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Case report

Delayed-onset and recurrent limb weakness associated with West Nile virus infection

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Human neurologic illness following infection with West Nile virus (WNV) may include meningitis, encephalitis, and acute flaccid paralysis (AFP). Most WNV-associated AFP is due to involvement of the spinal motor neurons producing an anterior (polio)myelitis. WNV poliomyelitis is typically characterized by acute and rapidly progressing limb weakness occurring early in the course of illness, which is followed by death or clinical plateauing with subsequent improvement to varying degrees. We describe four cases of WNV poliomyelitis in which the limb weakness was characterized by an atypical temporal pattern, including one case with onset several weeks after illness onset, and three cases developing relapsing or recurrent limb weakness following a period of clinical plateauing or improvement. Delayed onset or recurrent features may be due to persistence of viral infection or delayed neuroinvasion with delayed injury by excitotoxic or other mechanisms, by immune-mediated mechanisms, or a combination thereof. Further clinical and pathogenesis studies are needed to better understand the mechanisms for these phenomena. Clinicians should be aware of these clinical patterns in patients with WNV poliomyelitis. *Journal of NeuroVirology* (2010) **16,** 93–100.

Keywords: myelitis; neuroinvasive disease; poliomyelitis; West Nile virus

Introduction

West Nile virus (WNV) is a neurotropic flavivirus that is naturally transmitted to humans through the bite of infected mosquitoes of the *Culex* spp. (Hayes, 2005). Most human infections are asymptomatic, and most clinical illness is characterized by a mild, self-limited febrile syndrome associated with fatigue, myalgias, and rash. A small percentage of cases, particularly older persons and immunocompromised individuals, develop West Nile neuroinvasive disease (WNND) characterized by aseptic meningitis or encephalitis; however, a smaller number of persons may develop acute flaccid paralysis as a manifestation of WNND (Li *et al*, 2003). This is most commonly due to viral infection of spinal anterior horn cells, resulting in anterior (polio)myelitis. WNV poliomyelitis typically has an onset within a short time after development of initial symptoms, with rapid progression to clinical nadir evolving over hours to days. It is generally associated with a monophasic course, with death in a minority of cases and, in others, development of a clinical plateau, with

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varying degrees of subsequent improvement. We describe four cases of WNV poliomyelitis characterized by unusual features, including delayed onset of weakness or recurrent limb weakness following a period of clinical plateauing or improvement (Table 1).

Case 1

A 40-year-old previously healthy woman from New Mexico developed a sensation of muscle tightness in her lower back on August 14, 2003. The following day, she developed acute fever and headache. On day 3 after onset, she presented to an emergency department with fever, headache, photophobia, nausea, and difficulty concentrating. There was no demonstrable weakness on examination. A lumbar puncture was performed, and showed a cerebrospinal fluid (CSF) white blood cell (WBC) count of 263/mm^3 (74% lymphocytes), protein of 98 mg/dl, and glucose of 51 mg/ dl. She was hospitalized overnight and discharged the following day. On day 7 of illness, she sought serologic testing for WNV; WNV-specific immunoglobulin M (IgM) antibodies were identified in a single titer by testing from the state health department laboratory. On about day 13 of illness, she developed weakness and pain in the right leg, as well as a sensation of "twitching" in muscles diffusely, with the right leg most affected. There was no other associated weakness, and there was no subjective numbness. Over the next several days the right leg weakness gradually worsened, first to the point of requiring a cane, and then to the point of inability to ambulate. There was no weakness in the left leg or the upper extremities, and there was no bowel or bladder dysfunction.

She presented to a neurologist on day 40 of illness, where examination was notable for normal strength and sensation in the upper extremities and left lower extremity, but diffuse weakness of the right lower extremity, with 3/5 strength of proximal leg muscles, and 4/5 weakness of ankle flexion; there was mild atrophy present in proximal and distal right leg muscles, and no fasciculations were noted. She was diffusely hyporeflexic, but with absent deep tendon reflexes (DTRs) in the right leg. Over the next several months, she gradually improved in strength, remaining essentially unable to ambulate, but was not hospitalized. She noted leg "twitching," hand tremors, and photophobia lasting several months. By November, she was able to ambulate with aid of a cane; neurologic examination on November 24 (90 days after onset) demonstrated mild weakness (4+/5) of right proximal leg muscles and normal strength distally. By March 2004, she had achieved normal strength and gait. Serum tested in December 2004 demonstrated a WNV-specific IgG antibody titer of 2.53 and IgM antibody titer of 0.26 by IgM antibody capture–enzyme-linked immunosorbent assay (MAC-ELISA). Electrodiagnostics performed in December 2004 demonstrated slightly prolonged right tibial F-wave, and "neurogenic" motor units suggestive of chronic denervation in quadriceps bilaterally.

