

One-Year Sequelae in Patients with West Nile Virus Encephalitis and Meningitis in Louisiana

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West Nile Virus (WNV) infection can be severe and complicated by neuroinvasive disease, such as meningitis and encephalitis. Not much is known about the one-year sequelae following a complicated WNV infection. From July to December 2002, the first large outbreak of WNV in the Southern United States occurred in Louisiana. This epidemic resulted in 329 cases of WNV infection including 125 cases of West Nile fever and 204 cases complicated by meningitis and encephalitis. One year later, during the fall of 2003, a telephone survey was conducted to understand the one-year effects of severe WNV infections. WNV case fatality rate was 19.6%. Death certificates of all the deceased were reviewed to verify the mortality rate from WNV infection. The telephone survey revealed that one-year sequelae from severe WNV infections are common and can affect the body and mind. In addition, it can change a person's perception of the state of their health.

West Nile Virus (WNV) was first identified in 1937 in the West Nile district of Uganda.¹ In the past, the course of WNV infection was benign, but only since 1957 in Israel did the virulence worsen with the first natural cases of encephalitis.² The long-term sequelae of severe WNV infections are not very well understood, even for the European WNV epidemics of the late 1990s. In 1999, WNV was recognized for the first time in the western hemisphere at New York,³ but the sequelae have only been described up to eight months post-infection.⁴ Recent surveillance data reveals that cases of human WNV infections have spread from the east coast across the continental United States to the west.⁵ As WNV becomes more widespread, it will be important for clinicians to understand the long-term consequences of severe WNV infections.

A WNV epidemic occurred in Louisiana from July to December 2002. During this epidemic, 329 cases of WNV infection were identified. Among the cases, 204 cases were complicated by neuroinvasive disease, such as meningitis and encephalitis, and 125 cases were the more mild and indolent form, West Nile fever.⁶ Serology was used to confirm WNV infection for all suspected WNV cases.⁷ The number of cases of WNV is most likely an underestimate, since it is likely that some of the people with the more indolent course of WNV infection did not recognize the need to present to a physician for evaluation and therefore were not diagnosed. This was the first large outbreak of WNV in the southern United States.

During the 2003 regular session of the Senate of the Legislature of Louisiana, Senate Resolution Number 103 was passed which requested the Department of Health and Hospitals to study the impact of West Nile virus on survivors of the illness.⁸ As part of the regular mandated activities of the Office of Public Health (OPH), this survey was performed. The primary objective of this paper is to describe the one-year physical and psychological morbidity symptoms in a population infected by WNV

and complicated by meningitis and encephalitis. Secondary objectives are to compare the severity of the disease morbidity with regards to severity of the initial infection and demographic characteristics, and to find the mortality rate due to WNV infection.

POPULATION & METHODS

As the WNV epidemic was unfolding in 2002, a surveillance system was put in place to collect information into an Microsoft (MS) Access® database. In order to conduct a cross-sectional study one year after the acute WNV infection, information from this database was used to contact this cohort of patients who had developed WNV encephalitis or meningitis.

From the database, all 204 cases that were previously diagnosed with central nervous system (CNS) involvement were selected. One hundred twenty-seven people completed the survey and will be referred to as "responders."

Case Definition: Cases were classified as meningitis, encephalitis, or flaccid paralysis based on the following case definition:

All cases must have evidence of acute viral infection of the central nervous system including one or more of the following⁹:

- fever >38°C (>100°F) or hypothermia <35°C.
- an abnormal cerebrospinal fluid (CSF) profile suggesting a viral etiology: a negative bacterial stain and culture with pleocytosis (WBC ≥ 5 cells/mm³) or elevated protein level (>40 mg/dl).

All cases must have evidence of recent West Nile viral infection, which was confirmed by tests for specific WNV antibodies¹⁰⁻¹²:

- in acute phase serum by IgM antibody capture enzyme linked immuno-sorbent assay (MAC-ELISA) confirmed by plaque neutralization assay.

· in acute phase CSF by MAC-ELISA
The clinical classification was based on the following criteria:⁹

Encephalitis: Evidence of CNS involvement such as altered mental status (altered level of consciousness, confusion, agitation, disorientation, or lethargy) or other cortical signs (cranial nerve palsies, paresis or paralysis, Parkinsonian signs, tremors, ataxia, or convulsions).

Meningitis: Clinical signs of meningeal inflammation including nuchal rigidity, Kernig's or Brudzinski's sign, photophobia or phonophobia.

