Clinical Characteristics and Functional Outcomes of West Nile Fever

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Background: **West Nile fever, considered a nonsevere manifestation of West Nile virus infection, has not been clinically well described in the United States. In 2002, Illinois had 884 documented cases of West Nile virus infection with 66 associated deaths.**

Objective: **To describe the symptoms and functional outcomes of West Nile fever.**

Design: **Case series.**

Setting: **Illinois.**

Patients: **98 community-dwelling patients with laboratory evidence of West Nile virus infection but no history of clinical evidence of meningitis, encephalitis, or acute flaccid paralysis.**

Intervention: **Outpatient interviews.**

Measurements: **Presence and duration of patient-reported symptoms of infection, symptom-associated absenteeism, health care use, and impact on daily activities.**

Results: **Of 98 patients, 96% had fatigue for a median of 36 days, 81% had fever for a median of 5 days, 71% had headache for a median of 10 days, 61% had muscle weakness for a median of 28 days, and 53% had difficulty concentrating for a median of 14 days. Thirty respondents reported hospitalization, with a median stay of 5 days. At 30 days after onset, 63% of respondents continued to have symptoms. Duration did not vary significantly with increased age. Among the 72 patients who normally attended work or school, 57 (79%) could not attend because of illness (median absence, 10 days).**

Limitations: **Recall bias could have been introduced by the delay between illness onset and interview and by self-reporting of illness information.**

Conclusions: **West Nile fever is a more severe illness than has previously been documented. Mandatory reporting of West Nile fever cases in addition to West Nile meningoencephalitis cases could allow more accurate and timely recognition of the geographic distribution of West Nile virus infections and could inform public health interventions.**

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West Nile virus is a mosquito-borne pathogen with a wide geographic distribution in the eastern hemisphere (1). The first documented West Nile virus infections in the United States occurred in 1999 in New York City (2). Since then, the distribution of the virus has expanded rapidly and the number of infections has increased (3–5). In 2002, 4156 cases of West Nile virus disease and 284 deaths were reported throughout the United States (6), compared with 62 cases and 7 deaths in 1999 (2). Illinois had 884 documented cases with 66 deaths in 2002 (7). In 2003, the expansion continued; 9858 cases and 262 deaths were reported nationally (8).

Since the initial identification and isolation of West Nile virus in 1937 (9), associated outbreaks have typically been characterized by mild febrile illnesses (10). Starting in the mid-1990s, however, the frequency and severity of outbreaks increased (11). Recent outbreaks in Romania, Russia, and Israel involved hundreds of persons and high rates of severe neurologic disease and fatalities (12–14).

Most recent studies on infections caused by West Nile virus have focused on persons with neurologic disease, such as meningitis or encephalitis (10). However, 3 serologic studies of persons in the United States and Romania found that meningitis or encephalitis occurred in only about 1 of 150 infected persons (12, 15, 16). In addition, the serologic study conducted by Mostashari and colleagues (15) during the 1999 New York City outbreak found that most infections are not clinically apparent; only approximately 20% of infected persons developed symptoms that could be attributed to the virus. On the basis of the number of meningitis and encephalitis cases reported in 1999, the authors estimated that 3500 to 13 000 West Nile virus infections occurred throughout the greater New York City area that year.

West Nile fever is often the term used to describe symptomatic infections without neurologic disease. The typical description is a febrile illness of sudden onset lasting 3 to 6 days and often accompanied by malaise, anorexia, nausea, vomiting, eye pain, headache, myalgias, and rash (17). Clinical characterization of West Nile fever cases, however, is poor (10).

METHODS

Case Finding and Case Definition

Human cases of aseptic meningitis and encephalitis are reportable conditions in Illinois. In 2002, the Illinois Department of Public Health tested all cerebrospinal fluid and blood specimens submitted for suspected arboviral infection, regardless of clinical picture. In addition, the Illinois Department of Public Health accepted positive results on laboratory tests for West Nile virus infection from commercial laboratories. Whenever the Illinois Department of Public Health notified a local health authority of a West Nile virus–positive result in a resident of its jurisdiction, the local health authority conducted an epidemiologic investigation of the case.

Persons who had positive test results but did not meet

the Centers for Disease Control and Prevention definition for meningitis or encephalitis and did not satisfy published criteria for diagnosis of West Nile virus–associated acute flaccid paralysis (18) were considered to have West Nile fever. As part of the West Nile virus outbreak investigation conducted by the Illinois Department of Public Health and the Chicago Department of Public Health, West Nile fever cases were characterized in terms of reported symptoms and illness severity.

