

The Long-Term Outcomes of Human West Nile Virus Infection

James J. Sejvar

Divisions of Vector-Borne Infectious Diseases and Viral and Rickettsial Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Since its introduction to North America in 1999, human infection with West Nile virus (WNV) has resulted in considerable acute morbidity and mortality. Although the ongoing epidemic has resulted in a great increase in our understanding of the acute clinical features of human illness and helped to define associated clinical syndromes, far less is known about potential long-term clinical and functional sequelae. Several recent assessments, however, suggest that patients—even those with apparently mild cases of acute disease—frequently have subjective, somatic complaints following WNV infection. Persistent movement disorders, cognitive complaints, and functional disability may occur after West Nile neuroinvasive disease. West Nile poliomyelitis may result in limb weakness and ongoing morbidity that is likely to be long term. Although further assessment is needed, the long-term neurological and functional sequelae of WNV infection are likely to represent a considerable source of morbidity in patients long after their recovery from acute illness.

The ongoing epidemic of North American West Nile virus (WNV) infection serves as a reminder of the ability of novel viruses to emerge and thrive in unexpected settings. Since its appearance in New York City in 1999, WNV infection has caused considerable acute morbidity and mortality. The number of cases has decreased in recent years; however, the future epidemiology of the virus remains unclear, and it is likely that WNV will remain a source of significant human illness in the foreseeable future.

Acute morbidity and mortality associated with human WNV infection have been more clearly defined. As of November 2006, >23,500 cases of human WNV infection (including 9700 cases of neuroinvasive disease and 904 cases that resulted in fatalities) that occurred in the United States were reported to the Centers for Disease Control and Prevention [1]. However, acute morbidity and mortality associated with WNV infection quite likely

represent the “tip of the iceberg” with respect to the long-term public health and economic impact. Experience with other viral encephalitides suggests that long-term physical, functional, and cognitive problems in individuals surviving acute illness may be substantial, and although these long-term effects are more difficult to assess than the short-term effects of disease, they represent a tremendous source of ongoing morbidity.

As the eighth year of the WNV infection epidemic in North America begins, this article summarizes the current state of knowledge about the short-term and long-term outcomes of human WNV infection, assesses the current impact of long-term functional disability associated with WNV infection, and suggests areas of future research and direction for assessing the long-term effects of WNV infection in humans.

HISTORICAL DATA ON OUTCOMES OF WNV INFECTION

Reports of human WNV infection from areas of endemicity in Africa and the Middle East suggest that WNV infection in these areas has historically resulted in mild, uncomplicated disease in the small proportion of individuals (primarily children) developing symptomatic illness [2]. Long-term outcomes in these areas have not been detailed but could be presumed to be favorable and unremarkable. More recent epidemics of WNV infection in Israel and Eastern Europe have been more consistent with the North American experience, with more frequent

Received 29 December 2006; accepted 28 February 2007; electronically published 2 May 2007.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention.

Reprints or correspondence: Dr. James J. Sejvar, Div. of Vector-Borne Infectious Diseases, Div. of Viral and Rickettsial Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd., MS A-39, Atlanta, GA 30333 (zea3@cdc.gov).

Clinical Infectious Diseases 2007;44:1617–24

© 2007 by the Infectious Diseases Society of America. All rights reserved.

1058-4838/2007/4412-0015\$15.00

DOI: 10.1086/518281

development of neurologic illness, particularly in older persons or in those who are immunocompromised [3, 4]. However, data on long-term outcomes and sequelae following acute illness during these outbreaks have not been well-described.

Because of the sheer number of cases and the ongoing nature of the epidemic, the North American experience has resulted in a tremendous increase in our understanding of short-term clinical features of WNV-associated syndromes. Most human infections are subclinical, and most persons developing illness develop febrile illness (e.g., West Nile fever [WNF]), accompanied by other systemic symptoms, including myalgias, malaise, headache, and gastrointestinal distress. The minority of patients develop neuroinvasive disease, including West Nile meningitis (WNM), West Nile encephalitis (WNE), and West Nile poliomyelitis (WNP) [2, 5]. The acute features of each of these syndromes are shown in table 1.

SHORT-TERM AND LONG-TERM OUTCOMES OF WNV INFECTION

The distinction between a “short-term” and a “long-term” outcome of illness is somewhat arbitrary. For the purposes of this discussion, a “short-term” outcome is defined as including the acute illness and the immediate posthospitalization and convalescent period; a “long-term” outcome is defined as including events that occur for months to years following acute illness. Although much has been described about the acute and short-term features of human WNV infection, far less is known about possible long-term or chronic sequelae.

