortality.

## Discussion

In the last decade in Italy was observed a great circulation of WNV with an increased number of WNND cases ([Nikolay, 2015](#)) sustained by environmental and climatic favorable conditions ([Marini et al., 2021](#)). Due to absence of inter-human transmission and the role of mosquito vectors in the circulation of this pathogen, the public perception of this illness in the general population is limited; furthermore, effective

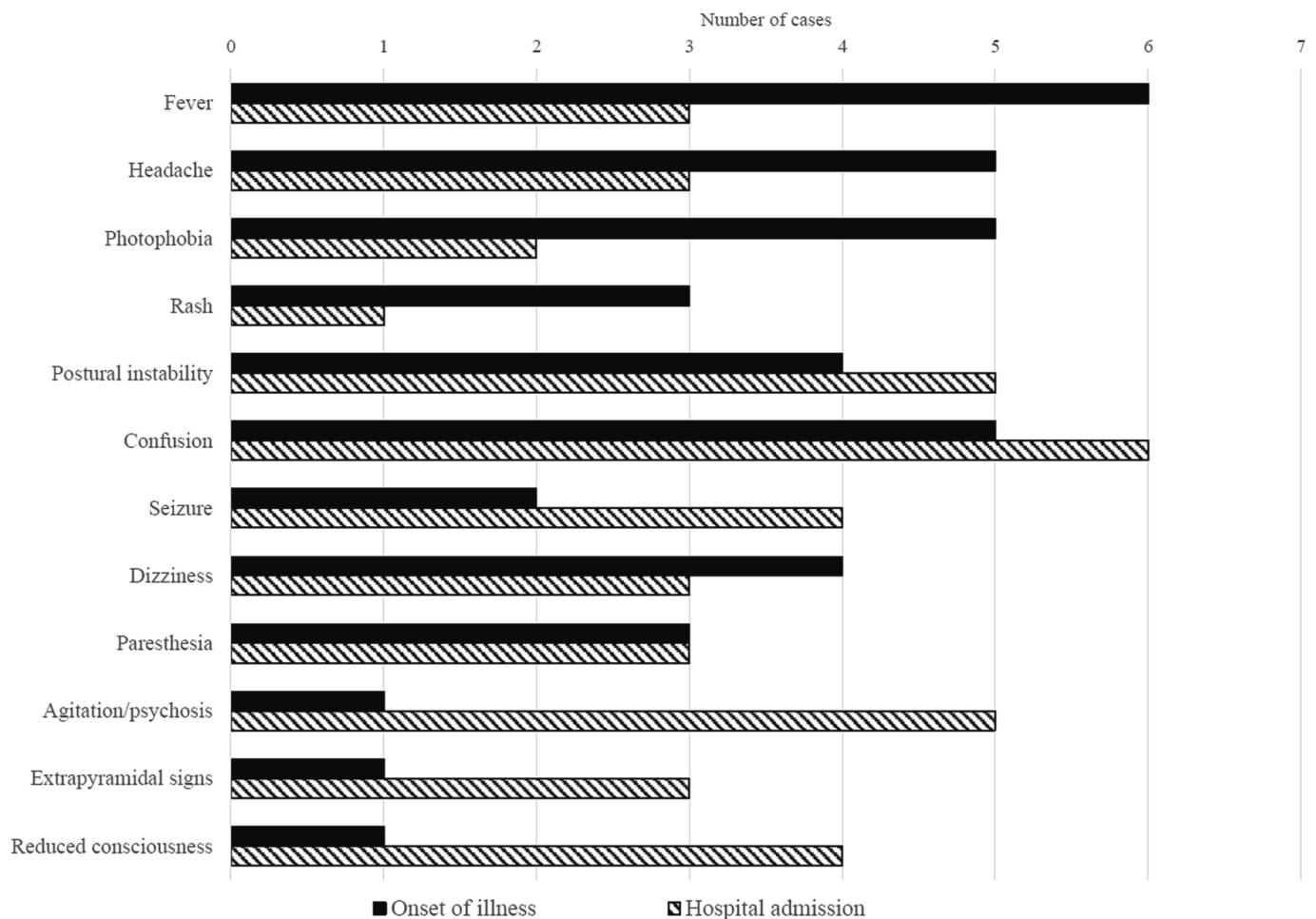


Fig. 1. Clinical presentation observed in the study population at the onset of illness and hospital admission.

measures as environmental intervention or appropriate prevention are not applied on a large scale, but with only sporadic and occasional disposition (*West Nile Virus*, xxxx). In the 2022 were notified 588 confirmed WNV infection in Italy, with 295 WNNND cases (50.2 %) and 37 deaths (6.3 %); in Piedmont were reported 39 WNNND cases with 6 deaths (15 %). The incidence trend is increasing compared to 2019–2021 (<https://www.iss.it/dashboard>).

