MAJOR ARTICLE

West Nile Virus Disease: A Descriptive Study of 228 Patients Hospitalized in a 4-County Region of Colorado in 2003

Amy V. Bode,[1,a] James J. Sejvar,[3] W. John Pape,[2] Grant L. Campbell,[1] and Anthony A. Marfin[1,a]

[1]Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, and [2]Colorado Department of Public Health and Environment, Denver, Colorado; and [3]Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. Risk factors for complications of West Nile virus disease and prognosis in hospitalized patients are incompletely understood.

Methods. Demographic characteristics and data regarding potential risk factors, hospitalization, and dispositions were abstracted from medical records for residents of 4 Colorado counties who were hospitalized in 2003 with West Nile virus disease. Univariate and multivariate analyses were used to identify factors associated with West Nile encephalitis (WNE), limb weakness, or death by comparing factors among persons with the outcome of interest with factors among those without the outcome of interest.

Results. Medical records of 221 patients were reviewed; 103 had West Nile meningitis, 65 had WNE, and 53 had West Nile fever. Respiratory failure, limb weakness, and cardiac arrhythmia occurred in all groups, with significantly more cases of each in the WNE group. Age, alcohol abuse, and diabetes were associated with WNE. Age and WNE were associated with limb weakness. The mortality rate in the WNE group was 18%; age, immunosuppression, requirement of mechanical ventilation, and history of stroke were associated with death. Only 21% of patients with WNE who survived returned to a prehospitalization level of function. The estimated incidence of West Nile fever cases that required hospitalization was 6.0 cases per 100,000 persons; West Nile fever was associated with arrhythmia, limb weakness, and respiratory failure.

Conclusions. Persons with diabetes and a reported history of alcohol abuse and older persons appear to be at increased risk of developing WNE. Patients with WNE who have a history of stroke, who require mechanical ventilation, or who are immunosuppressed appear to be more likely to die. Respiratory failure, limb weakness, and arrhythmia occurred in all 3 categories, but there were significantly more cases of all in the WNE group.

From 1999, when West Nile virus (WNV) was introduced to the United States, through 2005, more than 19,500 cases of WNV disease were reported to the Centers for Disease Control and Prevention (CDC), including nearly 8300 neuroinvasive cases (i.e., West Nile encephalitis [WNE] and West Nile meningitis [WNM]) [1, 2]. The 2002 and 2005 points in the epidemic were the largest consecutive epidemics of neurotropic flavivirus disease ever observed in North America [1–4]; thousands of hospitalizations and >700 deaths occurred. Patients who survive neuroinvasive WNV disease, especially those with encephalitis, often require prolonged acute care hospitalization, prolonged nursing home care, and long-term ventilator support [5–8]. The spectrum of serious neurologic manifestations of WNV disease has recently been expanded to include acute flaccid paralysis, a syndrome that is most commonly due to anterior horn cell (i.e., poliomyelitis) involvement [8, 9]. The incidence and natural history of this condition need delineation. In addition, the morbidity and economic costs associated with West Nile fever (WNF), which is ~20 times more common than neuroinvasive WNV disease, are probably underappreciated [5]. In a recent retrospective study, 30% of sur

Received 25 October 2005; accepted 10 January 2005; electronically published 30 March 2006.

[a] Present affiliations: Public Health–Seattle and King County, Washington (A.V.B.); and Division of Global Migration and Quarantine, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Seattle, Washington (A.A.M.).

Reprints or correspondence: Dr. Amy Bode (amy.bode@metrokc.gov).

Clinical Infectious Diseases 2006; 42:1234–40

This article is in the public domain, and no copyright is claimed.

1058-4838/2006/4209-0003

Downloaded from https://academic.oup.com/cid/article-abstract/42/9/1234/314293 by Northwestern University Library user on 23 January 2019

veyed patients with WNF required hospitalization for the illness [10].

In 2003, Colorado reported 2947 cases of WNV disease to the CDC, including 621 neuroinvasive cases of disease and 63 cases that involved fatalities [11], with illness onset dates from 11 June to 28 October. Of these 2947 cases, 1531 (52%) were reported from 4 counties in northern Colorado (Boulder, Denver, Larimer, and Weld counties), which have a population of 1.28 million persons, comprising only 30% of Colorado's population [12]. Of the 1531 patients, 333 (22%) were hospitalized. In 2003, we conducted a population-based medical record review of 228 (69%) of these 333 cases to describe the short-term outcomes for the determined clinical syndromes and to identify possible risk factors for development of WNE, acute flaccid paralysis, and fatal outcome.