WNF. During the early years of the outbreak of WNV infection in North America, WNF was frequently described as a

mild, benign, self-limited illness. Indeed, this manifestation tends to occur in younger individuals and is generally associated with few physical or neurological sequelae. However, recent data suggest that WNF may be associated with more-significant ongoing problems than were initially appreciated. WNF in older adults may be associated with significant mortality [6]; although the ultimate cause of death in fatal cases of WNF is not entirely clear, the cause may be related to exacerbation of underlying comorbid conditions [6–8]. Older age is an independent risk factor for poorer outcome of WNF [6]. Even among young, previously healthy individuals, WNF may be associated with considerable short-term morbidity, with the occurrence of persistent systemic symptoms and absenteeism [9]. A particularly notable persistent symptom following WNV infection, both WNF and neuroinvasive disease, is extreme fatigue. Although fatigue may occur after resolution of other viral illnesses, the frequency and severity with which WNV-associated fatigue is reported is impressive. Nearly 96% of patients with WNF in 1 series described postillness fatigue that lasted a median of 36 days [9]. Self-assessed somatic complaints, such as fatigue, weakness, and concentration problems, may be described as frequently by persons recovering from WNF as by those recovering from neuroinvasive disease [10, 11]. Although the underlying mechanisms resulting in persistent morbidity following WNF remain unclear, mounting data suggest that “mild” WNV infection may be associated with significant short-term and long-term morbidity.

WNV-associated neuroinvasive disease. Although few analyses have assessed the outcomes of patients with WNM specifically, available data suggest that the short-term and long-

Table 1. Estimated percentage of overall infections, median ages affected, acute clinical features, and estimated case-fatality rate of the acute clinical syndromes associated with human West Nile virus (WNV) infection.^a

Variable	WNF	WNND		
		WNM	WNE	WNP
Estimated percentage of overall infections	20	<1 ^b	<1 ^b	<1 ^b
Estimated percentage of WNND cases	Not applicable	35–40	55–60	Unknown but may be 5–10 ^c
Acute clinical features	Abrupt onset of fever, headache, malaise, fatigue, anorexia, and nausea	Symptoms of WNF, plus meningismus (nuchal rigidity, photo- and phonophobia); cerebrospinal fluid with pleocytosis; WBC count generally <500 cells/mm ³	Symptoms of WNF, plus encephalopathy (altered mental status, lethargy), and/or focal neurologic signs (weakness, cranial nerve palsies); movement disorders, including tremor, parkinsonism, and ataxia, may be frequent	Acute onset of limb weakness or paralysis; weakness is typically asymmetric and abrupt; involved limbs typically are flaccid and areflexic; respiratory muscles may be involved; WNP may occur in the absence of fever or other features suggestive of WNV infection
Estimated case-fatality rate, %	<1	<1	20	10–50

NOTE. WNND, West Nile neuroinvasive disease.

^a Syndromes include West Nile fever (WNF), West Nile meningitis (WNM), West Nile encephalitis (WNE), and West Nile poliomyelitis (WNP).

^b Overall, WNND represents ~1% of human WNV infections.

^c WNP may occur in the context of any other manifestation of WNV infection or in isolation, without associated fever, meningitis, or encephalitis.

term outcomes of this manifestation are similar to those of WNF; indeed, there is significant clinical overlap between these syndromes. WNM probably accounts for ~40% of cases of West Nile neuroinvasive disease (WNND); the median age of patients with WNM is similar to that of patients with WNF overall, although among hospitalized patients, the age of persons with WNM may be considerably less than that of those with WNF or WNE [7]. Patients with WNM frequently require hospitalization for pain control for acute severe headache or rehydration because of prolonged nausea, vomiting, and poor oral intake [5]. Outcomes and disposition at hospital discharge among patients with WNM are generally favorable, and most patients return home to independent living after relatively short hospital stays. However, similar to patients with WNF, persons recovering from WNM frequently have persistent subjective complaints of fatigue, weakness, and memory and concentration problems [12].

WNE is associated with considerable short-term and long-term morbidity and mortality. WNE occurs more frequently in older persons (aged >55 years) and in those with underlying immunosuppression [2]. Patients with WNE are hospitalized longer [13] and experience medical complications (e.g., bronchopneumonia and cardiac arrhythmias) at greater rates than do patients with other forms of WNV illness [7, 13]. Acute mortality associated with WNE has been surprisingly consistent among studies, with most in-hospital case-fatality rates estimated to be ~20% [7, 14, 15]. Acute cause of death in patients with WNE has not been adequately delineated to date, but in many cases, death appears to be a result of acute respiratory failure or sudden cardiac complications [7, 14, 16]. Even after hospitalization, patients with WNE continue to experience long-term mortality at higher rates than the general population, with 1-year postinfection mortality rates comparable to those of patients with severe, chronic noninfectious diseases [17].

