Outcomes in Patients With Severe West Nile Neuroinvasive Disease

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Objective: To assess the long-term outcomes of patients hospitalized with severe West Nile neuroinvasive disease.

Design: Retrospective cohort.

Setting: Patients admitted to a referral center (Saint Mary's Hospital, Mayo Clinic).

Participants: Twenty-six patients with West Nile neuroinvasive disease were identified by retrospective search of electronic database of Saint Mary's Hospital from January 1999 to November 2016.

Interventions: Retrospective electronic medical records review and prospective telephone follow-up.

Measurements and Main Results: Functional disability and cognitive outcomes were evaluated with the modified Rankin Scale and the Telephone Interview for Cognitive Status scores. Data on the time that the patient returned home after the hospitalization for West Nile neuroinvasive disease and the time of return to work were also collected. We identified 26 patients (81% males), 59 ± 17 years old. After a median hospital stay of 14.5 days (3–126), four patients died and 90% of survivors had a modified Rankin Scale of 3–5. Two additional patients died, and 80% of survivors had a modified Rankin Scale of 0–2 after a median follow-up of 73 months (1–144). Seven patients had cognitive impairment, which was severe in two of them. The combination of encephalitis and acute flaccid paralysis at presentation was associated with lower likelihood of returning home within 1 month after discharge ($p < 0.01$). Patients who required mechanical ventilation were more likely to have a modified Rankin Scale of 3–5 at last follow-up ($p = 0.03$), less likely to return home within 1 month of discharge ($p < 0.01$), less likely to return to their jobs ($p < 0.01$), and showed a trend toward having cognitive impairment ($p = 0.05$).

Conclusions: Despite having poor outcomes at discharge, most West Nile neuroinvasive disease survivors with severe early disability can recover functional independence in the long term, justifying aggressive support during the acute phase and extensive rehabilitation efforts. (*Crit Care Med* 2018; 46:e955–e958)

Key Words: acute flaccid paralysis; critical care; encephalitis; prognosis; West Nile virus

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West Nile virus is responsible for most cases of epidemic meningoencephalitis in North America. Nervous system involvement (West Nile neuroinvasive disease [WNND]) occurs in 1% of patients and can manifest with meningitis, encephalitis, acute flaccid paralysis, or a combination of these clinical expressions (1).

Mortality and early disability of patients with WNND are high, particularly in those who require intensive care (2). Given WNND low prevalence and substantial early mortality, long-term data on the outcomes of severely affected patients are lacking. This information is important to guide counseling on goals of care in the acute setting. In this study, we assessed the long-term outcomes of patients hospitalized with severe WNND.

MATERIALS AND METHODS

Patients greater than 18 years old hospitalized with WNND from January 1999 to November 2016 were identified from Saint Mary's Hospital electronic database as previously published. Data presented here represent the prospective follow-up of an already published cohort of patients with WNND (2).

Demographic data, presenting symptoms, length of hospitalization, in-hospital mortality, modified Rankin Scale (mRS) at discharge, and disposition were collected by retrospective chart review.

Patients were contacted by telephone to complete a standardized set of questions.

Functional and cognitive outcomes were evaluated with the mRS and the Telephone Interview for Cognitive status modified (TICs-m), respectively. Cognitive impairment

was defined as a TICs-m score less than or equal to 31 and severe cognitive impairment as TICS-m less than or equal to 27. We also obtained information on the time that the patient returned home after the hospitalization and the time of return to work. Those patients who could not be reached after four attempts over the course of 2 months were classified as nonresponders. The mRS scores of nonresponders and patients who declined the telephonic interview were obtained by reviewing the most recent entry on the electronic medical records that contained clear documentation of functional status.

Univariate analyses were performed to assess clinical and demographic factors associated with the length of hospitalization, disposition, and short- and long-term functional and cognitive outcomes. Continuous variables were analyzed using the Student *t* test. Categorical variables were analyzed with chi-square or Fisher exact tests as appropriate. *p* values less than 0.05 were considered significant. Data were analyzed using JMP Pro 10.0.0 (SAS Institute, Cary, NC, 1989–2012).

The study was approved by the Mayo Clinic's Institutional Review Board.

