MAJOR ARTICLE

Long-Term Clinical and Neuropsychological Outcomes of West Nile Virus Infection

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Background. Since its introduction in 1999, West Nile virus has rapidly become the most common arboviral infection in North America. Little is known about the long-term clinical sequelae of West Nile virus infection.

Methods. A total of 49 patients with laboratory-confirmed West Nile virus infection were identified through state-based surveillance. Stratification for disease severity was based on hospitalization during the infection episode. Assessment occurred a mean of 13 months after diagnosis. Medical records were reviewed, and a complete neurologic examination was performed. Standardized surveys for quality of life, functional ability, fatigue, and depression were performed for all subjects. An extensive battery of neuropsychological tests was performed to assess cognitive function.

Results. Self-reported fatigue, memory problems, extremity weakness, word-finding difficulty, and headache were common complaints. Standardized survey data confirmed an overall sense of poor physical health, fatigue, depression, and moderate-to-severe disability in 24 (49%), 24 (49%), 12 (24%), and 4 (8%) patients, respectively. New tremor was seen or reported for 10 (20%) of the patients. Neuropsychological testing showed abnormalities of motor skills, attention, and executive functions. Univariate analysis of multiple risk factors did not identify any predictors of adverse outcomes.

Conclusions. Multiple somatic complaints, tremor, and abnormalities in motor skills and executive functions are common long-term problems among patients who have had West Nile virus infection. Patients with milder illness are just as likely as patients with more-severe illness to experience adverse outcomes.

West Nile virus (WNV) is a mosquito-borne flavivirus that is transmitted primarily among birds, with humans acting as incidental hosts. In 1999, WNV was introduced into North America for the first time with a localized epidemic in the New York City metropolitan area [1]. Since that time, it has spread dramatically across the United States [2, 3]. In 2003, it was responsible for the largest epidemic of arboviral infection in North America, with >9000 human cases and 264 deaths [2]. North Dakota was at the center of this epidemic, with 617 reported cases. Ninety-four cases were classified as cases of neuroinvasive disease, with 5 related deaths [4].

Although most WNV infections are asymptomatic, ~20% of patients will develop a flulike illness called West Nile fever [5, 6]. This manifestation has generally been considered to be a benign, self-limited condition [7, 8]. Up to 1% of patients may develop neuroinvasive disease in the form of meningitis, encephalitis, or acute flaccid paralysis [6].

Few studies have addressed the long-term outcomes of WNV infection. Those that have show variable rates of fatigue, headache, movement disorders, cognitive dysfunction, muscle weakness, dizziness, and disability [9–14]. Most of these studies were limited by a small sample size, short-term follow-up, retrospective analysis, a focus on patients with neuroinvasive disease, and reliance on subjective symptom reporting (most often by phone interview). Only 1 study specifically addressed outcomes of West Nile fever [12].

Epidemiologic data concerning other flaviviruses (namely, Japanese B and St. Louis encephalitis) reveal cognitive and psychosocial consequences long after acute neurologic deficits have faded [15, 16]. Similarly, other studies suggest that 56% of patients report con-

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centration and memory impairment even 1 year after an episode of meningoencephalitis [17, 18]. No studies to date have looked at formal neuropsychological testing to objectively assess cognitive impairment in patients with WNV infection.

We studied patients with both West Nile fever and neuroinvasive disease (West Nile meningitis or encephalitis) ~1 year after infection. In addition to reviewing current symptomatology and performing a thorough neurologic examination, we used a number of objective, standardized surveys to assess current health status, fatigue, functional ability, and depression. Furthermore, we assessed cognitive function by performing a battery of standardized neuropsychological tests.

PATIENTS AND METHODS

Patients. Patients who received a laboratory-confirmed diagnosis of WNV infection during 2003 by IgM capture ELISA either from serum or CSF samples were identified from state-based surveillance and a search of our laboratory records. In cooperation with the North Dakota Department of Health, surviving patients from 10 counties in eastern North Dakota were invited by letter to participate. Patients were strongly encouraged to participate whether their current health status was good or poor. Patients who did not respond to the letter were sent a second mailing encouraging participation, and patients from our institution received a telephone call, as well. Health Insurance Portability and Accountability Act regulations were carefully followed. The MeritCare Health System Institutional Review Board approved the study. All participants reviewed and signed a written informed consent form.