Acute Flaccid Paralysis (AFP): Acute onset of limb weakness with marked progression over 48 hours and at least two of the following:

- areflexia/hyporeflexia of affected limb(s)
- absence of pain, paresthesia, or numbness in affected limb(s)
- electrodiagnostic studies consistent with an anterior horn cell pathological process
- spinal-cord magnetic-resonance imaging documenting an abnormally increased signal in the anterior gray matter.

The diagnosis of AFP took precedence in cases that also had symptoms and/or signs of encephalitis or meningitis.

Mortality: For the people who were reported to be dead following WNV infection, death certificates were reviewed to confirm the mortality and to clarify whether death was a result of the WNV infection.

Telephone Survey: A standard semi-structured telephone survey was conducted from September 11, 2003 to October 21, 2003 to collect information on morbidity. With respect to residual symptoms, responders were instructed to provide information only on symptoms that may have lingered since the time of their WNV infection. To assess for changes in functional status, respondents were asked about their hobbies and occupations at the time of their infection and then at the time of the interview. To get a sense of the severity of morbidity, respondents were asked to list the number of hospitalizations they have had since the time of their WNV infection, the admitting diagnosis, and the admission date. Each patient may have had multiple hospitalizations following the acute WNV infection period.

Analysis: The data was entered into an MS Access[®] database and analyzed using Epi Info 2002 and MS Excel. Statistical associations are expressed with odds ratios (OR) and 95% confidence intervals (CI) of the OR. Morbidity data was stratified by age, race, and gender.

RESULTS

Out of 204 patients with neuroinvasive WNV disease, 27 patients were already known to be deceased before the initiation of the one-year follow-up survey. Among the 27 already deceased, 25 deaths were due to complica-

Table 1. Demographic Characteristics of Responders versus Non-responders

	% Responders n=127	% Non-responders n=45
Age Groups (years)		
0-29	19.7	17.8
30-44	18.1	20.0
45-59	22.8	28.9
60-74	22.8	11.1
75+	16.5	22.2
	chi-square=3.53, p=0.47	
Gender	n=127	n=45
Male	45.7	55.6
Female	54.3	44.4
	OR=1.49, 95%CI=(0.17, 3.12), p=0.26	
Race	n=108	n=39
Black	27.8	51.3
White	72.2	48.7
	OR=2.74, 95%CI=(1.20, 6.25), p=0.008	
Clinical Status	n=118	n=45
Meningitis	44.9	24.4
Encephalitis	55.1	75.6
	OR=0.40, 95%CI=(0.17, 0.91), p=0.02	

tions of WNV, and 2 deaths were due to other causes. Of the 177 remaining patients to be interviewed, 127 completed the survey, 5 were deceased, and 45 did not complete the survey. Of the 45 that did not complete the survey, 4 refused, and 41 could not be reached. Of the 177 cases not deceased, follow-up was obtained for 74.6% of the cases; for the 131 people contacted by telephone, the response rate, or the proportion who completed a survey among those who were contacted, was 96.9%.

Responders Versus Non-responders

When comparing people who responded and people who did not, the distribution of people among five age groups (0-29, 30-44, 45-59, 60-74, 75+) showed no significant difference ($p = 0.47$), and there was also no significant difference with regards to gender (male/female OR = 1.49; CI = 0.17-3.12). People who responded had a mean age of 51.82 years ($\sigma = 1.83$). People who were non-responders had a mean age of 50.11 years ($\sigma = 3.04$).

While responders were not different from non-responders with respect to age or gender, there were differences in race and clinical classification. With respect to race, 80.4% of the whites were and 60.0% of the blacks were responders (OR = 2.74; CI = 1.20-6.25). In addition, 82.8% of patients with meningitis and 65.7% of patients with encephalitis were responders to the survey (OR = 0.4; CI = 0.17-0.91). This difference does persist after stratification by age group (0-44 and 45+ age groups) with a summary Mantel-Haenszel, $p = 0.02$. A more detailed comparison of responders versus non-responders is presented in Table 1.

Table 2. Characteristics of Cases Complicated by Meningitis versus Encephalitis

	% Encephalitis n=65	% Meningitis n=53
Age Groups (years)		
0-29	10.8	34.0
30-44	12.3	26.4
45-59	18.5	22.6
60-74	30.8	15.1
75+	27.7	1.9
	chi-square=25.88, p=0.00003	
Gender	n=65	n=53
Male	52.3	37.7
Female	47.7	62.3
	OR=0.55, 95%CI=(0.25, 1.23), p=0.12	
Race	n=57	n=44
Black	31.6	20.5
White	68.4	79.5
	OR=0.56, 95%CI=(0.20, 1.53), p=0.21	

Morbidity

The mean age for the people who developed meningitis was 40.55 years ($\sigma = 2.04$). For the people who developed encephalitis, the mean age was 58.20 years ($\sigma = 2.01$). A comparison of other demographic characteristics for patients with meningitis versus those with encephalitis is presented in Table 2.