METHODS

A retrospective medical record review of cases of WNV disease was conducted at the 17 hospitals in Boulder, Weld, Larimer, and Denver counties that reported WNV-associated hospitalizations from July through October 2003. We found cases by contacting infection-control practitioners and physicians and reviewing Colorado's reportable disease surveillance system, which received reports from health care providers. Only records for the index hospitalization of residents of 1 of these 4 counties with illness onset from July through October 2003 and serologic evidence of a recent WNV infection [5] were reviewed. Cases were classified as WNE if fever (temperature, >38°C) and at least 1 of the following characteristics were present: acutely altered mental status (i.e., disorientation, obtundation, stupor, coma, or personality change that lasted >24 h), neuroimaging findings consistent with acute cerebral inflammation, or electroencephalography findings consistent with encephalitis. WNM was defined as fever, pleocytosis (WBC count, ⩾5 cells/mm^3), and at least 1 clinical sign or symptom of meningitis (stiff neck, nuchal rigidity, headache, or photophobia) without mental status changes or neuroimaging or electroencephalography findings consistent with encephalitis. WNF was defined as fever without signs or symptoms of WNE or WNM. Limb weakness was defined as paresis or paralysis of 1 or more limbs within 48 h of illness onset and could be simultaneously diagnosed with WNE, WNM, or WNF. All patients had WNV-specific IgM antibody present in acute-phase serum or CSF specimens; testing was performed at the Colorado Department of Public Health and Environment laboratory (Denver) [13].

The following data were abstracted from the medical and nursing records: demographic data; clinical history, including illness onset date and symptoms; past medical history; presence of immunosuppression; findings of physical and neurologic examinations (e.g., paresis or paralysis, cranial nerve palsies, tremors, myoclonus, abnormal reflexes, and sensory deficits); diagnostic test results; and therapeutic interventions. Alcohol abuse, diabetes mellitus, and autoimmune disease (e.g., rheumatoid arthritis) were noted when listed as medical problems in the attending physician's admission history. Immunosuppression was noted when the patient had a disease that affects the immune system (i.e., HIV infection, previous organ transplantation, lymphoma, leukemia, and myelodysplasia), was taking an immunosuppressive drug regimen (i.e., daily doses of systemic corticosteroids [⩾20 mg of prednisone per day or its physiologic equivalent], disease-modifying antirheumatic drugs [e.g., etanercept and infliximab], or other immunosuppressive drugs [e.g., tacrolimus]), or had received chemotherapy within 6 months of WNV illness onset.

SPSS for Windows, version 12.0 (SPSS), was used for statistical analyses. Variables associated with WNE, limb weakness, or death were identified by comparing persons with the outcome of interest with those hospitalized with WNF, those with illness without limb weakness, or those with WNE who were discharged alive, respectively. These groups were compared in univariate analysis using a χ^2 or 2-tailed Fisher's exact test; results are reported as a relative risk with 95% CIs. Ages were compared using the Wilcoxon 2-sample test. Variables with P values >.25 on univariate analysis were excluded from further analysis. Stepwise, forward, and backward logistic regression models were applied. Variables were added or dropped on the basis of the log-likelihood ratio and log-likelihood test results. Results are reported as adjusted ORs with 95% CIs.

RESULTS

Overview. Of 333 persons hospitalized with illness attributed to WNV infection, we reviewed the medical records of 228 consecutively hospitalized persons with illness onset from 20 July through 16 September 2003. Seven patients were excluded from additional analysis (6 patients did not have fever, and 1 patient later received a diagnosis of St. Louis encephalitis virus infection [14]). Of the 6 patients without fever, 5 had neurologic symptoms (severe headaches and/or vertigo), and 1 had an exacerbation of chronic obstructive pulmonary disease. These consecutively hospitalized patients represented at least 65% of the residents from each county that were hospitalized with a WNV illness in 2003, except for Denver County, for which they represented 50% of Denver County residents hospitalized with WNV illness.