Patients had to have an illness compatible with WNV infection, such as West Nile fever (defined as a history of acute febrile illness and associated headache, myalgias, anorexia, lymphadenopathy, or rash), West Nile meningitis (West Nile fever plus evidence of meningeal involvement by symptoms of nuchal rigidity or CSF pleocytosis with $\geqslant$5 leukocytes/mm^3), West Nile encephalitis (West Nile fever plus an additional history of a depressed level of consciousness, lethargy, or personality change lasting $\geqslant$24 h), or acute flaccid paralysis (acute onset of asymmetric limb weakness with marked progression over a 48-h period and either abnormal findings of electrodiagnostic studies consistent with anterior horn cell dysfunction or abnormal gray matter visible on spinal cord MRI).

Patients were excluded from the study if they had a history of baseline dementia, learning disability, traumatic brain injury, or severe mental or physical illness. They were also excluded if they had developed any intercurrent illness that, in the opinion of the investigators, could substantially confound the study results (e.g., 1 patient was excluded from the study because he developed a lymphoma after his WNV infection).

Assessments. Patients were assessed 10.5–15.8 months after the date of their diagnosis (mean duration, 13 months). A standard form was used for abstracting demographic data, medical history, clinical features of the acute illness, and current symptoms. A thorough neurological examination was performed by a physician for all patients, including tests for cranial nerves II–XII, motor strength in upper and lower extremities, sensory testing for pinprick and vibration, deep tendon reflexes, gait, coordination, and assessment for movement abnormalities.

Standardized surveys for quality of life (short form health survey 12, version 2; SF-12v2), functional ability (Barthel Index and Modified Rankin score), fatigue (Modified Fatigue Impact Scale), and depression (Beck Depression Inventory II) were performed for all subjects. The SF-12v2 is a widely used tool that assesses an individual's overall health. It is broken down into a physical composite score and mental composite score. Overall poor health was defined by an SF-12v2 score of $\leqslant$42 on the physical composite score and $\leqslant$45 on the mental composite score. These scores represent values below the 25th percentile for the general population [19]. Moderate-to-severe depression was defined as a Beck Depression Inventory II score $\geqslant$19 [20]. Moderate-to-severe disability was defined as a Barthel Index score $\leqslant$75 or a Modified Rankin score $\geqslant$3, and moderate-to-severe fatigue was defined as a Modified Fatigue Impact Scale score $\geqslant$38 [21–23]. Patients were also tested for the persistence of IgM antibodies to WNV in the serum.

Trained research assistants performed an extensive battery of standardized neuropsychological tests to assess multiple aspects of cognitive function. These included standard tests of attention, executive functions, language, learning and memory, motor function, verbal intellectual function, and visual spatial function. All patients demonstrated adequate effort on a standardized measure (the Test of Memory Malingering). Selected variables were chosen a priori from each subtest to be used in examination of the data. Scores were compared with published norms corresponding to the patient's age, sex, and/or educational level [24–27]. Score groupings were presented as SDs from the mean. Patients scoring 1–2 SDs below the mean were considered to have mild-to-moderate impairment, and patients scoring >2 SDs below the mean were considered to have severe impairment.

Statistical analysis. Hospitalized patients ($n = 15$) were compared with patients who were not hospitalized ($n = 34$) using the independent samples t test for continuous measures, the Mann-Whitney nonparametric test for ordinal measures, and Fisher's exact test for dichotomous measures. Univariate ORs and 95% CIs were calculated between underlying risk factors and adverse outcomes.

RESULTS

A total of 122 patients were identified by state-based surveillance. Sixty-three households (52%) responded to the invitation. Three (5%) of the patients had died, 9 (14%) refused to

participate, and 51 (81%) agreed to participate. One patient was legally blind and participated in all aspects of the study that did not require direct visual interaction. Two patients were excluded from the study because of prior neurologic disease (traumatic brain injury and multiple sclerosis, respectively). Forty-nine patients completed the study. Table 1 shows the baseline characteristics of the study patients. Overall, 11 (22%) of the patients were classified as having West Nile meningitis or encephalitis, and 38 (78%) had West Nile fever. Hospitalization occurred for 15 (31%) of the subjects. All nonhospitalized patients and 4 of the hospitalized patients were characterized as having West Nile fever. The 4 hospitalized patients with a diagnosis of West Nile fever had not undergone lumbar puncture, which may have limited our ability to categorize their disease state accurately.