Answers to whether the following remaining signs and symptoms persisted were obtained from patients who had suffered from WNV encephalitis and meningitis: Weakness, incontinence, chronic headache, joint pain, muscle ache, paresthesias, tremors, altered mental status, confusion, slurred speech, seizures, vision problems, hearing difficulties, balance difficulties, chronic fatigue, depression, anxiety, hyperactivity, emotional lability, aggressivity, agitation and panic attacks. To assess whether severity of neuroinvasive disease was a factor in level of morbidity, responders who had suffered from meningitis were compared to responders who suffered from encephalitis.

Out of 127 responders, nine reported no one-year sequelae, and seven only had one sequela. Twenty-eight reported more than 15 sequelae. The frequencies of reported symptoms among the the population with neuroinvasive disease who reported at least one symptom are presented in Table 3.

There were no significant differences between those with meningitis and encephalitis except for presence of chronic headaches (21.5% among encephalitis patients, 43.4% among meningitis patients, OR = 0.36, CI = 0.15-0.86) and auditory impairment (36.9% among those with encephalitis, 13.2% among those with meningitis, OR = 3.85, CI = 1.39-11.05).

Although there was not a statistically significant relationship between the following symptoms and the severity of WNV neuroinvasive disease, the following trends were observed: seizures (10.8% among encephali-

Table 3. Frequency of symptoms among responders who reported at least one symptom.

Symptom	% of respondents n=118
Pains	
Chronic Headache	31.4
Joint Pain	46.6
Muscle Ache	49.2
Sensory	
Paresthesia	43.2
Tremor	35.6
Motor	
Weakness	50.0
Mental State	
Altered Mental Status	38.1
Confusion	36.4
Seizures	6.8
Coma	0.0
Other CNS	
Slurred Speech	17.8
Visual Impairment	43.2
Auditory Impairment	26.3
Balance Problems	41.5
Mood	
Depression	40.7
Anxiety	37.3
Hyperactivity	16.9
Emotional Lability	39.8
Aggressivity	33.9
Agitation	45.8
Panic Attack	20.3
Chronic Fatigue	54.2
Urinary Incontinence	18.6

tis patients, 1.9% among meningitis patients, OR = 6.28, $p = 0.06$ 1-tailed Fisher's Exact), balance difficulties (49.2% among those with encephalitis, 32.1% among those with meningitis, OR = 2.05, CI = 0.90-4.69).

A Mantel-Haenszel test weighted odds ratio (MH-OR) was calculated to take into account the effect of age on chronic headache association with meningitis. It showed no significant difference in each age stratum and a weighted MH-OR of 0.56 (CI = 0.21-1.48). The same test was used to test the association between auditory problems and encephalitis. There was a significant association between encephalitis and auditory impairment among those aged 45 years and older (OR = 6.88; CI = 1.31-47.96) but not among the younger age group aged 0 to 44 years (OR = 1.35; CI = 0.21-8.21), and the weighted MH-OR was 3.51 (CI = 1.12-10.17).

Hospitalizations

Twenty-nine percent of the responders had been hospitalized at least once after their initial hospitalization for West Nile infection. Of all the responders, 14% were re-admitted at least once for medical problems that were related to WNV infection, and 18.6% were re-admitted at least once for non-WNV related medical problems. Stratification by age group (0-44 years old) and (clinical severity (encephalitis versus meningitis) showed no significant relationship (MH-OR = 0.86, CI = 0.24-3.20) in hospitalization rates.

Functional Status

Twenty-four percent of the responders had changed jobs during the year after their West Nile infection. There was no significant difference ($p = 0.18$) between encephalitis cases (20.0%) and meningitis cases (28.3%) with respect to people changing jobs. Stratification by age group (0-44 years old) and clinical severity (encephalitis versus meningitis) also showed no significant difference (MH-OR = 0.89, CI = 0.33-2.44) with respect to occupational status.

Forty-nine percent of the responders changed their hobby or leisure activities within the year after the West Nile infection. With respect to changes in hobby, there was no significant difference ($p = 0.22$) between encephalitis cases (43.1%) and meningitis cases (32.1%). When stratifying the results by age, however, a significant difference was noted between hobby status and age (OR = 0.36, CI 0.15-0.84). With increasing age (age +45), there was increasing likelihood that a change in hobby occurred after WNV infection complicated by neuroinvasive disease.