We classified cases of West Nile virus disease on the basis of the Centers for Disease Control and Prevention case definitions for meningitis and encephalitis due to arboviral disease (19). The laboratory criterion for a confirmed diagnosis of West Nile virus disease was West Nile virus IgM in cerebrospinal fluid or West Nile virus genomic sequences in blood or cerebrospinal fluid. The laboratory criterion for a probable diagnosis of West Nile virus disease was West Nile virus IgM in serum. Cases were then classified on the basis of reported clinical criteria. We excluded patients with meningitis (fever, headache, stiff neck, and pleocytosis) or encephalitis (fever, headache, altered mental status, and pleocytosis). Patients with acute, progressive, asymmetric weakness, with or without the signs and symptoms of meningitis or encephalitis, were excluded because of the possibility of acute flaccid paralysis. The remaining patients were classified as having West Nile fever, defined as West Nile virus IgM or genomic sequences in serum but no symptoms or signs of meningitis, encephalitis, or acute flaccid paralysis.

To ensure the exclusion of patients exhibiting more serious neurologic signs, we checked West Nile fever case reports before interviews to confirm that no patients had had lumbar puncture performed or cerebrospinal fluid submitted for laboratory evaluation and that confusion was not listed on the case report as a symptom. We confirmed this information with patients at the time of the interview. In addition, we obtained information from hospital records of selected patients when necessary to verify classification of illness.

Data Collection

To assess the clinical syndrome and functional outcomes of West Nile fever, we interviewed affected patients by telephone using a standard questionnaire. The questionnaire contained questions about the presence and duration of 18 different symptoms, hospitalization and other medical visits, medications taken or prescribed, the impact of the illness on daily activities, the amount of work or school missed, and underlying medical conditions during the illness (diabetes mellitus, history of cancer of any type, hypertension, heart disease, liver disease, kidney disease, and history of organ transplantation or immunosuppression). We determined duration of illness using self-reported illness information obtained at the time of the interview. Patients who lived in areas under the jurisdiction of participating local health departments and who were able to independently answer questions were eligible for inclusion.

Context

The frequency of infection with West Nile virus is increasing rapidly in the United States. While the most fatal and closely studied manifestations of the disease are meningitis and encephalitis, little is known about the symptoms and clinical outcomes of West Nile fever.

Contribution

The authors interviewed 98 people with nonparalytic West Nile fever following recovery. Muscle weakness, fatigue, headache, difficulty concentrating, and fever were common manifestations. Approximately one third of patients required hospitalization. Median time to full recovery was 60 days.

Implications

Even in the absence of neurologic manifestations, West Nile virus infection is a potentially severe and debilitating illness.

–The Editors

Statistical Analysis

We used Epi Info (version 6.04b, Centers for Disease Control and Prevention, Atlanta, Georgia) and SAS (version 8.2, SAS Institute, Inc., Cary, North Carolina) to analyze the collected data. Simple proportions and medians were generated to describe the frequencies with which symptoms were reported, symptom duration, and the effects of symptoms on daily activities. We used the *t*-test to determine the statistical significance of differences in the means of continuous data and the Mantel–Haenszel chi-square test to determine the statistical significance of differences in proportions. We calculated 95% CIs of proportions using Wald methods. Because some individuals had continuing symptoms at the time of the interview, we examined the relationship between age and duration of illness using proportional hazards modeling; illness durations in persons with continuing symptoms were considered to be censored. We assessed the proportional hazards assumptions by introducing a time-dependent covariate—the interaction between age and time—to test whether there was a systematic increase or decrease in the effect of age across time. We assessed possible confounding due to hospitalization and underlying illness by including terms in the proportional hazards regression model.

RESULTS

In 2002, 331 West Nile virus infections reported in Illinois residents met the case definition for West Nile fever. Of these, 140 persons (42%) lived in jurisdictions of participating local health departments and were eligible for

Table 1. **Characteristics of Respondents and Nonrespondents***

Characteristic	Respondents (*n* = 98), *n* (%)	Nonrespondents (*n* = 233), *n* (%)
Age		
<25 y	4 (4)	13 (6)
25–44 y	28 (29)	59 (25)
45–64 y	43 (44)	101 (43)
≥65 y	23 (23)	60 (26)
Women	52 (53)	123 (53)
Race or ethnicity		NA
White	88 (90)	
Black	5 (5)	
Hispanic	4 (4)	
Not given	1 (1)	
Reported underlying illness		NA
Hypertension	29 (30)	
Diabetes	12 (12)	
Heart disease	11 (11)	
Cancer	5 (5)	
Kidney disease	2 (2)	
Liver disease	1 (1)	
Organ transplant	1 (1)	
Other immunosuppression	1 (1)	