Subjective reporting of persistent symptoms revealed a high prevalence of multiple somatic complaints (table 2). The most frequent symptoms were fatigue, memory problems, extremity symptoms (e.g., pain, weakness, and numbness), joint pain, word-finding difficulties, and headaches. Nonhospitalized patients were more likely to self-report fatigue (OR, 10.67; 95% CI, 1.83–62.1), word-finding difficulties (OR, 6.5; 95% CI, 1.27–33.29), and excessive sleepiness (OR not calculable).

Physical examination revealed the presence of tremor in 6 patients, and 4 other patients reported a history of intermittent tremor that could not be elicited at the time of examination. The observed tremors were characterized in 5 of the patients as upper extremity intention tremors with a frequency of 3–6 Hz. One patient had a tremor of the head. The 4 patients with a history of tremor all described intention tremors of the upper

Table 1. Demographic and clinical characteristics of study patients with a diagnosis of West Nile virus (WNV) infection.

Variable	Hospitalized group (n = 15)	Nonhospitalized group (n = 34)	P
Age			
Mean years ± SD	57.1 ± 11.9	50.7 ± 12.6	.100
⩾60 years	7 (46.7)	8 (23.5)	.177
Sex			
Male	7 (46.7)	13 (38.2)	.754
Female	8 (53.3)	21 (61.8)	
Education			
Less than high school	1 (6.7)	2 (5.9)	.903
High school diploma or general educational development degree	7 (46.7)	17 (50.0)	
Some college or more	7 (46.7)	15 (44.1)	
Preexisting conditions			
Hypertension	6 (40.0)	6 (17.6)	.148
Diabetes	3 (20.0)	3 (8.8)	.353
Immunosuppression	3 (20.0)	7 (20.6)	1.000
Seizures	…	…	
Depression	1 (6.7)	4 (11.8)	1.000
ADHD	…	1 (2.9)	1.000
Stroke	…	…	
Headaches	1 (6.7)	3 (8.8)	1.000
Bladder problems	3 (20.0)	3 (8.8)	.353
Neuropathy	…	…	
Current tobacco use	3 (20.0)	9 (26.5)	.731
Current alcohol use	8 (57.1)	23 (67.7)	.522
Hospitalization, mean days ± SD	11.5 ± 13.5	…	
Return to work, mean days ± SD	47.8 ± 57.8	9.6 ± 16.9	.106
Disease category			
WNV fever	4 (26.7)	34 (100.0)	<.0001
WNV meningitis	6 (40.0)	…	
WNV encephalitis	5 (33.3)	…	

NOTE. Data are no. (%) of patients, unless otherwise indicated. ADHD, attention deficit hyperactivity disorder.

Table 2. Self-reported symptoms of study patients with a diagnosis of West Nile virus infection.

Symptom	No. (%) of patients		
	Hospitalized group (n = 15)	Nonhospitalized group (n = 34)	P
Fatigue	9 (60.0)	32 (94.1)	.007
Memory problems	7 (46.7)	22 (64.7)	.345
Extremity weakness	7 (46.7)	17 (50.0)	1.000
Extremity numbness or tingling	6 (40.0)	13 (38.2)	1.000
Extremity pain or myalgia	8 (53.3)	15 (44.1)	.169
Joint pain	5 (33.3)	17 (50)	.347
Word-finding difficulty	2 (13.3)	17 (50.0)	.025
Headache of new pattern or severity	5 (33.3)	13 (38.2)	1.000
Balance problems	6 (40.0)	8 (23.5)	.309
Excessive sleep	0 (0.0)	12 (35.3)	.010
Light headedness	4 (26.7)	9 (26.5)	1.000
Slowness of movements	4 (26.7)	9 (26.5)	1.000
Tremor[a]	4 (26.6)	6 (17.6)	.470
Bladder urgency	3 (20.0)	6 (17.6)	1.000
Decreased hearing	3 (20.0)	8 (23.5)	1.000
Difficulty with walking	3 (20.0)	2 (5.9)	.160
Decreased sleep	2 (13.3)	5 (14.7)	1.000
Dizziness	2 (13.3)	6 (17.6)	1.000
Shuffling when walking	2 (13.3)	2 (5.9)	.576
Slurring of speech	2 (13.3)	1 (2.9)	.218
Swallowing difficulties	2 (13.3)	6 (17.6)	1.000
Double vision	1 (6.7)	4 (11.8)	1.000
Facial weakness or droop	1 (6.7)	0 (0.0)	.306
Falls	1 (6.7)	1 (2.9)	.523
Fever	1 (6.7)	3 (8.8)	1.000
Occasional urinary incontinence	1 (6.7)	1 (2.9)	.523
Rash	1 (6.7)	2 (5.9)	1.000
Confusion	0	5 (14.7)	.306
Episodic visual loss	0	2 (5.9)	1.000

[a] Six patients had observed tremor on physical examination.

extremities. The patient with acute flaccid paralysis had persistent severe and disabling deficits with lower extremity paralysis and right upper extremity and truncal weakness.

