Demographic and Clinical Factors Associated with Persistent Symptoms after West Nile Virus Infection

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Abstract. Prognosis varies among persons with West Nile virus (WNV) infection, but the most important factors associated with persistent symptoms are not clear. In this cross-sectional study, 265 persons with symptomatic WNV infection during 2006–2008 completed a survey a mean of 7.7 months after diagnosis. We determined the association of demographic and clinical characteristics to the most common symptoms. Of 214 persons infected ≥ 6 months, 53% reported one or more persistent symptoms, including fatigue, muscle aches, decreased activity, difficulty with memory, and difficulty concentrating. Persons with neuroinvasive disease, hypertension, or diabetes were significantly more likely to report persistent symptoms, whereas age, sex, and time since infection were not associated with persistent symptoms. In conclusion, persistent symptoms persisted in most persons for more than six months after symptomatic WNV infection. Improved strategies for prevention and treatment are needed.

INTRODUCTION

West Nile virus (WNV) was introduced into North America in 1999 and has now become endemic in the United States with outbreaks each summer and fall.¹ The virus initially spread throughout the eastern parts of the United States and gradually moved westward. In 2008, human WNV cases were reported in 45 states.² Most human WNV infections are asymptomatic.³ Among persons with clinical illness, the features of acute illness range from uncomplicated West Nile fever to neuroinvasive conditions such as meningitis, encephalitis, and acute flaccid paralysis.

After acute illness, many persons recover to their previous state of health. However, 20–50% of persons with clinically diagnosed WNV infection report persistent sequelae including somatic symptoms, cognitive and memory problems, depression, and balance and mobility difficulties.^{4–14} Conclusions regarding the duration of such symptoms have been somewhat inconsistent, with several studies reporting persistent symptoms at 6 and 12 months after the acute infection,^{4–6,8,10,12,13} whereas a recent study concluded that nearly all persons with WNV will recover full function within one year after infection.¹³

The reasons for variation in clinical outcomes remain relatively unknown. Previous studies suggest that older age, neuroinvasive disease, medical comorbidities, and more recent infection are associated with more clinically severe outcomes.^{4–14} In many of these studies, the clinical outcome was limited to one or two specific signs and symptoms (e.g., neurologic dysfunction, memory test, presence of specific symptom). Our study objectives were to determine the prevalence of long-term symptoms among persons diagnosed with WNV during 2006–2008 and to determine the association of age, sex, neuroinvasive disease status, hypertension or diabetes, and time since acute infection on the most common individual symptoms.

MATERIALS AND METHODS

Participants were recruited from persons with WNV who were reported to two of the seven district health departments in Idaho during 2006–2008. All persons were classified as having either confirmed (95%) or probable (5%) WNV infections according to standard case definitions that include a positive IgM test result for WNV and a compatible clinical syndrome.² In 2006, Idaho had the greatest number of WNV infections in the United States, and the state continued to be among the top 10 in terms of total reported cases in 2007–2008.¹⁵ As part of a larger study designed to study the immunology of WNV infection,¹⁶ health department staff mailed questionnaires to 407 persons with a newly reported diagnosis of WNV infection; 280 persons returned them (response = 69%). We excluded 3 persons whose surveys included more than 50% missing data, and 12 persons who were asymptomatic at baseline diagnosis. Compared with all persons with WNV who were reported to the two district health departments during this period, the survey respondents were slightly more likely to be female (60% versus 51%), but similar in terms of the proportion with neuroinvasive disease (21% versus 21%). All study procedures were approved by institutional review boards at participating universities and the two local health departments.

The questionnaires included items that assessed demographic characteristics, presence of diabetes or hypertension, initial severity of illness (e.g., hospitalization), and impact on work. Time since acute infection was calculated as the number of days from the date of disease onset (self-report) to the date that the questionnaire was completed and rounded to the nearest month. Collaborators at the district health departments provided information on neuroinvasive disease status based on epidemiologic investigation and defined according to standardized case definitions.²

Symptom Measures. The questionnaire assessed 17 prominent symptoms that have been associated with WNV infection.^{8,17–20} Specifically, persons were asked to report if they “had any of the following symptoms with your West Nile virus infection”. For each symptom reported, persons were asked to “indicate how severe the symptom was (options low/mild, medium, or severe), and “how long did the symptom last”, (options = 1–2 days,

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3–7 days, 1–2 weeks, and >2 weeks, and still have it). Using these distinctions, we categorized each symptom as being persistent if participants rated it as “still have it” and the severity was rated as moderate or severe. Participants reporting only mild persistent symptoms were categorized as no longer exhibiting the symptom.