* $P > 0.2$ for all comparisons (Mantel–Haenszel chi-square test). NA = not available.

inclusion in the study. No information was obtained on 191 individuals (58%) who lived in jurisdictions of nonparticipating health departments. Of the 140 persons eligible for inclusion, 29 were not interviewed because of incorrect telephone numbers; 9 could not be reached in at least 3 attempts; 3 were unwilling or unable to participate; and 1, who was 3 years of age, was not evaluated. The remaining 98 patients, who did not report having a lumbar puncture and had no record of submission of cerebrospinal fluid for laboratory testing, were enrolled in the study.

Interviews were conducted from 18 December 2002 to 27 April 2003, a median of 168 days (range, 84 to 254 days) after illness onset. Thirty-eight of 98 patients (39%) had ongoing symptoms at the time of the interview. Questionnaire responses were missing for fever duration in 4 patients, for presence of fever in 1 patient, for duration of muscle weakness in 1 patient, and for duration of rash in 2 patients. Patients with missing responses were not included in the calculated proportions. One patient had unclear information about onset of illness, and date of laboratory diagnosis was used in place of illness onset date. In addition, 1 patient had unclear duration information and was excluded from the analysis of illness duration. The respondents were not significantly different in terms of sex and age from nonparticipating Illinois patients with West Nile fever (**Table 1**).

Laboratory Confirmation

Standard laboratory methods were used to identify evidence of West Nile virus infection in the serum specimens of the 98 enrolled patients with West Nile fever. The Illinois Department of Public Health laboratory performed West Nile virus–specific IgM antibody-capture enzyme-linked immunosorbent assay (20) on at least 1 serum sample for 93 of the 98 patients. This assay was also used to identify 2 case-patients at Focus Laboratories (Cypress, California) and 1 case-patient at the California Department of Public Health Laboratory. Diagnosis was confirmed in 2 case-patients by using real-time reverse transcriptase polymerase chain reaction on serum specimens (American Medical Laboratories, Chantilly, Virginia) (21).

Associated Symptoms

The most frequently reported and longest-lasting symptom was fatigue (reported by 94 respondents, lasting a median of 36 days) (**Table 2**). In addition to fatigue, more than half of the respondents reported fever, headache, muscle pain or aches, muscle weakness, rash, neck pain or stiffness, and difficulty concentrating. After fatigue, muscle weakness had the longest reported median duration (28 days), and 83% of the respondents with muscle weakness reported a duration longer than 7 days. Eight symptoms had a median duration longer than 7 days. Sore throat, runny nose, cough, and shortness of breath were each reported by 20 or fewer respondents.

Thirty respondents reported hospitalization (median length of stay, 5 days [range, 1 to 56 days]) (**Table 3**). Rates of hospitalization differed by age group: 3% (1 of 32) among those 44 years of age or younger, 26% (11 of 43) among those 45 to 64 years of age, and 78% (18 of 23) among those 65 years of age or older. The 68 respondents who were not hospitalized were seen in an outpatient setting. Thirty-six respondents reported having been prescribed medication, and 9 reported receiving physical or occupational therapy. Of 72 respondents who attended school or work at the time of onset, 57 (79%) missed days because of their illnesses (median duration of absence, 10 days [range, 1 day to >3 months]). Eighty-nine respondents reported reduction in their normal out-of-home activities (for example, shopping, yard work, or errands), and 82 reported limitations in their household activities (for example, cooking, cleaning, and dressing) as a result of their illnesses. Forty-seven respondents reported difficulty walking because of their illnesses, and of the 76 respondents who normally exercised, 69 (91%) reduced the amount they exercised because of their illnesses.

Eighty-nine respondents reported that it took more than 7 days (median duration, 60 days) for their health to return to normal. Duration of illness, as measured by the time needed for complete resolution, did not vary significantly by age measured as a continuous variable or categorized as a dichotomous variable (age <65 years vs. age ≥65 years). When terms for hospitalization and underlying illness were included in the Cox proportional hazards regression model, the statistical significance of the term for age did not change. That is, duration of illness was not associated with age, even when we controlled for hospitalization and underlying illness.