Case 2

A 44-year-old male from northern Colorado with no prior medical conditions or immune suppression developed acute fever, headache, and myalgias around August 15, 2003. The following day he experienced lower extremity weakness, right greater than left, which progressed in severity over the next 72 h to the point that he was unable to ambulate. Weakness was associated with sharp pain in the affected limbs. On day 4 of illness, he presented to hospital, where he continued to complain of headache, myalgias, and lower extremity pain and weakness. Neurologic evaluation at admission demonstrated a left abducens nerve palsy and asymmetric lower extremity weakness, with 3/5 strength in right hip and knee flexion/extension, 2/5 strength in right dorsi/plantar flexion, and 4/5 strength in left leg muscles diffusely. Knee and ankle DTRs were absent bilaterally. There were no sensory deficits. CSF examination demonstrated 168 WBCs/mm^3 (87% lymphocytes), protein of 87 mg/dl, glucose of 55 mg/dl. WNV-specific IgM antibodies were detected in the CSF. There were no features of meningitis, and mental status was normal. There was no bowel or bladder dysfunction.

Electrodiagnostics performed on August 25 demonstrated normal conduction velocities, decreased motor amplitudes, and slightly prolonged F-waves in lower extremity nerves, and normal sural sensory studies, consistent with a severe asymmetric process involving motor axons and/ or anterior horn cells. By day 15 of illness, he had gradually improved in strength, with 4/5 strength in right knee flexion/extension and 3/5 strength in right dorsi/plantar flexion, and the abducens palsy had resolved. However, on day 20 of illness, he developed rapidly worsening lower extremity weakness, and within 24 h had developed bilateral lower extremity flaccid paralysis. He complained of upper extremity weakness and shortness of breath. Due to declining arterial blood gas measurements and respiratory distress, he was intubated. On day 22 of illness, he developed acute ventricular fibrillation, was unable to be resuscitated, and died. Autopsy was not performed.

Case 3

A 64-year-old woman from New England had a history of follicular lymphoma diagnosed in 2005, transformed to diffuse B-cell lymphoma in 2008 and subsequently treated with rituximab,

Table 1 Dates of illness and weakness onset, clinical course, interval between illness onset and weakness relapse, method of laboratory diagnosis of West Nile virus (WNV) infection, and outcome at last follow-up for 4 cases of WNV-associated delayed-onset or relapsing limb weakness

Case	Age/ Sex	Date of illness onset	Date of weakness onset	Clinical course	Onset-relapse interval	WNV laboratory diagnosis	Outcome
1	40/F	08/14/2003	08/27/2003	Initial development of fever, headache, and "muscle tightness" in the lower back, followed by clinical stabilization. On day 13 of illness, developed acute asymmetric lower extremity weakness, worse in the right leg.	N/A	WNV-specific serum IgM antibody detected during acute illness; elevated serum IgG antibody titers detected in convalescent sample	Recovery of normal strength and ambulation by 7 months after acute illness
2	44/M	08/15/2003	08/16/2003	Acute onset of fever, headache, and myalgias, followed 1 day later by rapidly worsening asymmetric lower extremity weakness. Clinical plateauing followed by improvement over next 1.5 weeks. Subsequently experienced rapidly worsening upper and lower extremity weakness.	20 days	WNV-specific IgM antibodies detected in CSF	Developed acute cardiac arrhythmia and died on day 23 of illness.
3	64/F	09/16/2009	09/18/2009	Acute onset of fever and headache followed by mild progressing leg weakness and encephalopathy. Clinical improvement was followed by acute worsening of leg weakness	35 days	WNV RNA detected in autologous bone marrow transplant specimen (prior to illness onset) and in acute serum specimen after illness onset	Recovery of strength, with trace weakness of distal right leg muscles and mild difficulty with ambulation by 6 months after acute illness.
4	68/M	08/07/2008	08/07/2008	Acute fever, headache, and nausea, accompanied by progressive asymmetric weakness of legs. Clinical stabilization, followed by delayed acute worsening of leg weakness.	49 days	WNV-specific antibodies detected in convalescent serum	Gradual improvement in lower extremity strength. By 5 months after illness onset, still with marked right leg weakness and mild distal left leg weakness

cyclophosphamide, doxorubicin, vincristine, and prednisone. An autologous donation of the patient's blood for stem cell transplantation obtained on September 12, 2008, had tested positive for WNV RNA by nucleic acid amplification testing (NAAT), and was destroyed. On September 16th, she presented with fever up to 102°F and chills. Two days after fever onset, she was admitted to hospital with complaints of fever, chills, and progressing leg weakness. She was treated with antibiotics, and discharged on day 4 of illness; serology for WNV antibodies was negative, but serum was WNV polymerase chain reaction (PCR)-positive. She was readmitted on day 8 with increasing fevers, fatigue, weakness, and decline in mental status. She was transferred the same day to intensive care, and treated with polyclonal intravenous immune globulin and antibiotics. CSF at admission demonstrated 165 WBCs/mm^3 (43% lymphocytes, 41% neutrophils), 15 red blood cells (RBCs)/mm^3, protein of 124 mg/dl, and glucose of 47 mg/dl; testing for WNV RNA and WNV-specific antibodies was negative. The patient remained febrile and encephalopathic for the next 7 days, but by day 12 began to improve. At this time, she had generalized fatigue, but no focal weakness was noted. Convalescent serum collected 16 days after onset was negative for WNV RNA or WNV-specific antibodies.