Testing for the presence of IgM antibodies to WNV showed persistence of antibodies in 6 (40%) of the patients in the hospitalized group and in 2 (6%) of the patients in the nonhospitalized group ($P = .008$).

Standardized survey data for overall health, disability, depression, and fatigue are reported in table 3. On the SF-12v2 survey, 24 (49%) and 16 (33%) of the patients scored low on the physical and mental component scores, respectively. On the Beck Depression Inventory II, 12 (24%) of the patients scored in the range of moderate-to-severe depression. Only 5 (10%) of the patients had reported a history of depression before their illness, and in most cases, depression had been well controlled with treatment. High scores on the Modified Fatigue Impact Scale were seen in 24 (49%) of the patients. Barthel Index and Modified Rankin Scale scores indicated that 4 (8%) of the patients had some degree of significant ongoing disability.

Table 4 summarizes the data from the neuropsychological ratings. Depending on the specific test, assessments of executive functions revealed mild-to-moderate impairments in 7%–36% of the patients. On the Wisconsin Card Sorting Test, 5 (15%) of the nonhospitalized group showed severe impairment. The Wechsler Memory Scale III Visual Reproduction I, a measure of immediate visual memory, showed lower scores for 18 (37%) of the subjects. All of the remaining tests of cognitive function appeared to have normal results. Results of the neuropsychological tests for motor function showed that 34 (69%) of the patients overall had abnormalities in motor speed (on finger-tapping test of the nondominant hand), and in 21 (43%) of the patients, these impairments were severe. We looked for

Table 3. Standardized survey data for study patients with a diagnosis of West Nile virus infection.

Survey	Hospitalized group (n = 15)	Nonhospitalized group (n = 34)	P
Quality of health			
SF-12v2			
Mean physical composite score ± SD	43.7 ± 9.3	40.8 ± 10.1	.341
Mean mental composite score ± SD	51.6 ± 11.5	47.8 ± 10.2	.262
Poor health on physical composite score, no. (%) of patients	7 (46.7)	17 (50)	1.000
Poor health on mental composite score, no. (%) of patients	4 (26.7)	12 (35.3)	.740
Depression			
BDI-II, mean score ± SD	9.8 ± 10.9	11.4 ± 8.5	.593
Moderate-to-severe depression, no. (%) of patients	4 (26.7)	8 (23.5)	1.000
Disability			
MRS, mean score ± SD	1.7 ± 1.1	1.24 ± 0.8	.126
BI, mean score ± SD	97 ± 6.2	99.7 ± 1.7	.022
Moderate-to-severe disability, no. (%) of patients	2 (13.3)	2 (5.9)	.582
Fatigue			
MFIS, mean score ± SD	32.4 ± 21.3	38.8 ± 17.4	.327
Moderate to severe fatigue, no. (%) of patients	5 (35.7)	19 (55.9)	.342

NOTE. BDI-II, Beck Depression Inventory II; BI, Barthel Index; MFIS, Modified Fatigue Impact Scale; MRS, Modified Rankin Score; SF-12v2, short form health survey 12, version 2.

associations between abnormalities found on the neuropsychological tests and fatigue, poor sense of overall health, and depression. Fatigue, as measured by a high Modified Fatigue Impact Scale score, correlated with poor performance on the Wechsler Memory Scale III Visual Reproduction test (P = .019) and the Brief Test of Attention (P = .018), but it was not correlated with abnormalities seen on the motor function tests or tests of executive function. Depression was significantly correlated with poor manual dexterity as measured by performance on the Purdue pegboard (P = .01), and a poor physical composite score on the SF-12v2 correlated with poor motor speed on the dominant hand finger tapping test (P = .002) but not with the results of the other neuropsychological tests.