Table 2. **Self-Reported Illness Outcomes of the 98 Respondents with West Nile Fever**

Outcome	Total Patients, *n (%)* [95% CI]	Patients Reporting Duration, *n (%)**		Median Duration, *d*
		>7 Days	>30 Days	
Symptom†				
Fatigue	94 (96 [90–99])	77 (82)	47 (50)	36
Fever	79 (81 [72–87])	22 (28)	2 (3)	5
Headache	70 (71 [62–79])	40 (57)	8 (11)	10
Muscle pain or aches	61 (62 [52–71])	37 (61)	13 (21)	14
Muscle weakness	60 (61 [51–70])	50 (83)	24 (40)	28
Rash	56 (57 [47–66])	12 (21)	1 (2)	7
Neck pain or stiffness	54 (55 [45–65])	31 (57)	11 (20)	12
Difficulty concentrating	52 (53 [43–63])	34 (65)	13 (25)	14
Joint pain or aches	36 (37 [28–47])	20 (56)	9 (25)	14
Vomiting	27 (28 [20–37])	4 (15)	0 (0)	3
Diarrhea	26 (27 [19–36])	6 (23)	1 (4)	5
Sensitivity to light	21 (21 [14–31])	12 (57)	2 (10)	14
Medical care				
Hospitalization	30 (31 [22–40])	12 (40)	1 (3)	5
Prescribed medication	36 (37 [28–47])			
Physical or occupational therapy	9 (9 [5–17])			
Lifestyle impact				
Missed work or school‡	57 (79 [68–87])	33 (58)	4 (7)	10
Household activities limited	82 (84 [75–90])			
Outside-of-home activities limited	89 (91 [83–95])			
Exercise reduced§	69 (91 [82–96])			
Difficulty walking	47 (48 [38–58])			
Time required to get "back to normal"	–	89 (91)	62 (63)	60

* Duration figures exclude patients who did not report the outcome. Percentages were calculated as the number of patients reporting outcome duration >7 days (or >30 days) divided by the total number of patients reporting the outcome, except for time required to get "back to normal," for which percentages are based on the total number of patients. Responses of "do not remember" or no response were excluded for the following symptoms: duration of fever ($n = 4$), duration of rash ($n = 2$), presence of fever ($n = 1$), and duration of muscle weakness ($n = 1$).
† Symptoms reported by ≤20 patients are not shown.
‡ Responses limited to 72 patients reporting working or attending school outside the home.
§ Responses limited to 76 patients reporting that they normally exercise.

Additional Patient Information

The finding that nearly one third of the sample was hospitalized triggered additional scrutiny of this subgroup. The surveillance system relied in part on reports of clinical diagnosis from providers; because this rate of hospitalization seemed unusually high, we used additional measures to verify the accuracy of classification within the sample. We retrieved information from hospital charts about admission diagnoses, discharge diagnoses, and performance of procedures for 12 of the 30 hospitalized patients. None had admission or discharge diagnoses of meningitis or encephalitis or any record of lumbar puncture during their hospital stay. A descriptive comparison of hospitalized and nonhospitalized patients is shown in **Table 3**.

Similarly, 9 of the 98 patients in our sample reported receiving physical or occupational therapy, a treatment usually prescribed for patients with acute flaccid paralysis. To address the possibility that patients with acute flaccid paralysis were misclassified as having West Nile fever and erroneously included in our sample, we collected and reviewed information from the hospital charts about admission and discharge diagnoses for 5 of the 9 patients reporting physical or occupational therapy. None of these 5 patients had admission or discharge information that suggested the acute, progressive, asymmetric weakness typical of acute flaccid paralysis.

DISCUSSION

Previous characterizations of West Nile fever have generally described it as a mild, acute syndrome lasting 3 to 6 days and consisting of fever, malaise, headache, myalgia, nausea, vomiting, and rash (10). This information is largely anecdotal because systematic follow-up of patients with West Nile fever has not previously been done. Our findings indicate that West Nile fever can often be more severe than previously recognized. In the patients we interviewed, the median time needed to recover to a point considered "back to normal" was 60 days. In addition, approximately one third of the patients in our study required hospitalization and half could not attend school or work for 10 days. This degree of severity, as represented by length of illness, did not significantly differ among age groups when we controlled for underlying illness and for hospitalization. Time required for recovery was similar in younger respondents and in older respondents. The severity of illness demonstrated in our report might be due to postulated changes in the epidemiologic characteristics of West Nile virus infection. Previous researchers have suggested that slight genetic differences in the virus itself might account for the higher morbidity and mortality seen in recent outbreaks of West Nile virus infection compared with earlier outbreaks (11, 14).