Statistical Analyses. We conducted descriptive analyses to describe the study sample and to present the proportion of persons with symptoms among those who completed the survey ≥ 6 months and ≥ 9 months after the initial infection. Bivariate analyses were used to determine whether individual signs or symptoms varied by sex or baseline neuroinvasive status. Multivariate logistic regression analyses were then conducted to determine the association between the clinical and demographic variables of interest and six of the most commonly reported symptoms. Variables in the models included age (continuous per year), neuroinvasive disease at illness onset (yes versus no), sex, presence of hypertension or diabetes (yes or no), and time since acute infection (in months). All analyses were conducted by using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

The mean age of the cohort was 52 years (range, 18–88 years), 159 (60%) were female, and 242 (92%) were white (Table 1). Most participants were infected in 2006 ($n = 211$), followed by 2007 ($n = 36$) and 2008 ($n = 5$), which is proportional to the overall numbers of WNV case numbers in Idaho during these years. Most persons completed the questionnaire 6–9 months after acute infection (mean $\pm$ SD = 7.7 ± 2.7 months). Thirty percent had hypertension (27%) and/or diabetes (11%). At the time of acute illness, 53 persons (20%) had neuroinvasive disease, and 208 (80%) had West Nile fever. Of those 53 persons with neuroinvasive disease, 83% were hospitalized at least one night and 32% required post-hospitalization care in a nursing home. Additional details regarding the acute health conditions, use of health resources, and impact of WNV infection on work are shown in Table 1.

Symptoms. More than half (53%) of persons reported one or more persistent symptoms that were rated as moderate or severe in severity. The most commonly reported persistent symptoms were fatigue (34%), decreased activity (27%), difficulty with memory (25%), difficulty concentrating (23%), muscle aches (19%), weakness (19%), balance problems (18%), and vision change (17%). The percentage of persons reporting persistent symptoms was similar in persons completing the survey at least 6 months after diagnosis ($n = 214$) and those persons with at least 9 months of follow-up ($n = 86$) is shown in Table 2. As expected, persons with neuroinvasive disease at onset had a significantly higher prevalence for most signs and symptoms (Table 2).

Multivariate Analyses. Results from multivariable analyses conducted to identify clinical and demographic variables that were independently associated with having one of the six most common symptoms are shown in Table 3. Neuroinvasive disease was significantly associated with an increased likelihood of persistent fatigue, muscle aches, decreased activity, and balance problems, but had relatively little independent impact on memory or concentration problems. Persons having hypertension or diabetes were also significantly more likely to have persistent symptoms. In contrast, age, sex, and time since

TABLE 1
Characteristics of 265 persons with West Nile virus infection, Idaho, 2006–2008

Characteristics	No.	%
Age group (years)		
< 40	50	19
40–49	65	25
50–64	96	37
≥ 65	50	19
Age (years, mean $\pm$ SD)	51.7 $\pm$ 14.5	
Sex		
Male	106	40
Female	159	60
Race		
White	242	92
Hispanic	11	4
Black	7	3
Other	4	2
Comorbid health conditions		
Hypertension	72	27
Diabetes	29	11
Hypertension or diabetes	80	30
Year infected		
2006	211	84
2007	36	14
2008	5	2
Time since acute infection (months)		
< 6	31	13
6–9	127	52
≥ 9	86	35
Time since acute infection (months, mean $\pm$ SD)	7.7 $\pm$ 2.7	
Recruitment location		
Southwest Health District	104	39
Central Health District	161	61
Acute illness		
West Nile fever	208	80
Neuroinvasive disease		
Encephalitis	8	3
Meningitis	14	5
Meningoencephalitis	10	4
Other	21	8
Site of diagnosis		
Doctor's office	165	63
Emergency department	38	14
Hospital	59	22
Not sure	1	0.4
Spinal tap performed (self-report)	49	19
Hospitalized one night	65	25
Among those with neuroinvasive disease	44/53	83
Among those without neuroinvasive disease	19/208	9
Required nursing home	19	7
Among those with neuroinvasive disease	17/53	32
Among those without neuroinvasive disease	2/208	1
Working before infection	174	66
Missed ≥ 2 weeks of work	63/174	36
Stopped working or works less	31/174	18

infection were each statistically significantly associated with only one or two of the chronic symptoms after adjusting for neuroinvasive disease and hypertension/diabetes (Table 3).

DISCUSSION

This report presents findings from a cohort of more than 200 persons with a diagnosis of WNV infection during 2006–2008. The findings suggest that at least half of persons with clinically diagnosed WNV infection will continue to have persistent symptoms 6–9 months after diagnosis. The most common persistent symptoms associated with WNV included physical symptoms (fatigue, muscle aches, weakness, headache), cognitive

TABLE 2

Persistent symptoms among 265 persons with West Nile Virus infection according to time since initial infection and baseline neuroinvasive disease status, Idaho, 2006–2008