Mortality

At the end of 2002, there were 27 deaths recorded among the encephalitis cases, 25 were attributed to WNV disease complications, 2 to other conditions. During the survey of the population that developed severe WNV complications, an additional 5 deaths were recorded, attributed to WNV. With a total of 30 deaths over cases (204 - 41 not contacted), the case fatality rate was 19.6% among those with neuroinvasive WNV disease over one year. The case fatality rate was 3% for age 0 to 44, 9% for the age group 45-59, 15% for those 60 to 74 and 39% for those 75 and older. The overall case fatality rate was not calculated because the total number of cases, 329, is most likely an underestimate, and calculation using this figure would not be accurate.

DISCUSSION

One year after they were infected with the West Nile Virus, the response rate to the telephone survey was high (97%) and people were open to this surveillance; the survey was well received.

The survey would only be marginally affected by the non-response of patients since there was no significant difference between responders and non-responders by age and gender. This was not the case for race, but previous studies in Louisiana have shown no significant difference in clinical severity of WNV infection by race. Perhaps race, which is associated with socioeconomic level, affected how permanent contact information, such as addresses and telephone numbers, existed in certain households. This, in turn, would affect the interviewer's ability to contact people, which would affect response rates among different populations.

West Nile infection used to result in mild indolent

symptoms and a fever, but since the 1950s, the severity of illness has worsened. Recent observations in Europe and New York City show a shift to disease that is more neuroinvasive. With this shift, it appears that one-year sequelae are associated with severe infection. The results of this study reveal that there are, indeed, important one-year sequelae associated with West Nile infection. The most common symptoms among the infected were chronic fatigue (54.2%), weakness (50.0%), muscle ache (49.2%), joint pain (46.6%), and agitation (45.8%). In addition, there were some status changes associated with WNV neuroinvasive disease with regards to hobby and work with a statistically significant change in hobby among older patients. Unfortunately, this study is limited by the fact that there was no control group to compare with the infected patients when looking at the presence of sequelae.

It is unclear how factors, such as age, may interact and affect the findings of this study. With increasing age, there seems to be higher morbidity. It is possible, however, that some of the sequelae that were studied in this paper were simply more common with older people, regardless of whether people were infected in the past with WNV. Perhaps the neuroinvasive complications of WNV caused the rates of sequelae to be higher in older age groups compared to the uninfected. Comparing study responders with a control group could have clarified the background rate of the sequelae that were studied.

Other limitations to this study include the fact that sequelae, functional status, and hospitalization events were self-reported. For the time allotted to do this surveillance study, it was not feasible to pull all the outpatient and hospital charts of responders to verify the existence and accuracy of these symptoms and hospitalizations. In addition, the mortality rate may have been underestimated. For the people who were non-responders, a review of the state death registry could have clarified if some of these people were deceased or not, but due to time limitations, this also was not performed.

Possible means of pathogenesis with regards to neuroinvasive disease includes weakening of the blood brain barrier through chronic conditions. Industrialized countries, such as Romania and the United States, where recent WNV outbreaks have occurred, tend to have high prevalences of chronic diseases of the circulatory system. Past observations have shown that with a WNV infection, chronic conditions, such as diabetes and immunosuppression, may predispose a person to death.^{10,11} It is possible that certain conditions, such as diabetes mellitus and hypertension, contribute to the increased permeability of blood vessels due to their deleterious effects on the microvasculature. With leaky vessels in place, the West Nile virus could easily pass from the blood to the brain and cause neuroinvasive disease as well as increased mortality. Unfortunately, this type of information cannot necessarily be gleaned from the death certificates that were available for review. Perhaps future re-

search could clarify the effect of other co-morbid conditions on the severity of WNV infection.

Many of the one-year sequelae are non-specific and are a result of physical impairment. A large percentage of cases may also have residual symptoms due to psychological effects. When the West Nile Outbreak occurred from July to December 2002, it was a major media event and caused much anxiety among the population. At that time, WNV infection was mysterious, terrifying, potentially life-threatening, and its long-term effects were unknown to the general public. Studies have shown that outbreaks may induce mass panic in a population.¹² All the attention and anxiety surrounding the outbreak could have predisposed people to increased psychological trauma during the epidemic. Even though the acute WNV infection is now over, perhaps the high rate of self-perception of poor health status is a residual effect of the anxiety and trauma that resulted from the WNV infection. In future years, as people become more familiar with the effects of WNV infection, perhaps the anxiety about WNV outbreaks will decrease, and self-perception of health status of the recently infected will improve. Future research of the psychological aspect of WNV infection as well as comparative studies, possibly between the USA and Romania outbreaks, could serve to elucidate these theories further.

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