Persistent neurologic sequelae can occur in patients with WNE who survive acute illness. In many cases, the movement disorders and extrapyramidal involvement associated with acute WNE are transient, lasting days or weeks [5, 18, 19]. However, these movement disorders may persist for months or years. Six (38%) of 16 subjects observed after the 2002 Louisiana epidemic of WNV infection continued to display tremors and parkinsonism at 8 months after resolution of acute illness [5]. In a study in North Dakota [10], new or persistent tremor was observed or reported in 20% of patients 1 year after resolution of acute illness, and 18% of patients with WNND from a cohort in northern Colorado continued to have persistent tremors, parkinsonism, and ataxia >1.5 years after resolution of acute illness. In many instances, the tremors and parkinsonism were mild and not functionally disabling; however, in some cases, tremors and bradykinesia impacted daily activities, such as eating and dressing.

Patients with WNE frequently require placement in assisted living situations after hospitalization for acute illness. Among patients hospitalized with WNE in Colorado, 75% required some amount of assisted care after hospitalization for acute illness [7]; a similar percentage was reported in a study of patients in Ontario [14]. Physical, occupational, or speech therapy is frequently required following acute WNE, with estimates of the percentage of patients requiring ≥ 1 form of rehabilitation ranging from 47% to 65% [12, 13]. However, initial severity of neurological status in patients with WNE is not necessarily indicative of ultimate functional outcome, with several studies suggesting that even patients with severe encephalopathy and poor acute neurologic status may fully recover; such individuals tend to have better pre-illness health status [5]. Although no formal assessments have been performed on the economic impact and long-term costs associated with prolonged institutionalization and rehabilitation following WNND, some patients require months of intensive care and ventilatory support [20], and the economic impact from those with the most-severe illness could be considerable.

WNP. There is increasing data on the long-term outcomes of West Nile flaccid paralysis, or poliomyelitis, suggesting that it is associated with tremendous morbidity and mortality. WNP occurs as a result of viral involvement of the lower motor neurons or anterior horn cells of the spinal cord, resulting in an acute flaccid paralysis more typically associated with poliovirus infection. Although reliable estimates have been difficult to obtain, at least 1 study suggests that WNP accounts for ~10% of persons hospitalized with WNND [7]; however, this is possibly an underestimate, because WNP is difficult to assess in acutely moribund or comatose patients. Short-term morbidity associated with WNP can be substantial. A wide range of presentations and degrees of limb weakness may occur [16, 20–22], ranging from mild monoplegia to flaccid quadriplegia and respiratory failure. Cranial nerve involvement, particularly facial nerve palsy, has also been observed, and although the exact frequency with which this condition occurs in cases of WNP is difficult to ascertain from published case series, it may be as high as 70% of cases [16]. The most severe manifestation of WNP is acute neuromuscular respiratory failure resulting from involvement of diaphragmatic and intercostal respiratory muscle innervation. Although successful extubation and recovery can occur, respiratory involvement is associated with high mortality, with fatality rates of >50%. Patients who are successfully extubated may experience dyspnea and require supplemental oxygen for years following acute illness [16, 20]. Because WNP can occur in the context of any of the other conditions associated with WNV infection, it is likely that some patients with WNE and altered mental status who require emergent intubation have, in fact, developed acute respiratory failure attributable to anterior horn cell involvement. Early dysarthria and

dysphagia appear to be predictive of subsequent respiratory failure, and all patients with WNV infection should be closely monitored for these conditions [16].

Most strength recovery by patients with WNP appears to occur during the first 6–8 months following weakness onset, with a subsequent plateauing, during which additional strength recovery may occur (but to a less notable degree) (figure 1) [20, 23]. This pattern is consistent with recovery from poliovirus poliomyelitis [24]. Milder weakness (<2 unit decrements by manual muscle testing) and fewer involved limbs tend to be associated with better recovery. Importantly, however, initial severity of paralysis does not necessarily predict eventual strength outcome, and some patients with profound quadriplegia can experience complete strength recovery [16, 23]. The pathophysiology underlying this phenomenon may be substantial yet reversible damage to some motor neurons that can eventually recover, and this recovery may result in strength improvement. Determination of the number of surviving spinal motor units using electrophysiologic techniques shows promise to be a way of potentially predicting eventual strength recovery [23]. The role of physical and occupational therapies in eventual WNP outcomes remains largely anecdotal. Various degrees of improvement following physical and occupational therapy regimens have been documented [25, 26], but limited numbers of patients and absence of data on control subjects preclude any meaningful comments on the possible role of physical and/or occupational therapy for strength improvement. Clearly, physical and/or occupational therapy is important in patients with persistent profound weakness, to prevent severe contractures, atrophy, and joint problems. It is likely that experience gained from management of poliovirus poliomyelitis will con-

tinue to guide physical and occupational therapy regimens for rehabilitation from WNP.