On day 24, the patient was transferred to inpatient rehabilitation. She was alert and oriented, with no cranial nerve abnormalities. She was noted to be diffusely mildly weak, with slightly diminished DTRs globally, and with intact sensation. She continued to progressively improve; however, on day 35 of illness, she developed acute worsening of left proximal leg weakness, which worsened over the next 24 h. The following day, neurologic evaluation demonstrated 3/5 strength in left hip flexors and extensors, and 2/5 strength in left knee and ankle flexors and extensors; there was no bowel or bladder dysfunction. A magnetic resonance imaging (MRI) of the lumbosacral spine demonstrated diffuse degenerative joint disease with very mild central canal stenosis but no cord abnormalities. Electrodiagnostics performed on day 37 (Table 2) demonstrated normal distal latencies and conduction velocities, with decreased motor amplitudes in lower extremity nerves greater on the right, consistent with a severe asymmetric process involving motor axons and/or anterior horn cells. Electromyography (EMG) of the lower extremities showed neuropathic changes, greater proximally, and spontaneous activity in paraspinal muscles. Repeat CSF drawn on day 37 demonstrated 28 WBCs/mm^3 (96% lymphocytes), 1 RBC/mm^3, protein of 156 mg/dl, and glucose of 51 mg/dl; CSF testing was negative for WNV antibodies or RNA. She was acutely rehospitalized, and over the next several days, her weakness stabilized. She was discharged on day 58, wheelchair-dependent. Over the next several months, she gradually improved and was able to ambulate with crutches.

Case 4

A 68–year-old male from Minnedosa, Manitoba, had no significant previous medical problems except for a remote occipital infarct and right knee arthroscopic surgery. On about August 7, 2008, he developed an illness with fever, mild headache, nausea, and anorexia. From the onset of this illness, he experienced progressive weakness and aching discomfort in his legs, more marked on the right side. He was admitted to hospital on day 14 of illness. On examination his temperature was 39°C. He had moderate weakness in the right leg (grade 3/5 strength), mild left leg weakness (grade 4/5 strength), worse proximally, and mild distal left arm weakness and reduced DTRs in the legs, and no Babinski's signs. Sensory examination was normal. CSF showed 143 WBCs/mm^3 (96% mononuclear), protein 78 mg/dl, and glucose 30 mg/dl (serum 53). A convalescent serum drawn 95 days after illness onset was positive for WNV-specific antibodies. MRI of the spinal cord showed mild enhancement of the conus medullaris and bilateral ventral roots in a symmetrical distribution. He remained stable in hospital and was transferred for rehabilitation on day 22.

There was little change in his neurological status until September 25 (day 49), when over a period of about 24 h he developed worsening of his leg weakness. Right leg strength became 0/5 and the left leg 3/5. Sensation was normal. Bladder and bowel function remained intact. Repeat CSF showed 6 WBCs/mm^3 (100% mononuclear), protein 80 mg/dl, and glucose 38 mg/dl. Repeat spinal MRI was unchanged. Electromyography (Table 2) showed widely distributed moderate to marked reinnervation changes with reduction of recruitment, with fibrillations in the right quadriceps muscle and the left tibialis anterior. He was discharged from hospital on day 60 without any significant improvement in his weakness. However, after discharge he noted progressive improvement beginning later in the month. Examination on January 28, 2009 (day 174) showed right leg strength of 2/5 and left leg strength of 5/5 proximally and 4/5 distally. He has had impotence since the onset of the acute illness.