Univariate analysis was performed to assess for risk factors for adverse outcomes. Patients were defined as having an adverse outcome if they had any of the following: presence or history of tremor, poor scores on the standardized surveys (as defined in Patients and Methods), or any abnormality with respect to any of the tested neuropsychological domains. Risk factors were defined as age >60 years, male sex, hospitalization, West Nile fever, hypertension, diabetes mellitus, immunosuppression (defined as history of cancer, current corticosteroid use, or consumption of ⩾14 alcoholic beverages per week), preceding depression, current tobacco use, and presence of persistent IgM antibodies to WNV. No significant associations were found between any of the assessed risk factors and adverse outcomes.

DISCUSSION

Our study suggests that patients with WNV infection experience significant long-term morbidity. Similar to earlier studies, we found very high rates of self-reported fatigue, memory impairment, weakness, headache, joint pain, and balance problems [9, 10, 12–14]. Only 1 of these studies looked specifically at patients with West Nile fever whose cases were managed on an outpatient basis [12]. They reported significant persistence of somatic complaints in a large number of patients, although follow-up was reported only for the 30-day period after illness onset. Fatigue was particularly prominent among our patients, with 41 (84%) of our patients self-reporting fatigue and nearly one-half having scores similar to those for patients with moderate-to-severe multiple sclerosis on the Modified Fatigue Impact Scale [23, 28]. Of note, patients with more-severe illness did not report more chronic symptoms than patients with milder illness. On the contrary, some of the few statistically significant associations found in our study were higher rates of fatigue, word-finding difficulties, and excessive sleepiness in the

Table 4. Neuropsychological test results for study patients with a diagnosis of West Nile virus infection.

Domain, test	No. (%) of patients						
	Hospitalized group (n = 15)			Nonhospitalized group (n = 34)			
	Within 1 SD of norm	1–2 SDs below the norm	>2 SDs below the norm	Within 1 SD of norm	1–2 SDs below the norm	>2 SD below the norm	P
Attention							
BTA	13 (86.7)	2 (13.3)	0	30 (88.2)	4 (11.8)	0	1.000
PASAT 3	15 (100.0)	0	0	34 (100.0)	0	0	NC
PASAT 2	14 (100.0)	0	0	34 (100.0)	0	0	NC
Executive functions							
WCST categories	9 (64.3)	5 (35.7)	0	25 (73.5)	4 (11.8)	5 (14.7)	.074
WCST perseverative errors	10 (71.4)	4 (28.6)	0	28 (84.8)	5 (15.2)	0	.419
D-KEFS number letter switch	13 (92.9)	1 (7.1)	0	31 (91.2)	3 (8.8)	0	1.000
COWA	11 (73.3)	4 (26.7)	0	23 (67.6)	11 (32.4)	0	.750
Language							
Boston naming test	12 (85.7)	1 (7.1)	1 (7.1)	31 (91.2)	3 (8.8)	0	.287
Learning and memory							
WMS-III logical memory I	11 (73.3)	3 (20.0)	1 (6.7)	28 (82.4)	5 (14.7)	1 (2.9)	.727
WMS-III logical memory II	13 (86.7)	2 (13.3)	0	31 (93.9)	2 (6.1)	0	.579
WMS-III visual reproduction I	9 (64.3)	5 (35.7)	0	21 (61.8)	12 (35.3)	1 (2.9)	.810
WMS-III visual reproduction II	13 (92.9)	1 (7.1)	0	33 (97.1)	1 (2.9)	0	.503
CVLT-II	15 (100.0)	0	0	32 (94.1)	2 (5.9)	0	1.000
Motor functions							
FTT dominant hand	7 (46.7)	2 (13.3)	6 (40.0)	13 (38.2)	12 (35.3)	9 (26.5)	.278
FTT nondominant hand	6 (40.0)	3 (20.0)	6 (40.0)	8 (24.2)	10 (30.3)	15 (45.5)	.509
Purdue pegboard (both hands)	6 (42.9)	4 (28.6)	4 (28.6)	18 (52.9)	12 (35.3)	4 (11.8)	.356
Verbal intellectual functions							
WAIS-III vocabulary subtest	11 (73.3)	4 (26.7)	0	30 (88.2)	3 (8.8)	1 (2.9)	.219
NAART	10 (71.4)	4 (28.6)	0	33 (97.1)	1 (2.9)	0	.021
Visual spatial functions							
JOLO	12 (85.7)	1 (7.1)	1 (7.1)	28 (82.4)	4 (11.8)	2 (5.9)	.886
WAIS-III block design	13 (92.9)	1 (7.1)	0	32 (94.1)	2 (5.9)	0	1.000