Table 3. **Characteristics and Self-Reported Illness Outcomes of Hospitalized and Nonhospitalized Patients with West Nile Fever***

Variable	Hospitalized Patients (n = 30)	Nonhospitalized Patients (n = 68)
Women, *n (%)*†	18 (60)	34 (50)
Mean age, *y*‡	64.7	45.7
Symptom, *n (%)*§		
Fatigue	27 (90 [74–97])	67 (99 [91–100])
Fever	28 (93 [78–99])	51 (76 [63–84])
Headache	15 (50 [33–67])	55 (81 [70–89])
Muscle pain or aches	15 (50 [33–67])	46 (68 [56–78])
Muscle weakness	21 (70 [52–83])	39 (57 [46–68])
Rash	7 (23 [12–41])	49 (72 [60–81])
Neck pain or stiffness	13 (43 [27–61])	41 (60 [48–71])
Difficulty concentrating	18 (60 [42–75])	34 (50 [38–62])
Joint pain or aches	8 (27 [14–45])	28 (41 [30–53])
Vomiting	13 (43 [27–61])	14 (21 [13–32])
Diarrhea	10 (33 [19–51])	16 (24 [15–35])
Sensitivity to light	5 (17 [7–34])	16 (24 [15–35])
Lifestyle impact, *n (%)*		
Missed work or school‖	10 (91 [60–100])	47 (77 [65–86])
Household activities limited	26 (87 [70–95])	56 (82 [71–90])
Outside-of-home activities limited	28 (93 [78–99])	61 (90 [80–95])
Exercise reduced¶	21 (91 [72–99])	48 (91 [79–96])
Difficulty walking**	20 (67 [49–81])	27 (40 [29–52])
Not "back to normal" at 30 d	25 (83 [66–93])	36 (53 [41–64])

* Values in square brackets are 95% CIs.
† $P > 0.2$ (Mantel–Haenszel chi-square test).
‡ $P < 0.001$ (t-test).
§ Symptoms reported by ≤20 patients are not shown. Presence of fever ($n = 1$) was excluded because of lack of response.
‖ Responses limited to 11 hospitalized and 61 nonhospitalized patients reporting working or attending school outside the home.
¶ Responses limited to 23 hospitalized patients and 53 nonhospitalized patients reporting that they normally exercise.
** One nonhospitalized patient reported preexisting inability to walk and was excluded.

Our findings have several limitations. First, interviews were conducted several months after the outbreak, and recall bias could have influenced responses. Second, in persons with continuing symptoms, duration of illness was calculated as the time between the date of illness onset and the date of interview and could have resulted in an underestimate of actual duration. Third, the differentiation of West Nile fever from West Nile meningoencephalitis relies on the provider's clinical assessment. Although we limited misclassification by verifying that no patient had a lumbar puncture or had cerebrospinal fluid submitted for laboratory analysis, the clinical diagnosis of attending physicians was the ultimate determinant, and some degree of misclassification could have been present.

Because 2002 was the first year that West Nile virus infection in humans was identified in Illinois, laboratory evidence of human infection was assumed to be due to acute illness rather than past exposure. Testing for West Nile virus infection was widespread during the well-publicized 2002 epidemic, raising the possibility that incidental and asymptomatic West Nile virus infections were uncovered in patients with unrelated but serious disease processes. In this situation, some adverse health outcomes could have been spuriously attributed to West Nile fever.

Because our investigation was limited to patients who actively sought medical care, diagnostic access bias might have affected the composition of the overall sample of patients with West Nile fever from which our smaller sample was drawn. In addition, because persons with milder illnesses might have been less likely to seek medical care and therefore less likely to be tested, our study probably reflects the more severe end of the spectrum of West Nile virus disease.

Recognition of West Nile fever as a syndrome associated with substantial morbidity also suggests that the reporting of human West Nile virus disease should not be limited to West Nile meningoencephalitis. West Nile fever is currently not a reportable illness in most jurisdictions and is therefore not typically included in West Nile virus surveillance. Mandatory reporting of West Nile fever in addition to meningoencephalitis could enhance surveillance and allow more accurate and timely recognition of the geographic distribution of human West Nile virus infection, thereby informing public health interventions such as the "adulticiding" of mosquitoes. Furthermore, routine reporting of West Nile fever could allow a more thorough accounting of the overall cost and impact of West Nile virus infection in humans. As the geographic distribution of West Nile virus widens, the need for much more information about the symptoms and sequelae of infection increases. Additional studies of patients with West Nile fever are needed to more accurately assess the public health impact of this large but poorly studied subset of West Nile virus infection.

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