Symptoms	Overall (n = 265) (%)	≥ 6 Months after infection (n = 214) (%)	≥ 9 Months after infection (n = 86) (%)	Neuroinvasive disease		P*
				Yes (n = 53)	No (n = 208)	
Fatigue (felt tired)	34	34	42	48	31	0.02
Decreased activity	27	25	33	51	20	< 0.01
Difficulty with memory	25	26	34	35	22	0.07
Difficulty concentrating	23	23	34	29	21	0.25
Muscle aches (sore all over)	19	17	22	31	16	0.01
Weakness (felt weak all over)	19	17	21	36	15	< 0.01
Vision change	17	17	20	31	14	< 0.01
Balance problems	18	16	21	39	12	< 0.01
Headache	16	13	15	21	15	0.28
Irritability	13	12	17	12	14	0.68
Pain or “pins and needles”	13	11	17	24	10	< 0.01
Diarrhea or intestinal problem	10	10	13	15	8	0.13
Tremor (shaking)	7	6	7	17	4	< 0.01
Bladder or urine problem	5	4	4	11	4	0.03
Loss of appetite	5	5	7	10	4	0.14
Fever or chills	4	2	4	6	3	0.43
Nausea or vomiting	3	1	2	4	2	0.63
Any persistent symptom	55	53	63	71.7	50	< 0.01

* Statistical comparisons by neuroinvasive disease status.

symptoms (difficulty with memory and concentration), and functional sequelae (decreased activity, vision and balance problems). These findings are consistent with symptoms reported in other studies,^{4–13,17–20} some of which also provide objective evidence of impaired motor speed and manual dexterity¹⁰ and impaired concentration.²¹

One of the primary study objectives was to determine whether various clinical or demographic characteristics were associated with an increase in symptom burden. As in many other studies, persons with neuroinvasive disease were most likely to report persistent signs and symptoms.^{10,20,21} However, persons with West Nile fever also report a significant symptom burden, with nearly half of the persons in our sample (49%) reporting at least one chronic symptom that they attributed to the initial infection. Comorbid illness such as hypertension and diabetes has been associated with increased severity of acute WNV illness and with increased persistence of symptoms.^{11,22} Although most previous studies report that older age is associated with worse outcomes, particularly in those ≥ 65 years of age,^{4,6,8,9} we found that age was less strongly associated with signs and symptoms after adjustment for other factors including neuroinvasive disease and co-morbid illness such as hypertension and diabetes. The results provide little evidence that symptoms were less common over time, although nearly all of our participants completed the survey within 12 months of infection and a longer follow-up time would be needed to make more definitive conclusions. Several reports provide evidence of continued symptoms after 12 months,^{6,9} whereas

a recent study of 156 persons with WNV in Canada found that nearly all persons returned to their baseline state of health within 12 months.¹³

Our study includes one of the larger cohorts of persons with WNV infection to date, with an excellent response rate and data collected over several years of the epidemic. However, several limitations should be noted. The study only includes persons with diagnosed WNV infection, who likely represent persons with worse disease at baseline compared with mild and asymptomatic cases that went unidentified. The lack of a comparison group is also a limitation. Although we specifically asked persons about symptoms caused by their WNV infection, it is possible they had symptoms before infection or that the symptoms have resulted from a different reason. Sampling bias is possible if persons who responded to the survey were not typical of the overall population of persons. Although study respondents were more likely to be female than the overall population of diagnosed persons with WNV, the proportion with neuroinvasive disease was the same in the sample and the overall population.

In summary, this study found that at least half of persons with symptomatic WNV infection report persistent symptoms that are rated as moderate or severe in quality for at least six months after the initial infection. Persons with neuroinvasive disease or who had diabetes or hypertension were most likely to have persistent symptoms, although persons with West Nile fever also demonstrated a significant symptom burden.⁷ A greater understanding of the reasons for such diversity in

TABLE 3

Multivariate analysis of factors associated with persistence of individual symptoms in persons infected with West Nile virus, Idaho, 2006–2008*

Factors	Signs and symptoms					
	Fatigue	Muscle aches	Decreased activity	Difficulty with memory	Difficulty concentrating	Balance problems
Neuroinvasive disease	1.5 (0.7–3.1)	2.1 (0.9–4.8)	3.3 (1.5–6.9)	1.2 (0.6–2.6)	1.0 (0.4–2.2)	2.9 (1.3–6.7)
Age (per year)	1.02 (0.9–1.04)	1.0 (0.99–1.04)	1.03 (1.00–1.05)	1.01 (0.99–1.03)	1.01 (0.99–1.04)	1.03 (1.0–1.06)
Female sex	2.0 (1.0–3.7)	1.3 (0.6–2.7)	1.6 (0.8–3.3)	1.4 (0.7–2.7)	1.7 (0.9–3.4)	2.1 (0.9–4.7)
Hypertension or diabetes	2.6 (1.3–5.0)	2.1 (1.0–4.6)	2.8 (1.4–5.6)	1.9 (0.9–3.8)	1.7 (0.8–3.6)	2.5 (1.1–5.6)
Time since infection (months)	1.1 (0.98–1.2)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.1 (0.9–1.2)	1.1 (0.99–1.2)	1.0 (0.8–1.1)

* Values are odds ratios and 95% confidence intervals. Values in **bold** are statistically significant ($P < 0.05$).

persistent health problems associated with West Nile virus will help to better define the overall burden of disease and help to guide prognosis discussions, treatment options, vaccine development, and other prevention strategies.

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