RESULTS

Twenty-six patients (81% males), 59 ± 17 years old, were hospitalized for WNND during the study period. Patients presented with a combination of encephalitis and acute flaccid (*n* = 11), encephalitis (*n* = 12), acute flaccid paralysis (*n* = 2), and meningitis (*n* = 1). Three patients developed coma (11.5%), and 14 patients (53%) required mechanical ventilation. After a median hospital stay of 14.5 days (range, 3–126), four patients died and 90% of survivors had a mRS of 3–5 (**Table 1**).

The median follow-up was 73 months (range, 1–144). Two patients died 20 and 64 months after discharge due to an intracranial neoplasm and unknown cause, respectively. Almost 80% of survivors had a mRS of 0–2 at the last assessment (Table 1).

Among 14 responders, seven had cognitive impairment, which was severe in two patients. Six patients were lost to follow-up due to invalid contact information (*n* = 2), denial to participation (*n* = 2), or no response (*n* = 2).

Most patients (*n* = 10) initially discharged to a facility were able to return to their home after a median of 3 months (range, 1–10). Eight patients returned to work; however, two of them had to be reassigned to a different role due to some residual disability. Four respondents had already retired before having WNND, but believed that they would not have been able to return to their previous occupation.

Older patients had more prolonged hospitalizations ($p < 0.01$). Males and those who presented with a combination of encephalitis and acute flaccid paralysis were less likely to be discharged home ($p = 0.03$ and 0.04). The need for mechanical ventilation was associated with longer hospital stay ($p = 0.03$), mRS 4–5 at discharge ($p = 0.01$), and lower likelihood of being discharged home ($p = 0.01$). Comatose patients had a nonsignificant trend toward longer hospitalization and higher in-hospital mortality ($p = 0.05$).

The clinical presentation with the combination of encephalitis and acute flaccid paralysis was associated with lower likelihood of returning home within 1 month after discharge ($p < 0.01$). Patients who required mechanical ventilation had more chances to have a mRS of 3–5 at last follow-up ($p = 0.03$), less likelihood of returning home within 1 month of discharge, and less likelihood of returning to their previous jobs ($p < 0.01$). Patients who required mechanical ventilation

TABLE 1. Patient Characteristics and Outcomes

Demographics	*n* = 26 (%)
Age (yr), mean ± SD	59 ± 17
Male gender, *n* (%)	21 (81)
Outcomes	
mRS at discharge	*n* = 26 (%)
6	4 (15.4)
5	7 (26.9)
4	4 (15.4)
3	9 (34.6)
2, 1, 0	2 (7.7)
Disposition	*n* = 22 (%)
Outside hospital	1 (4.5)
Home	4 (22.7)
Inpatient rehabilitation	14 (65.8)
Respiratory care unit	2 (9.1)
Skilled nursing facility	1 (4.5)
Length of hospitalization (d), median (range)	14.5 (3–126)
mRS at last follow-up	*n* = 26 (%)
6	6 (23)
5	1 (3.9)
4	2 (7.7)
3	1 (3.9)
2	4 (15.4)
1	10 (38.5)
0	2 (7.7)
Telephone Interview for Cognitive Status-modified	*n* = 14 (%)
> 31	7
≤ 31	5
≤ 27	2

mRS = modified Rankin Scale.