Clinical presentation. Of 221 persons included in the analysis, 103 (47%) had WNM, 65 (29%) had WNE, and 53 (24%) had WNF (table 1). Patients with WNM (median age, 43 years) were significantly younger than patients with WNF (median age, 59 years) and patients with WNE (median age, 62 years). On the basis of the total of 333 cases reported among residents

Downloaded from https://academic.oup.com/cid/article-abstract/42/9/1234/314293 by Northwestern University Library user on 23 January 2019

Table 1. Demographic and other characteristics of 221 patients hospitalized with West Nile meningitis (WNM), encephalitis (WNE), or fever (WNF) in northern Colorado in 2003.

Characteristic	Syndrome		
	WNM (n = 103)	WNE (n = 65)	WNF (n = 53)
Age, median years (range)	43 (5–79)	62 (33–86)	59 (19–87)
Male sex, % of patients	59	61	53
Death	0	12 (18)[a]	0
Respiratory failure	2 (2)	22 (34)[a]	3 (6)
Limb weakness	17 (17)	27 (42)[a]	6 (11)
Cardiac arrhythmia[b]	2 (2)	7 (11)[a]	4 (8)
Abnormal immune system findings			
Autoimmune disease	11 (11)	9 (14)	10 (19)
Organ transplantation	1 (1)	2 (3)	0
Immunosuppression	4 (4)	10 (15)	4 (8)
Premorbid condition			
Alcohol abuse	6 (6)	11 (17)	3 (6)
Cancer	3 (3)	12 (18)	5 (9)
Diabetes	11 (11)	16 (25)	5 (9)
Heart disease	6 (6)	17 (26)	14 (26)
Hypertension	15 (15)	29 (45)	19 (36)
Psychiatric disease	19 (18)	17 (26)	16 (30)
Renal disease	7 (7)	10 (15)	7 (13)
Thyroid disease	5 (5)	9 (14)	4 (8)
Tobacco use	32 (31)	26 (40)	14 (26)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] $P < .05$ for patients with WNM vs. patients with WNE.

[b] Excludes sinus tachycardia and sinus bradycardia. Includes second- or third-degree heart block (2 patients with WNE), atrial fibrillation (1 patient with WNM, 5 patients with WNE, and 3 patients with WNF), torsade de pointes (1 patient with WNF), and ventricular tachycardia (1 patient with WNM).

of this 4-county area, the incidence of WNV disease requiring hospitalization was 26.0 cases per 100,000 persons. Assuming that these 228 patients whose records we reviewed were similar to the other 105 patients, the incidences of WNE, WNM, and WNF cases that required hospitalization were 7.4, 11.7, and 6.0 cases per 100,000 persons, respectively.

In addition to the different signs and symptoms specified by the case definitions, the clinical presentation of WNE and WNM differed (table 2). Patients with WNM were significantly more likely than patients with WNE to have nausea, vomiting, myalgia, rash, back pain, and arthralgia. Patients with WNE were significantly more likely than patients with WNM to have memory problems, bulbar dysfunction (dysarthria and dysphagia), and focal motor abnormalities, including cranial nerve palsies. No differences in the frequency of tremor, limb weakness, myoclonus, and seizures were noted between these 2 groups. Although 20 patients (20%) with WNM had confusion and/or other mental status changes, these signs or symptoms lasted <24 h, and as a result, these persons were not classified as having cases of WNE.

Complications. Respiratory failure, limb weakness, and cardiac arrhythmia were noted in all 3 groups but were more common among patients with WNE (table 1). Of 65 patients with WNE, 22 (34%) underwent intubation and ventilation, compared with 2 (2%) of 103 patients who had WNM. Twenty-seven patients with WNE (42%) developed limb weakness, compared with 17 patients with WNM (17%); of 53 patients with WNF, only 6 (11%) developed limb weakness. Regardless of the clinical syndrome, patients with limb weakness were more likely to undergo intubation and ventilation. Of 50 patients with limb weakness, 19 (38%) underwent intubation, compared with only 8 (5%) of the 171 patients without limb weakness.