Cognitive and functional outcomes following WNV infection. There is a limited but growing body of literature on the long-term cognitive and functional outcomes following WNV infection (table 2). All studies appear to substantiate a significant amount of self-reported disability following both WNF and WNND. Persistent symptoms, including fatigue, muscle pain, muscle weakness, and headache, were self-reported by >20% of patients with WNF and by nearly 50% of patients with WNE at >90 days postillness among 656 surveyed patients in northern Colorado [13]. The median interval to full recovery following otherwise uncomplicated WNF among 91 patients in Chicago, Illinois, was >60 days, and persistent fatigue, muscle weakness, and headaches were frequently described [9]. Among 35 patients with acute WNV infection during the 1999 outbreak in New York City, only 37% had achieved self-reported recovery by 1 year; persistent physical, cognitive, and functional difficulties were reported by over one-half of patients up to 18 months following acute illness [12]. Self-reported somatic complaints, including fatigue, memory problems, and excessive sleepiness, were frequently described among 49 patients recovering from WNV infection in North Dakota >1 year after acute illness [10]. Surprisingly, most of these studies have found that patients with milder acute illness appear to be just as likely to describe persistent problems, such as fatigue, memory difficulties, and muscle pain, as are patients with WNND, and nonhospitalized patients are just as likely to describe ongoing functional difficulties as are hospitalized patients [10, 12]. One study has suggested that patients recovering from WNND self-describe cognitive complaints at a slightly

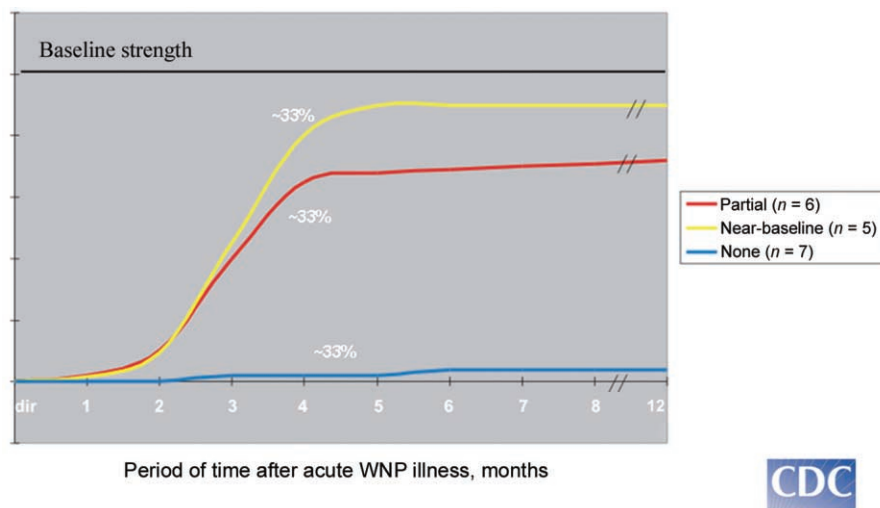


Figure 1. Graphical representation of temporal profiles of limb strength recovery in patients recovering from West Nile poliomyelitis (WNP). Data are based on 1-year outcomes of 18 patients assessed during the 2003 outbreak of West Nile virus infection in northern Colorado [16].

greater frequency than do patients recovering from WNF [11]. Overall, however, persistent subjective, functional impairment appears to be frequently reported among all WNV syndromes; younger age is more predictive of eventual functional recovery than is initial illness severity [12].

Although self-reported subjective cognitive and functional impairment following WNV infection occurs frequently, to date, measurements of neurocognitive performance using standardized, objective neuropsychological tests have been limited. Because of the prominent involvement of deep cortical brain structures in WNE, it might be expected that subcortical cognitive impairment, involving difficulties in registering new information, in immediate recall, and in attending to tasks, might result. One assessment of neurocognitive performance suggested that patients with WNND performed somewhat more poorly on the Telephone Interview for Cognitive Status—an easily administered, validated objective assessment for cognitive performance—compared with patients with WNF; however, the differences noted were subtle [11]. A study assessing neurocognitive impairment among 49 patients recovering from WNF and WNND in North Dakota used a battery of standardized tests of attention, executive function, learning and memory, and other cognitive domains [10]. The only clearly significant abnormalities found in the results of neurocognitive testing of patients with both WNND and mild disease were in the categories of manual dexterity and motor speed; results of tests of cognitive ability were generally within normal limits and were comparable between hospitalized and nonhospitalized patients. We observed similar findings among a cohort of 54 patients recovering from WNF, WNM, and WNE in Colorado, using computer-based neurocognitive tests. The impairment of motor speed and dexterity was consistent with the observed striatal-thalamic involvement in WNND; the finding of these abnormalities in patients without overt encephalitis raises the question of whether pathologic involvement of these structures may occur in less-severe clinical illness [10].