TABLE 2. Previous Studies on Outcomes after West Nile Neuroinvasive Disease

Study	*n*	Short-Term Outcomes	Long-Term Outcomes	Follow-Up	Limitations
Anastasiadou et al (3)	30	Mortality: 25%	Seven out of 22 survivors (30%) had a complete recovery, and three patients had permanent damage.	16 mo	No objective measures of functional disability No data on cognitive outcomes
Klee et al (4)	33	N/A	Full recovery at 1 yr: 37% Most patients had physical, cognitive, and functional deficits.	18 mo	No objective measures of functional disability
Carson et al (5)	11	N/A	Self-perception of poor physical health, fatigue, depression, and moderate-to-severe disability. Neuropsychologic testing showed abnormalities of motor skills, attention, and executive functions.	10.5–15.8 mo	Small sample No objective measure of functional disability
Sejvar et al (1)	16	Mortality: 6.25% ICU admission: 31.25% Disposition: home ($n = 13$), rehabilitation ($n = 2$)	Returned to their home within 4 mo: 100% Functionally independent: 73% Functionally dependent: 27% Cognitive impairment: 27%	8 mo	Small sample
Hart et al (6).	55	Mortality: 12.75 % Coma: $n = 14$ Weakness: $n = 27$ Cognitive impairment: $n = 25$ Cranial neuropathy: $n = 9$	Coma: $n = 1$ Cognitive impairment: $n = 9$ Cranial neuropathy: $n = 4$	90 d	No objective measures of functional disability
Athar et al (7)	30	–	Abnormal nerve conduction and/or needle electromyography due to anterior horn cell poliomyelitis: 33%	8.5 yr (1–12)	No objective measures of functional disability
Popovic et al (8)	52	Mortality: 17.3% mRS 3–5: 9.6% mRS 0–2: 73.1%	N/A	N/A	No data on long-term follow-up
Tsai et al (9)	393	Mortality: 4.3% Coma: 13%	N/A	N/A	No data on functional disability.
Hawkes et. al (2)	26	Mortality: 15.4% mRS 0–2: 7.7% mRS 3–5: 92.3%	N/A	N/A	No data on long-term follow-up

mRS = modified Rankin Scale, N/A = not applicable.

had a nonsignificant trend toward having cognitive impairment in the long term ($p = 0.05$). A mRS of 4–5 at discharge was associated with a less likelihood of returning home within a month and less likelihood to return to previous job ($p < 0.01$). However, it was not associated with functional dependence (mRS, 3–5) upon last follow-up ($p = 0.1$).

DISCUSSION

We report the functional and cognitive outcomes of a sizable cohort of patients with WNND with the longest follow-up to date. Fifteen percent of patients in our cohort died in the hospital, and a total of 23% were dead after a median follow-up of 73 months. However, nearly 80% of survivors had minimal or no disability upon long-term follow-up. Patients requiring mechanical ventilation had worse prognosis, but most of them still experienced substantial recovery in the long term.

These findings are novel and clinically relevant because they indicate that intensive support during the acute phase and extensive rehabilitation efforts after hospital discharge can often result in good functional recovery, even if such recovery is slow. This is particularly important because critical WNND is associated with a high acute morbidity as recently published by our group (2). Although several studies have

partially addressed this issue, most of them are limited by their small samples, absence of objective measures of functional disability, lack of cognitive outcomes, or short follow-up (1, 3–9) (**Table 2**).

The mortality of WNND in previous studies was between 6% and 25%, with most deaths occurring in the acute phase (1, 3, 6, 8, 9). This is comparable to our experience (2). The high disability at discharge and unfavorable disposition in our cohort could be explained, at least in part, by the profound severity of the neurologic disease at nadir, as illustrated by the high percentage of patients with a combination of encephalitis and acute flaccid paralysis and the large proportion who required mechanical ventilation. Prolonged hospitalizations with physical deconditioning could also play a role (2). Despite having poor outcomes at discharge, our data support that survivors with severe early disability can improve substantially and regain full function. The percentage of functionally independent patients increased from 7.7% at discharge to 61% at last follow-up. This resembles data from patients with acute infectious encephalitis of other etiologies (10). Yet, severely affected survivors from WNND may need a longer time to recover.

Remarkably, a significant proportion of WNND survivors had cognitive impairment and could not return to their previous occupation despite regaining functional independence. The frequency and degree of cognitive impairment in these patients may be more prominent than in other infectious encephalitis (10). Our dataset has limitations. First, a referral bias may account for the severity of WNND in our cohort. However, it does not change the fact that most of the patients recovered in the long term, supporting our main conclusions. Second, the cognitive outcomes could not be evaluated in those patients who were lost to follow-up, but the calculation of the mRS in all survivors provides a fair estimate of functional disability. Last, we do not have objective data on cognitive function before the acute infection, but most of our patients were employed and did not have functional restrictions before the hospitalization.

CONCLUSIONS

WNND is associated with significant short-term morbidity and mortality. Yet, even the most severely disabled survivors can recover functional independence in the long term, supporting intensive care in the acute setting. The need for mechanical ventilation identifies a group of WNND patients with worse short- and long-term prognosis, but those patients can still recover well. Persistent cognitive impairment is possible, though most commonly not severe, and some patients may not be able to return to their previous jobs. More research is necessary to refine our knowledge regarding persistent cognitive impairment and quality of life after severe WNND survivors.

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