Cardiac arrhythmia complicated each clinical syndrome (table 1). Excluding 26 patients in which sinus bradycardia or tachycardia was noted, abnormal cardiac rhythms were documented in 13 (7%) of 195 remaining patients, including second- and third-degree heart blocks that required temporary pacemakers (2 patients), exacerbation or new onset of atrial fibrillation (9 patients), ventricular tachycardia (1 patient), and

Downloaded from https://academic.oup.com/cid/article-abstract/42/9/1234/314293 by Northwestern University Library user on 23 January 2019

Table 2. Comparison of selected signs and symptoms present at hospital admission for patients with West Nile meningitis (WNM) and those with West Nile encephalitis (WNE).

Sign or symptom	No. (%) of patients with sign or symptom	
	WNM group (n = 103)	WNE group (n = 65)
Nausea[a]	76 (74)	32 (49)
Vomiting[a]	64 (62)	30 (46)
Myalgia[a]	63 (61)	20 (31)
Chills/rigors	43 (42)	22 (34)
Rash[a]	41 (40)	16 (25)
Back pain[a]	28 (27)	7 (11)
Arthralgia[a]	19 (18)	5 (8)
Dyspnea	14 (14)	13 (20)
Cough	14 (14)	12 (18)
Ataxia	44 (43)	21 (32)
Visual disturbance	27 (26)	12 (18)
Tremors	19 (18)	18 (28)
Limb weakness	12 (12)	5 (8)
Myoclonus	10 (10)	6 (9)
Bulbar dysfunction[a]	5 (5)	13 (20)
Dysarthria[a]	4 (3)	9 (14)
Dysphagia	2 (3)	4 (6)
Focal neurologic abnormalities[a]	3 (3)	10 (15)
Memory problems[a]	1 (1)	7 (11)
Seizures	1 (1)	4 (6)

[a] $P \leq .05$.

torsade de pointes (1 patient). Patients with WNE were more likely to develop arrhythmia than were other patients; of 65 patients with WNE, 7 (11%) developed arrhythmias other than sinus bradycardia or tachycardia, compared with 2 (2%) of 103 patients who had WNM.

Treatment. Of 221 patients, 176 (80%) were treated with broad-spectrum antibiotics, and 38 (17%) received at least 1 immunomodulating agent (e.g., parenteral corticosteroids, IFN, or intravenous immunoglobulin) as initial therapy. Of 17 patients with WNE who received parenteral corticosteroids, 3 (18%) died, compared with 9 (19%) of 48 patients who had WNE and who did not receive steroids.

Encephalitis. Alcohol abuse, diabetes, hypertension, and tobacco use were more commonly noted in the medical records of patients with WNE than in the records of other patients (table 1). In univariate analysis, age ⩾50 years, alcohol abuse, diabetes, and immunosuppression were significantly more commonly associated with WNE than WNF (table 3). In multivariate analysis, patients with alcohol abuse recorded in their past medical history were 7.5 times more likely to develop WNE, and those with diabetes were 4.1 times more likely. For each year of age, patients with WNE were 1.04 times more likely to develop WNE (table 3). Because no patients with WNF had undergone organ transplantation, this factor could not be included in multivariate analysis.

Limb weakness. Limb weakness was reported by 50 (23%) of 221 patients (table 1). Although also seen in patients with WNF and WNM, limb weakness was seen in a higher proportion of patients with WNE. Of 65 patients with WNE, 27 (42%) had limb weakness, compared with 17 (17%) of 103 patients who had WNM and 6 (11%) of 53 patients who had WNF. In univariate analysis, patients with WNE were 4.1 times more likely to have limb weakness than were other patients; patients with a recorded history of alcohol abuse were 2.5 times more likely, and patients aged ⩾50 years were 2.7 times more likely (table 4). In multivariate analysis, only WNE and age were significantly associated with limb weakness.

Outcome. All patients with fatal cases of disease had WNE; of 65 patients with WNE, 12 (18%) died during their index hospitalization (table 1). Two patients who died had quadriparesis and were removed from life support. Six patients did not undergo intubation, despite developing respiratory failure, and these patients died. Of the 12 patients with fatal cases of disease, in addition to WNV infection, 4 patients (33%) had respiratory failure, 2 (17%) had pneumonia, 2 (17%) had myocardial infarction, and 1 each had streptococcal meningitis, viral encephalitis, and myeloproliferative disorder noted as the primary discharge diagnosis. An autopsy was performed for the remaining patient who died, who had chronic myelomonocytic leukemia; a mediastinal hemorrhage was found and was noted as the primary cause of death.