In this case series we observed that WNNND affected almost exclusively subjects with older age and some comorbidities, especially diabetes and malignancies. Consequently, mortality rate is high (42.8 %) and only 2 patients were discharged without sequelae (28.6 %). These aspects are in accordance with what is reported in previous studies, and the clinical consequences of this illness may depends also by some factors: first, this diagnosis is more often “difficult to obtain”, due to the lack of perception of the risk also in the clinicians, with a consequent delay; in our cases, for example, 4 patients were treated at home with antibiotics after a fever onset like it was a simple flu-syndrome. In fact, the access to hospital occurs only after the appearance of major neurologic symptoms. Second, specific antiviral therapies against WNV are not available and major clinical intervention is the supportive treatment or with corticosteroids as preventive action against neurological sequelae (Kal et al., 2022); an “early” approach using corticosteroids,

fluids replacement and anti-epileptics drugs can limit the severity and duration of disease with less risk of further complications. Third, due to high mortality rate and frequent neurological sequelae, the impact of WNNND in a vulnerable population is not negligible and requires some possible interventions. Besides knowledge of this illness and a prompt diagnostic approach, we focused the attention on the environmental measures that can limit the vectors circulation: draining standing water from residential areas, spraying pesticides before the spread of mosquito vectors, use of skin repellents (...).

In conclusion, WNNND is a severe illness that may affects a vulnerable population especially in the summer period, with high mortality and morbidity; an early diagnosis based on the knowledge of the illness and risk factors may partially mitigate the negative effect of this infection.

#### CRedit authorship contribution statement

**Lucio Boglione:** Conceptualization, Methodology, Formal analysis, Data curation, Supervision. **Federica Poletti:** Supervision, Data curation. **Roberta Moglia:** Data curation. **Roberto Rostagno:** Data curation. **Marco Cantone:** Data curation. **Maria Esposito:** Data curation. **Silvio Borrè:** Data curation.