Collectively, these studies suggest that persistent subjective difficulties with memory, concentration, and cognition occur frequently following WNV infection, but these subjective symptoms do not necessarily correspond with poor performance on objective neurocognitive testing. Results of these studies should be interpreted with caution; however, the neurocognitive scores reflected in these studies were all obtained from patients recovering well enough to return home to independent living. Patients requiring continued institutionalization or intense assistance with daily activities have not been assessed and may have profound cognitive deficits. Additionally, the findings of difficulties with dexterity and subtle cognitive deficits in patients with WNND in some studies suggest that, in some cases, subtle abnormalities may result in significant functional im-

pairment in some patients. Additional studies of the overall neurocognitive impact of WNV infection are needed.

WNV INFECTION: FUTURE PERSPECTIVES

Over time, as ongoing studies gather additional data and greater numbers of patients are systematically assessed, long-term outcomes of WNV infection will become more apparent. There are several important clinical issues that are particularly relevant to long-term outcomes of WNV infection that should be evaluated over time.

WNV and parkinsonism. Researchers have commented on the frequent involvement of WNV infection in the basal ganglia with resultant parkinsonian features. Although in most patients, parkinsonism appears to be transient and self-limited, persistent parkinsonism has been observed in some patients >1.5 years following acute WNV infection [10]. Although not well-characterized, experience with other closely related flaviviruses has suggested that features of parkinsonism can recur up to 15 years after acute infection [28], and postencephalitic parkinsonism presumed to be attributable to other viral infections may occur years after acute encephalitis [29, 30]. Neuroimaging and histopathologic assessments have demonstrated that WNV and other flaviviruses frequently display distinct neurotropism for the basal ganglia, including the substantia nigra, resulting in neuronophagia and cell death [5, 31, 32]. In addition, animal models have demonstrated a decrease in dopaminergic cells, with resultant parkinsonism, following infection with Japanese encephalitis virus [33]. It is possible that substantia nigra involvement in WNND may predispose to the development of parkinsonism in the context of natural senescent loss of dopaminergic neurons due to ageing [34]; continued studies on the potential role of WNV in parkinsonian syndromes, which include histopathologic studies to assess for the typical neuropathology of postencephalitic parkinsonism, will be important future endeavors.

WNV and postpolio syndrome. Because WNP is clinically and pathophysiologically identical to poliovirus poliomyelitis, the possibility of development of a delayed “postpolio syndrome” following partial or complete recovery from WNP will require future assessment. Postpolio syndrome is characterized by the recurrence—years later—of paresis or paralysis in limbs previously affected by poliovirus infection. The presumed mechanism is thought to be progressive denervation of muscle fibers because of motor unit degeneration among motor neurons previously affected by poliomyelitis. Some estimates have suggested that postpolio syndrome may occur in up to 78% of survivors of poliovirus poliomyelitis [35]. The development of a similar delayed onset or recurrence of limb weakness among survivors of WNP is possible and even likely. Continued long-term assessment of persons recovering from limb weakness due

Table 2. Details of contemporary studies assessing the long-term outcomes of patients recovering from West Nile virus (WNV) infection.