In univariate analysis limited to patients with WNE, age ⩾50 years, receipt of vasopressor treatment, and a history of solid-

Table 3. Risk analysis for developing West Nile encephalitis (WNE) for 65 patients with WNE versus 53 patients with West Nile fever.

Risk factor	RR from univariate analysis (95% CI)	Adjusted OR from multivariate analysis (95% CI)[a]
Male sex	1.4 (0.7–3.0)	Not retained in model
Alcohol abuse	3.4 (0.9–12.9)	7.5 (1.5–37.8)
Diabetes	3.1 (1.1–9.2)	4.1 (1.2–13.6)
Cancer	2.2 (0.7–6.6)	Not retained in model
Hypertension	1.5 (0.7–3.2)	Not retained in model
Liver disease	3.4 (0.4–31.5)	Not retained in model
Age ⩾50 years	2.7 (1.2–6.5)	…
Age (per year)	…	1.04 (1.01–1.07)
Organ transplantation	Undefined[b]	…
Immunosuppression	2.2 (0.7–7.6)	Not retained in model

NOTE. Variables excluded from multivariate analysis were psychiatric, autoimmune, thyroid, renal, heart, and cerebrovascular disease; receipt of dialysis; current or past tobacco use; and seizures. RR, relative risk.

[a] Adjusted for listed risk factors except organ transplantation and age ⩾50 years.

[b] In this analysis, all persons with a history of organ transplantation developed WNE ($P = .2$).

Downloaded from https://academic.oup.com/cid/article-abstract/42/9/1234/314293 by Northwestern University Library user on 23 January 2019

Table 4. Risk analysis for the development of limb weakness among 221 patients who were hospitalized with West Nile virus disease.

Risk factor	RR from univariate analysis (95% CI)	Adjusted OR from multivariate analysis (95% CI)[a]
Male sex	0.9 (0.5–1.7)	Not retained in model
West Nile encephalitis	4.1 (2.1–8.0)	3.2 (1.5–6.5)
Alcohol abuse	2.5 (1.0–6.5)	Not retained in model
Autoimmune disease	0.6 (0.2–1.7)	Not retained in model
Diabetes	0.8 (0.3–2.0)	Not retained in model
Hypertension	1.5 (0.8–3.0)	Not retained in model
Thyroid disease	1.8 (0.6–5.1)	Not retained in model
Age ⩾50 years	2.7 (1.2–6.5)	…
Age (per year)	…	1.02 (1.0–1.04)
Immunosuppression	2.4 (0.9–6.5)	Not retained in model
Organ transplantation	Undefined[b]	…

NOTE. Variables excluded from multivariate analysis were psychiatric, liver, renal, heart, and cerebrovascular disease; cancer; receipt of dialysis; current or past tobacco use; and previous history of encephalitis and seizures. RR, relative risk.

[a] Adjusted for listed risk factors except organ transplantation and age ⩾50 years.

[b] In this analysis, all persons with a history of organ transplantation developed limb weakness ($P = .001$).

organ cancer, hypertension, stroke, or immunosuppression were associated with death. All 12 deaths occurred among patients with WNE who were aged ⩾50 years; no deaths occurred among 11 younger patients with WNE. In multivariate analysis, endotracheal intubation, a previous stroke, immunosuppression, and age ⩾50 years were retained in the final logistic model (table 5).

Of 209 persons who survived their index hospitalization, 131 (63%) returned home without an increased need for nursing or medical care, compared with their prehospitalization status. Among 53 patients with WNE who survived, 13 (25%) returned home without a need for increased care, compared with 118 (76%) of 156 patients with WNM or WNF (table 6).