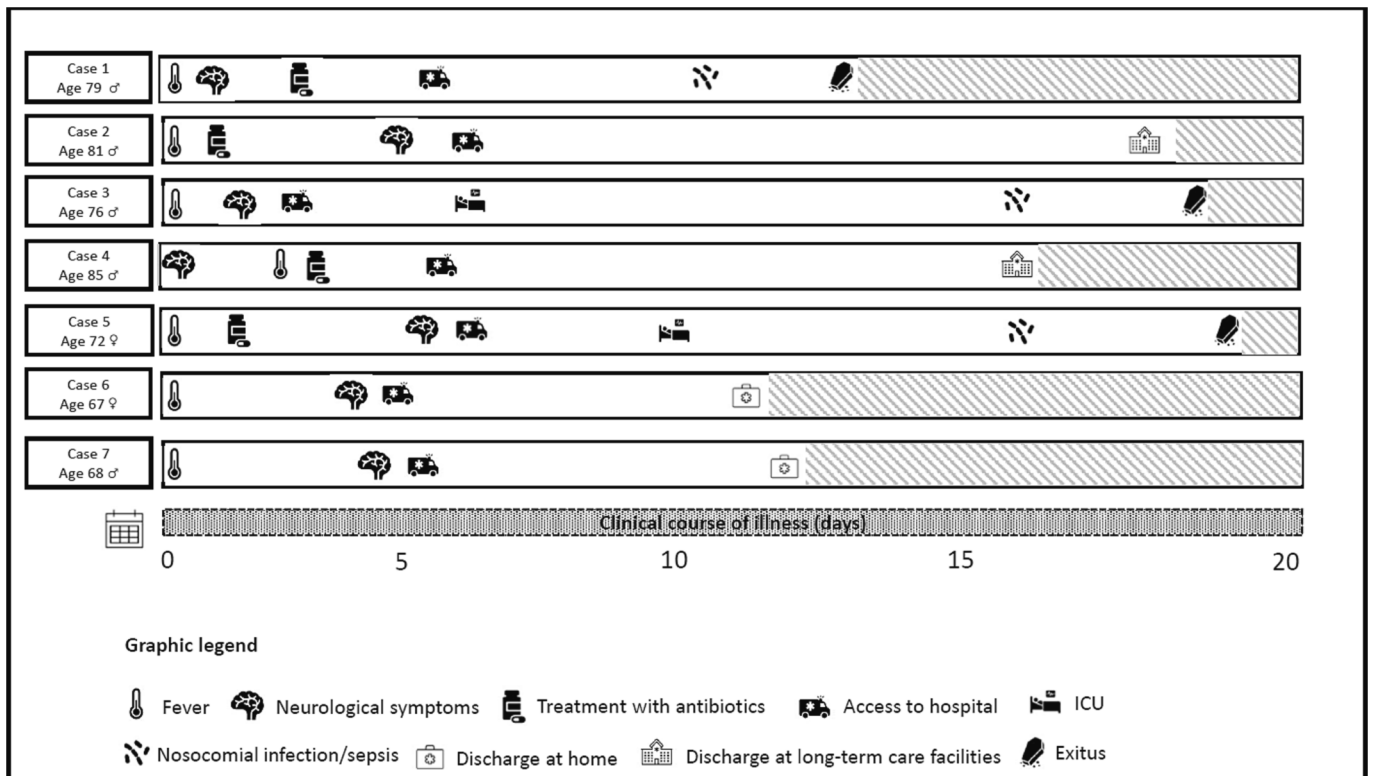


Fig. 2. Detailed clinical course of patients affected by WNND.

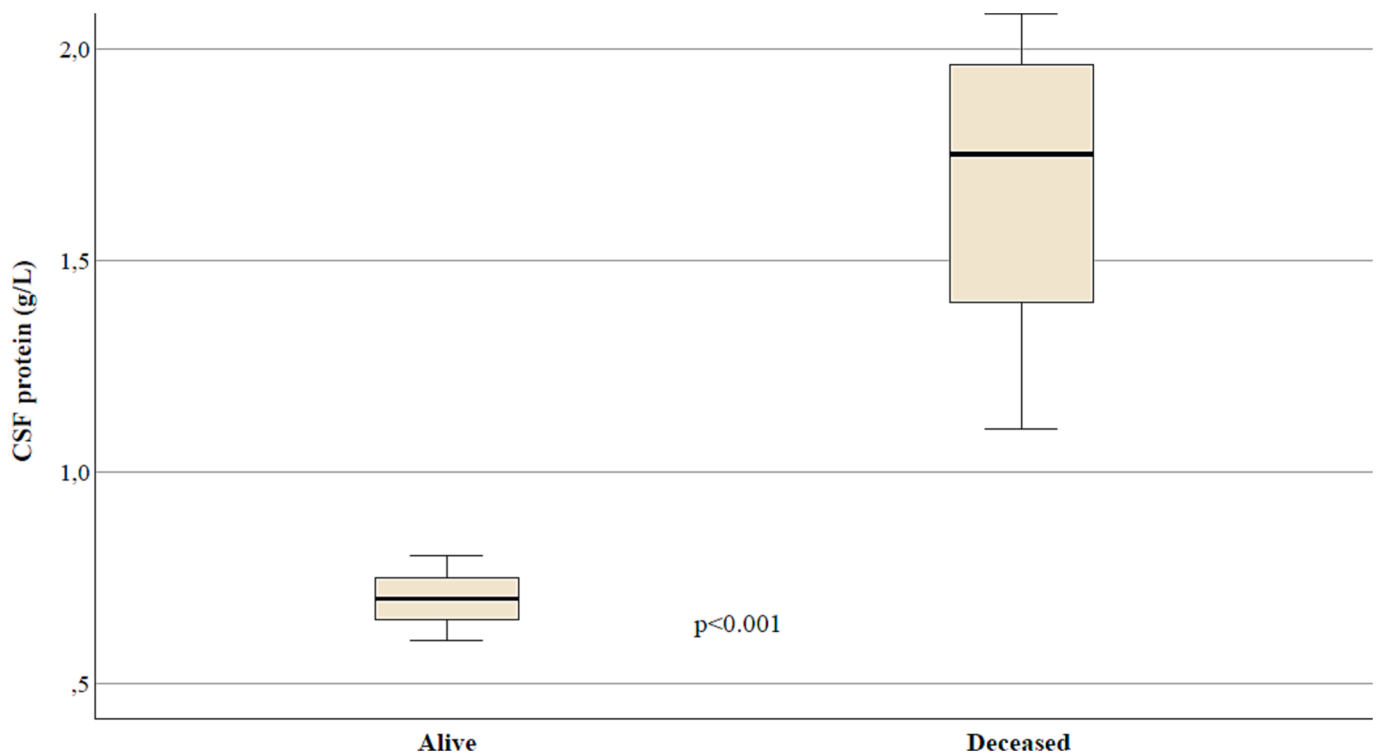


Fig. 3. Different CSF protein concentrations in patients affected by WNND according to clinical outcomes.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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