Study or studies (year)	No. of patients enrolled	Duration of time between acute illness and follow-up assessment	Method of assessment	Major findings
Assessing WNF, WNM, WNE, and WNP				
Sejvar et al. [5] (2003)	16 (8 with WNE, 5 with WNM, and 3 with WNP)	8 months	Longitudinal follow-up, neurological examination, and functionality questionnaire	The 5 patients with WNM had favorable outcomes with near-baseline recovery by 8 months; although 5 patients with WNE had favorable outcomes, persistent movement disorders and functional difficulties led to severe difficulties in others; WNP was associated with a poor prognosis, with 1 death and no substantive recovery in the remainder of the patients at 8 months
Watson et al. [9] (2004)	98 (all with WNF)	Median of 168 days (range, 84–264 days)	Patient telephone interview with standardized questionnaire	Of the 98 subjects with otherwise uncomplicated WNF, 96% experienced fatigue for a median of 36 days, 30 subjects were hospitalized for a median of 5 days, 63% of subjects continued to experience symptoms at 30 days after onset; the authors concluded that WNF is a more severe illness than previously documented
Klee et al. [12] (2004)	42 (22 with WNE, 11 with WNM, and 7 with WNF)	6, 12, and 18 months	Personal interview with administration of standardized questionnaire, with functional status assessed with validated assessment tool	The prevalence of physical, cognitive, and functional difficulties within the cohort was significantly higher at 1 year than at baseline, with only 37% of subjects considering themselves to be fully recovered; significant numbers of subjects continued to experience symptoms at 18 months; younger age was an independent predictor of recovery
Ou et al. [15] (2005)	127 (65 with WNE and 53 with WNM)	~1 year	Semistructured telephone interview gathering information on residual symptoms	22% of 127 subjects continued to describe multiple persistent sequelae at 1 year after infection, including somatic pain, memory and concentration difficulties, and fatigue; 14% of responders were readmitted to the hospital at some point because of WNV infection–related problems
Green et al. [17] (2005)	246 (118 with WNE, 33 with WNM, 69 with WNF, and 25 with other syndromes)	1 and 2 years (assessment of death rates)	Longitudinal assessment of vital status of cohort by crossmatching case identity numbers with national Israeli mortality data and comparing age-SMRs to national data	SMR among WNV-infected subjects was 2.5 times higher than expected at 1 year but was not significantly elevated by 2 years; this risk excess was greater for males and for older persons (aged >85 years); the 1-year postdischarge death risk of WNV infection was comparable to that of severe acute noninfectious illness
Gottfried et al. [27] (2005)	22 (17 with WNME and 5 with WNF)	1 year	Telephone survey using structured questionnaire	59% of persons with WNME were unable to return to baseline level of functioning after illness for a median of 90 days (range, 9–365 days); 3 persons with WNF were unable to return to baseline functioning for a median of 150 days (range, 90–180 days); 41% of subjects reported persistent sequelae, the most common being fatigue
Carson et al. [10] (2006)	49 (11 with WNE or WNM and 38 with WNF)	Mean of 13 months (range, 10.5–15.8 months)	Longitudinal assessment, including standardized, validated functional assessment tools (SF-12v2, Barthel index, modified Rankin scale, MFI, and Beck depression inventory), standardized neurocognitive battery, and neurological examination	Self-reported fatigue, somatic, and cognitive complaints were common among the cohort; objective neurocognitive impairment at neurocognitive testing was variable depending on the specific test but was observed in a larger percentage in results of tests of executive function and visual memory; tests of motor speed and manual dexterity were most significantly abnormal; 20% had persistent tremor observed or reported; no significant differences in reported symptoms or neurocognitive function were observed between hospitalized and nonhospitalized patients
Haaland et al. [11] (2006)	116 (64 with WNF and 52 with WNND)	9 months	Administration of TICS, telephone assessment of subjective cognitive complaints	Total TICS score was somewhat lower among the group with WNND than the group with WNF, suggesting poorer mental status with more severe disease; subjects with WNND reported more subjective cognitive problems than did subjects with WNF, with ~24% of subjects overall reporting persistent problems; the TICS score was correlated with subjective cognitive complaints; only 54% of patients with WNF achieved TICS scores considered to be in the normal range