DISCUSSION

This is, to our knowledge, the largest population-based study of hospitalized patients with WNV disease since WNV was introduced to North America in 1999. During the 2003 epidemic of WNV disease in Colorado, roughly 26 of every 100,000 residents of 4 northern Colorado counties were hospitalized with WNV illness. In this population-based study, many persons developed complications of WNV illness, including limb weakness (23%), respiratory failure (12%), and cardiac arrhythmia (6%). Age and a reported history of diabetes or alcohol abuse appeared to increase the risk of developing WNE. In patients with WNE, age, immunosuppression, endotracheal intubation, and a previous history of stroke were associated with a fatal outcome. Patients with WNE had greater morbidity and mortality during their index hospitalization; those who survived WNE were generally unable to return to their prehospitalization level of function. Although we were unable to specify the degree of risk of organ transplantation, 3 organ transplant recipients in this study had neuroinvasive disease, and 1 died during the index hospitalization. This report confirms earlier reports that transplant recipients are at increased risk for neuroinvasive WNV disease [15].

WNE resulted in greater rates of limb weakness and mechanical ventilation; both factors have been previously recognized as complications of WNE [6, 8, 16]. In this study, >40% of patients with WNE developed limb weakness, >30% required mechanical ventilation, and 18% died, predominantly as a result of respiratory failure. Along with depressed mental status, limb weakness has been highly associated with mechanical ventilation [16]. It is unknown, however, how much of this was necessitated by respiratory failure resulting from muscle weakness, how much was necessitated by depressed mental status, or how much was necessitated by a combination of factors. The mortality rate for patients with WNE in this study is consistent with previous reports that have suggested that the overall mortality rate for neuroinvasive WNV disease is 8%–12%, with little or no mortality among patients with WNM and a mortality rate of ~15%–25% among patients with WNE [1, 5].

An important objective of clinical encephalitis studies is to identify risk factors for development of encephalitis. This would allow better insight into pathophysiology and identification of persons who should be more closely monitored for develop-

Table 5. Risk analysis for fatal outcome during index hospitalization among 65 patients with West Nile encephalitis (12 fatal cases).

Risk factor	RR from univariate analysis (95% CI)	Adjusted OR from multivariate analysis (95% CI)[a]
Intubation	3.5 (1.0–12.9)	12.7 (1.2–139)
Vasopressor treatment	4.7 (1.2–19.0)	Not retained in model
Alcoholism	Undefined[b]	…
Current tobacco use	2.3 (0.6–8.3)	Not retained in model
Autoimmune disease	2.6 (0.5–12.4)	Not retained in model
Cancer	7.8 (1.9–32.2)	Not retained in model
Hypertension	4.6 (1.1–18.9)	Not retained in model
Diabetes	0.6 (0.1–2.9)	Not retained in model
Previous stroke	8.5 (1.2–58.2)	42.7 (2.4–756)
Limb weakness	3.6 (1.0–13.5)	Not retained in model
Immunosuppression	12.3 (2.7–56.2)	26.5 (3.0–234)
Age ⩾50 years	Undefined[b]	…
Age (per year)	…	1.14 (1.02–1.29)

NOTE. Variables excluded from multivariate analysis: sex; nosocomial infections; diabetes; psychiatric, heart, liver, thyroid, and renal disease; dialysis; seizures; intravenous corticosteroids; or previous history of encephalitis. RR, relative risk.

[a] Adjusted for listed risk factors except alcoholism and age ⩾50 years.

[b] In this analysis, all patients with WNE who reported alcoholism or who were aged ⩾50 years died ($P = .08$).

Downloaded from https://academic.oup.com/cid/article-abstract/42/9/1234/314293 by Northwestern University Library user on 23 January 2019

Table 6. Discharge disposition of 221 patients who had been hospitalized with West Nile virus disease, by clinical syndrome.

Placement at discharge	No. (%) of patients		
	WNM group (n = 103)	WNE group (n = 65)	WNF group (n = 53)
Rehabilitation facility	6 (6)	19 (29)	8 (15)
Long-term care facility	3 (3)	11 (17)	1 (2)
Home with assistance[a]	12 (11)	10 (15)	9 (17)
Home without assistance	82 (80)	13 (20)	36 (68)
Patient died	0	12 (18)	0

NOTE. WNE, West Nile encephalitis; WNF, West Nile fever; WNM, West Nile meningitis.