NOTE. BTA, Brief Test of Attention; COWA, Controlled Oral Word Association; CVLT-II, California Verbal Learning Test II; D-KEFS, Delis-Kaplan Executive Function System Trail Making Test Number Letter Switch; FTT, Finger Tapping Test; PASAT, Abbreviated Paced Auditory Serial Addition Test; JOLO, Judgment of Line Orientation; NAART, North American Adult Reading Test; NC, not calculable; WAIS-III, Wechsler Adult Intelligence Scale III; WCST, Wisconsin Card Sorting Test 64; WMS-III, Wechsler Memory Scale III.

nonhospitalized group of patients. The standardized surveys done in our study confirmed high rates of morbidity (e.g., depression, a poor sense of health quality, and fatigue).

Four patients demonstrated significant disability on the Modified Rankin Scale or Barthel Index. One patient had acute flaccid paralysis, and the other patient had previous blindness. Removing these 2 patients from the analysis would indicate that most patients returned to a reasonable level of functioning and independence despite their ongoing symptoms. This likely explains why some studies that limit their definition of adverse outcome primarily to disability tend to report a more favorable course for WNV infection [11].

Our study identified intention tremor in 10 (20%) of the patients. Furthermore, the most striking abnormalities identified by neuropsychological testing were identified by the tests of motor speed and manual dexterity. These abnormalities were not readily appreciated on the general neurological examination. Movement disorders have been frequently reported for patients with WNV infection, as well as for patients with other flavivirus infections, particularly in cases of acute illness [9, 29–31]. Most of these studies describe bradykinesia, rigidity, postural instability, and other features that are consistent with parkinsonism. These features are thought to be the clinical correlates of inflammatory and degenerative changes noted in the basal ganglia and cerebellum on MRI and autopsy studies of persons with flavivirus infection [29, 31, 32].

Depression and abnormalities in executive functions and memory input may also be seen in diseases that cause damage

to the basal ganglia and subcortical structures [33, 34]. Indeed, the constellation of clinical and neuropsychological abnormalities seen in our patients is not well explained on the basis of fatigue alone, and these abnormalities could all be potentially explained by subtle damage to the frontal-subcortical structures. It is particularly noteworthy that our patients continued to show clinical abnormalities 1 year after illness. Furthermore, patients with "milder" illness (i.e., nonhospitalized patients with West Nile fever) demonstrated equivalent rates of these abnormalities. This might suggest that West Nile fever is not a self-limited benign illness, as previously thought, and may, in fact, be a subclinical encephalitis with pathologic involvement of the related frontal and subcortical structures, as in patients with overt clinical encephalitis.

The frequent persistence of IgM antibodies to WNV for as long as 18 months after illness has been demonstrated in other studies [35, 36]. These studies did not show any risk factors for persistent antibodies. Our study showed a statistically significant association between hospitalization and the persistence of IgM antibodies (OR, 10.33; 95% CI, 1.77–60.30). The clinical significance of this finding is uncertain.

Our study has several limitations. We relied on the voluntary participation of subjects from a retrospective cohort. Less than one-half of the eligible patients agreed to participate in the study. Although our participation rates are comparable to those for other retrospective cohort studies, the possibility of selection bias, particularly in favor of patients with more-severe illness seeking attention, is a significant limitation. Health Insurance Portability and Accountability Act restrictions prevented us from knowing the identity of patients outside of our own institution and directly contacting them. The state health department acted as an intermediary on our behalf in sending out solicitation letters. This indirect contact may have limited our enrollment success. We tried to overcome this by emphasizing in more than 1 solicitation the importance of including all patients in the study, regardless of their current symptoms. Of the subjects who declined participation, most cited issues of travel as the main reason. Another limitation is that our sample size may have been inadequately powered to demonstrate statistically significant risk factors for adverse outcomes. This seems unlikely, given the overall high rates of defined adverse outcomes. Furthermore, for almost all of the selected comparisons, we did not observe trends toward statistically significant differences. Short of a multicenter cooperative trial, it will be difficult for any individual center to do such extensive testing on a much larger sample size.

WNV infection continues to be a major public health threat in North America, with significant associated mortality and long-term morbidity. Effective therapies for patients with acute infection are greatly needed. Increased efforts at vector control and vaccine development will continue to be important strategies to prevent this ongoing epidemic. Larger multicentered studies may help to identify groups at greater risk for adverse outcomes.

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