Patnaik et al. [13] (2006)	656 (531 with WNF, 84 with WNM, and 51 with WNE)	Median of 178 days (range, 102–299 days)	Self-administered survey mailed to patients identified through state-based surveillance	Symptom duration of >3 months was self-reported by 49% of subjects with WNE, 26% of subjects with WNM, and 20% of subjects with WNF; muscle weakness, muscle pain, and headache were the most frequently reported persistent symptoms; absence from work was commonly reported, with 78% of subjects with WNF missing a median of 16 days of work
Assessing West Nile flaccid paralysis (including WNP) specifically				
Marciniak et al. [25] (2004)	4 (all with WNP)	At admission to rehabilitation (range, 16–112 days after onset of acute illness), at discharge from rehabilitation (range, 35–106 days after onset of acute illness), and at 6 months after onset of acute illness	Longitudinal assessment of motor strength and functionality indices among 4 patients with WNP	2 patients with quadriplegia and 2 with bilateral lower extremity weakness were assessed; electrodiagnostic test results for all patients had findings consistent with WNP; all 4 patients experienced modest improvements in both motor strength and functionality; none reached baseline status or achieved independent ambulation by 6 months
Cao et al. [23] (2005)	12 (all with WNP), with 1 lost to follow-up after 6 weeks	Heterogeneous assessment to an end point of 21 months after onset of acute illness	Longitudinal neurologic examinations for 3 subjects; single clinic visit at month 20 for 2 subjects; intermittent telephone interview for 5 subjects; physical examination included manual muscle testing and electrodiagnostic testing; administration of ALSFRS at clinic visit or by telephone interview	Limb weakness in subjects was of variable severity and was markedly asymmetric, suggesting focal/segmental spinal involvement; range of strength recovery was also variable, ranging from minimal to nearly complete improvement of affected limbs; initial severity of weakness was not necessarily predictive of final strength outcome; electrophysiologic testing (specifically, MUNE assessment) correlated with degree of improvement in muscle strength
Sejvar et al. [16, 20] (2005, 2006)	32 (27 with WNP, 4 with features consistent with GBS, and 1 with brachial plexopathy)	At time of acute illness (within 18 days of onset, with 90% within 7 days of onset), at 4 months, and at 1 year	Longitudinal neurologic examination, standardized questionnaire, and self-administered functional assessment questionnaire	Distribution and severity of weakness at time of acute illness was heterogeneous; 38% of patients had ventilatory failure, requiring intubation and mechanical ventilation; at 4 months, 4 patients, all of whom experienced respiratory failure, died, and 2 remained intubated; the remaining 23 patients not lost to follow-up demonstrated varying degrees of strength improvement, ranging from minimal detectable improvement to complete recovery in 2 patients with GBS-like illness; 25% of patients continued to experience movement disorders at the 4-month follow-up visit; by 1 year, 3 more patients who had experienced respiratory failure died; 1 patient with WNP had regained baseline strength, and the remainder continued to experience varying degrees of persistent weakness; the greatest amount of strength recovery occurred between 1 and 6 months after acute illness; 41% of patients continued to experience other neurologic features (tremor and/or myoclonus), although these were generally not functionally impairing

NOTE. The review is limited to studies assessing >1 patient for a duration of ≥ 6 months following acute illness. ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; GBS, Guillain-Barré syndrome; MFI, multidimensional fatigue index score; MUNE, motor unit number estimate; SF-12v2, short-form health survey 12, version 2; SMR, standardized mortality rate; TICS, Telephone Interview for Cognitive Status; WNE, West Nile encephalitis; WNF, West Nile fever; WNM, West Nile meningitis; WNME, West Nile meningoencephalitis; WNND, West Nile neuroinvasive disease; WNP, West Nile poliomyelitis.

to WNP will be critical in assessing the epidemiology and frequency of this potential syndrome.

SUMMARY

As the future pattern of the epidemic of WNV infection declares itself, it is likely that WNV infection will continue to be a source of considerable morbidity and mortality. As greater numbers of affected individuals survive WNV infection, the possible long-term sequelae will likely become an increasingly important public health issue. The nature of these sequelae will be an important focus of subsequent investigations of the effects of WNV infection in humans.

Acknowledgments

Potential conflicts of interest. J.J.S.: no conflicts.