[a] Includes patients admitted from nursing homes who returned to nursing homes with an increased level of care.

ment of encephalitis and its complications or who may benefit from more-aggressive medical treatment and preventive measures (e.g., vaccination). Our study showed that older age is associated with development of WNE. Although a role has been hypothesized for age-or disease-related (e.g., diabetes, hypertension, and stroke) changes in the blood-brain barrier that allow greater viral entry, mechanisms underlying these possible associations remain unclear. Although a previous study has hypothesized a role for diabetes in WNE [6], ours is, to our knowledge, the first population-based study to show an association between WNE and diabetes or alcohol abuse.

Limb weakness was present in nearly 25% of patients and was more common than has been previously reported; many of these patients also had respiratory failure. The presence of WNE and age ⩾50 years were associated with development of limb weakness. Although it occurred more frequently among patients with neuroinvasive disease, in this study, limb weakness was also present in persons with WNV illness who did not have clinical evidence of encephalitis or meningitis. The use of retrospective medical record review, as opposed to a prospective study, limited our ability to determine the nature of reported limb weakness; however, many of these cases likely represented WNV-associated acute flaccid paralysis, which is predominantly due to spinal cord involvement, as has been demonstrated in other studies [9, 16, 17]. The 2003 Colorado epidemic of WNV disease was associated with a higher incidence of acute flaccid paralysis (4.7 cases per 100,000 persons) than has previously been reported [16].

Persons with encephalitis of any etiology are frequently hospitalized for close observation and supportive care. This study reinforces the importance of this practice for patient with WNE because of the potential need for ventilatory support, with or without acute flaccid paralysis. The initial signs and symptoms of WNE are different from those of WNM and should allow practitioners to identify patients at increased risk for respiratory failure. In this study, signs of bulbar dysfunction—particularly dysarthria—and abnormalities such as bladder dysfunction were more commonly observed among patients with WNE than among those with WNM. Even in the absence of confusion or obtundation, these important signs may presage respiratory failure.

Cardiac arrhythmias are a frequent complication in critically ill patients. Although myocarditis has been reported in WNV-infected patients [5, 18], specific arrhythmias have not been reported. This study documents new-onset atrial fibrillation, as well as the exacerbation of existing atrial fibrillation, in patients with WNF, WNM, and WNE. Two patients with WNE required temporary pacemakers for second- and third-degree heart block. Although myocarditis may be the cause of these arrhythmias, histopathologic documentation of vagal sympathetic ganglia involvement in patients with WNE [17] suggests dysautonomia as another possible etiology. Although the incidence and pathophysiology of cardiac arrhythmias in WNV disease are unclear, clinicians may consider instituting cardiac monitoring for patients who are admitted to the hospital for meningitis or encephalitis during the WNV transmission season.

We found that WNF, which has been considered to be a relatively benign illness [5], occurred in nearly one-fourth of hospitalized patients with WNV disease in the study area during a 2-month period in 2003. In a recent retrospective study of WNF, 30% of cases involved hospitalization [10]. Like this previous study, our findings suggest that WNF is associated with considerable morbidity, including limb weakness and arrhythmias, especially among middle-aged and older persons.

One limitation of our study was related to use of hospital charts as the data source. Only 50% of Denver county residents in this study had hospital records available for review by the end of 2003; we do not know whether unreviewed charts differed from those of the larger group or what the influence their information would have on our conclusions. Because this was a retrospective study, we were limited to the information obtained and recorded by the attending physician. Reported variables, such as alcohol or drug abuse, are a function of the physician's subjective standards and the rigor with which these factors are elicited and recorded. Similarly, discerning whether such habits occurred in the remote past or recently is often not possible. One other limitation is potential misclassification of patients by clinical diagnosis. For example, up to 20% of patients with WNM had symptoms of encephalopathy that lasted <24 h, according to their charts. Whether these symptoms lasted <24 h or, possibly, were not accurately noted or reported is not known. Given the prominence of obtundation, disorientation, or other symptoms of encephalopathy, and given the emphasis on such symptoms in physician and nursing records, it seems unlikely that clinicians would have failed to record them, making misclassification of WNE unlikely.

Downloaded from https://academic.oup.com/cid/article-abstract/42/9/1234/314293 by Northwestern University Library user on 23 January 2019

This population-based study confirms that increasing age, immunosuppression, and diabetes mellitus are associated with severe neuroinvasive WNV disease, and it suggests that patients who abuse alcohol may be at an increased risk. In addition, the results show that increasing age and WNE are risk factors for acute flaccid paralysis, that atrial fibrillation and heart block may be common among WNV-infected patients, and that WNF is associated with substantial morbidity, especially among elderly persons. Because no specific treatment for WNV disease exists, and because a human vaccine will not be soon available, health care providers should encourage use of personal protection during the WNV transmission season [18] and support sustained mosquito-control programs in their communities.

Acknowledgments

We acknowledge the contributions of the infection-control practitioners, infectious diseases clinicians, and neurologists of Boulder, Denver, Larimer, and Weld counties, Colorado; J. Lehman, K. Kniss, and P. Collins of the Centers for Disease Control and Prevention for logistical support; and L. Polakowski and D. Berndt of the University of Colorado Health Sciences Center for medical record review.

Potential conflicts of interest. All authors: no conflicts.

References

1. Hayes EB, Komar N, Nasci RS, Montgomery SP, O'Leary DR, Campbell GL. Epidemiology and transmission dynamics of West Nile virus disease. Emerg Infect Dis **2005**; 11:1167–73.
2. Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases. West Nile virus: statistics, surveillance, and control. Available at: http://www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount05_detailed.htm. Accessed 22 December 2005.
3. Centers for Disease Control and Prevention. West Nile virus activity—United States, November 20–25, 2003. MMWR Morb Mortal Wkly Rep **2003**; 52:1160.
4. Centers for Disease Control and Prevention. West Nile virus activity—United States, November 9–16, 2004. MMWR Morb Mortal Wkly Rep **2004**; 53:1071–2.
5. Campbell GL, Marfin AA, Lanciotti RS, Gubler DJ. West Nile virus. Lancet Infect Dis **2002**; 2:519–29.
6. Nash D, Mostashari F, Fine A, et al. The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med **2001**; 344:1807–14.
7. Weiss D, Carr D, Kellachan J, et al. Clinical findings of West Nile virus infection in hospitalized patients, New York and New Jersey, 2000. Emerg Infect Dis **2001**; 7:654–8.
8. 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.
9. Sejvar JJ, Haddad MB, Tierney BC, et al. Neurologic manifestations and outcome of West Nile virus infection. JAMA **2003**; 290:511–5.
10. Watson JT, Pertel PE, Jones RC, et al. Clinical characteristics and functional outcomes of West Nile fever. Ann Intern Med **2004**; 141:360–5.
11. Colorado Department of Public Health and Environment, Disease Control and Environmental Epidemiology Division. West Nile virus: human West Nile virus infections: Colorado, 2003. 7 April **2004**. Available at: http://www.cdphe.state.co.us/dc/zoonosis/wnv/HUMAN_WNV_03.HTML. Accessed 15 February 2006.
12. United States Census Bureau. Quick facts by state. **2000**. Available at: http://quickfacts.census.gov/qfd/states/08000.html. Accessed 15 February 2006.
13. Martin DA, Biggerstaff BJ, Allen B. Use of immunoglobulin M cross-reactions in differential diagnosis of human flaviviral encephalitis infections in the United States. Clin Diagn Lab Immunol **2002**; 9:544–9.
14. Sejvar JJ, Bode AV, Curiel M, Marfin AA. Post-infectious encephalomyelitis associated with St. Louis encephalitis virus infection. Neurology **2004**; 63:1719–21.
15. Kumar D, Drebot MA, Wong SJ, et al. A seroprevalence study of West Nile virus infection in solid-organ transplant recipients. Am J Transplant **2004**; 4:1883–8.
16. Sejvar JJ, Bode AV, Marfin AA, et al. West Nile virus-associated flaccid paralysis. Emerg Infect Dis **2005**; 11:1021–7.
17. Fratkin JD, Leis AA, Stokic DS, et al. Spinal cord neuropathology in human West Nile virus infection. Arch Pathol Lab Med **2004**; 128:533–7.
18. Omalu BI, Shakir AA, Wang G, et al. Fatal fulminant pan-meningopolioencephalitis due to West Nile virus. Brain Pathol **2003**; 13:465–72.

Downloaded from https://academic.oup.com/cid/article-abstract/42/9/1234/314293 by Northwestern University Library user on 23 January 2019