References

- Centers for Disease Control and Prevention. West Nile virus activity—United States, January 1–November 7, 2006. *MMWR Morb Mortal Wkly Rep* **2006**; 55:1204–5.
- Campbell GL, Marfin AA, Lanciotti RS, Gubler DJ. West Nile virus. *Lancet Infect Dis* **2002**; 2:519–29.
- Chowers MY, Lang R, Nassar F, et al. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. *Emerg Infect Dis* **2001**; 7:675–8.
- Campbell GL, Ceianu CS, Savage HM. Epidemic West Nile encephalitis in Romania: waiting for history to repeat itself. *Ann N Y Acad Sci* **2001**; 951:94–101.
- Sejvar JJ, Haddad MB, Tierney BC, et al. Neurologic manifestations and outcome of West Nile virus infection. *JAMA* **2003**; 290:511–5.
- Berner YN, Lang R, Chowers MY. Outcome of West Nile fever in older adults. *J Am Geriatr Soc* **2002**; 50:1844–6.
- Bode AV, Sejvar JJ, Pape WJ, Campbell GL, Marfin AA. West Nile virus disease: a descriptive study of 228 patients hospitalized in a 4-county region of Colorado in 2003. *Clin Infect Dis* **2006**; 42:1234–40.
- Emig M, Apple DJ. Severe West Nile virus disease in healthy adults. *Clin Infect Dis* **2004**; 38:289–92.
- Watson JT, Pertel PE, Jones RC, et al. Clinical characteristics and functional outcomes of West Nile fever. *Ann Intern Med* **2004**; 141:360–5.
- Carson PJ, Konweko P, Wold KS, et al. Long-term clinical and neuropsychological outcomes of West Nile virus infection. *Clin Infect Dis* **2006**; 43:723–30.
- Haaland KY, Sadek J, Pergam S, et al. Mental status after West Nile virus infection. *Emerg Infect Dis* **2006**; 12:1260–2.
- Klee AL, Maidin B, Edwin B, et al. Long-term prognosis for clinical West Nile virus infection. *Emerg Infect Dis* **2004**; 10:1405–11.
- Patnaik JL, Harmon H, Vogt RL. Follow-up of 2003 human West Nile virus infections, Denver, Colorado. *Emerg Infect Dis* **2006**; 12:1129–31.
- Pepperell C, Rau N, Krajden S, et al. West Nile virus infection in 2002: morbidity and mortality among patients admitted to hospital in south-central Ontario. *CMAJ* **2003**; 168:1399–405.
- Ou AC, Ratard RC. One-year sequelae in patients with West Nile virus encephalitis and meningitis in Louisiana. *J La State Med Soc* **2005**; 157:42–6.
- Sejvar JJ, Bode AV, Marfin AA, et al. West Nile virus–associated flaccid paralysis. *Emerg Infect Dis* **2005**; 11:1021–7.
- Green MS. Long-term death rates, West Nile virus epidemic, Israel, 2000. *Emerg Infect Dis* **2005**; 11:1754–7.
- Robinson RL, Shahida S, Madan N, Rao S, Khardori N. Transient parkinsonism in West Nile virus encephalitis. *Am J Med* **2003**; 115:252–3.
- Burton JM, Kern RZ, Halliday W, et al. Neurological manifestations of West Nile virus infection. *Can J Neurol Sci* **2004**; 31:185–93.
- Sejvar JJ, Bode AV, Marfin AA, et al. West Nile virus–associated flaccid paralysis outcome. *Emerg Infect Dis* **2006**; 12:514–6.
- Leis AA, Stokic DS, Webb RM, Slavinski SA, Fratkin J. Clinical spectrum of muscle weakness in human West Nile virus infection. *Muscle Nerve* **2003**; 28:302–8.
- Li J, Loeb JA, Shy ME, et al. Asymmetric flaccid paralysis: a neuromuscular presentation of West Nile virus infection. *Ann Neurol* **2003**; 53:703–10.
- Cao NJ, Ranganathan C, Kupsy WJ, Li J. Recovery and prognosticators of paralysis in West Nile virus infection. *J Neurol Sci* **2005**; 236:73–80.
- Guyton A. Reaction of the body to poliomyelitis and the recovery process. *Arch Int Med* **1949**; 83:27.
- Marciniak C, Sorosky S, Hynes C. Acute flaccid paralysis associated with West Nile virus: motor and functional improvement in 4 patients. *Arch Phys Med Rehabil* **2004**; 85:1933–8.
- Miller NH, Miller DJ, Goldberg JL. Physical therapist examination, evaluation, and intervention for a patient with West Nile virus paralysis. *Phys Ther* **2006**; 86:843–56.
- Gottfried K, Quinn R, Jones T. Clinical description and follow-up investigation of human West Nile virus cases. *South Med J* **2005**; 98:603–6.
- Kuno G. Persistence of arboviruses and antiviral antibodies in vertebrate hosts: its occurrence and impacts. *Rev Med Virol* **2001**; 11:165–90.
- Rail D, Scholtz C, Swash M. Post-encephalitic parkinsonism: current experience. *J Neurol Neurosurg Psychiatry* **1981**; 44:670–6.
- Mitsuyama Y, Fukunaga H, Takayama S. Parkinson's disease of post-encephalitic type following general paresis—an autopsied case. *Folia Psychiatr Neurol Jpn* **1983**; 37:85–93.
- Savant CS, Singhal BS, Jankovic J, Khan M, Virani A. *Substantia nigra* lesions in viral encephalitis. *Mov Disord* **2003**; 18:213–6.
- Guarner J, Shieh WJ, Hunter S, et al. Clinicopathologic study and laboratory diagnosis of 23 cases with West Nile virus encephalomyelitis. *Hum Pathol* **2004**; 35:983–90.
- Ogata A, Hamaue N, Terado M, Minami M, Nagashima K, Tashiro K. Isatin, an endogenous MAO inhibitor, improves bradykinesia and dopamine levels in a rat model of Parkinson's disease induced by Japanese encephalitis virus. *J Neurol Sci* **2003**; 206:79–83.
- Naoi M, Maruyama W. Cell death of dopamine neurons in aging and Parkinson's disease. *Mech Ageing Dev* **1999**; 111:175–88.
- Trojan DA, Cashman NR. Post-poliomyelitis syndrome. *Muscle Nerve* **2005**; 31:6–19.