Discussion

Although most WNND is manifest as meningitis or encephalitis, acute flaccid paralysis is another presentation of severe WNV infection, and may occur with or without concomitant meningoencephalitis (Flaherty *et al*, 2003; Li *et al*, 2003; Saad *et al*,

Table 2 Electrophysiologic data on 4 cases of West Nile virus–associated delayed onset or relapsing limb weakness

			Patient 1				Patient 2				Patient 3*				Patient 4			
			Amp (mV)		CV (m/s)		Amp (mV)		CV (m/s)		Amp (mV)		CV (m/s)		Amp (mV)		CV (m/s)	
	Stimulation site	Recording site	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
Median motor	Wrist	APB													12.0			
	Elbow	APB	11.4		56										10.8		48.7	
Median sensory#			99.9		—													
Ulnar motor	Wrist																	
	B Elbow		9.1		55													
Ulnar sensory#			34		—													
Peroneal motor	Ankle	EDB	—		—		0.7	1.2			0.7	1.0			0.11	1.3		
	Popliteal Fossa	EDB	2.7		47		1.0	3.1	47.0	44.0	0.4	0.9	42.7	49.0	0.22	1.1	18.5	45.7
Tibial motor	Ankle	AHB	24.9		41		0.9	2.2			1.6	3.5			0.14	5.0		
	Knee	AHB					0.8	2.7	47.0	49.0	1.2	4.0	46.0	41.2	0.22	2.6	31.8	37.3
Peroneal sensory#															9.0		38.9	
Sural sensory#			25		NR		12.4		28.3		15.5	7.39	29.5	28.34	1.6		44.6	
EMG			Scattered neurogenic motor units on activation with normal motor unit numbers. No evidence of acute denervation.				Reduced recruitment and increased spontaneous activity in lower extremities, proximal >distal.				Increased spontaneous activity, large, complex motor unit action potentials with polyphasia, and decreased recruitment in lower extremities, proximal >distal.				Widespread reduced recruitment; spontaneous activity noted in left tibialis anterior and right vastus lateralis, with no other spontaneous activity.			

*Right limb performed 10/23/2008; left limb and EMG performed 10/28/2008.
#Sensory study amplitudes recorded in μV.
Unless otherwise noted, blank spaces indicate study not performed. Dashes indicate no data available.

2005; Sejvar *et al*, 2003). Several etiologies of WNV-associated acute flaccid paralysis have been described, including acute inflammatory demyelinating polyradiculoneuropathy [AIDP] (Ahmed *et al*, 2000; Leis and Stokic, 2005), multifocal motor neuropathy (Sumner and Jones, 2008), and brachial plexopathy (Leis and Stokic, 2005; Sejvar *et al*, 2003). However, the most common etiology appears to be viral involvement of spinal anterior horn cells resulting in acute anterior (polio)myelitis (Al-Shekhlee and Katirji, 2004; Glass *et al*, 2002; Leis *et al*, 2002, 2003; Li *et al*, 2003; Saad *et al*, 2005; Sejvar *et al*, 2003). WNV poliomyelitis is characterized by the onset of flaccid limb weakness or paralysis associated with diminished or absent DTRs. Weakness is frequently asymmetric, and may be limited to one limb (Li *et al*, 2003; Sejvar *et al*, 2003). Although sensory loss is uncommon, weakness is frequently accompanied by aching or pain in affected limbs similar to that reported in poliovirus-associated poliomyelitis (Bendz, 1954). Approximately 30% of patients have involvement of the diaphragm and/or intercostal muscles resulting in acute neuromuscular respiratory failure; this manifestation is associated with high morbidity and mortality (Leis *et al*, 2003; Sejvar *et al*, 2003, 2005). Spinal MRI may demonstrate signal abnormalities in affected cord regions, particularly on T2-weighted sequences and/or gadolinium enhancement of nerve roots (Kraushaar *et al*, 2005; Li *et al*, 2003; Malzberg *et al*, 1993; Park *et al*, 2003). Electrodiagnostics will frequently demonstrate decreased motor amplitudes with normal conduction velocities, prolonged F-waves, and normal sensory studies, suggestive of involvement of motor axons and/or anterior horn cells (Al-Shekhlee and Katirji, 2004; Asbury *et al*, 1990; Glass *et al*, 2002; Leis *et al*, 2002; Li *et al*, 2003). CSF generally demonstrates a mild to moderate pleocytosis and elevated protein (Tyler *et al*, 2006). These electrodiagnostic and CSF findings are helpful in differentiating poliomyelitis due to WNV and other viruses from other etiologies of acute flaccid paralysis, such as AIDP and botulism.

WNV poliomyelitis generally presents early in the course of WNV illness; one series determined a median interval between illness onset and onset of limb weakness of 3 days (Sejvar *et al*, 2005), and weakness onset greater than 1 week after initial illness is unusual. Although data are limited, most studies suggest that weakness evolves rapidly over a period of days, followed by death or subsequent clinical plateauing followed by varying degrees of improvement (Li *et al*, 2003; Sejvar *et al*, 2005). About one third of patients will experience substantial limb strength recovery, a third less pronounced strength recovery, and a third experience little or no recovery from clinical nadir (Sejvar *et al*, 2006). Our patients differ from this clinical pattern. Case 1 had the first onset of limb weakness over 2 weeks after illness onset. Case 2 had worsening of weakness after a period of initial improvement, whereas Cases 3 and 4 had worsening after a period of clinical stabilization.

The underlying pathogenic mechanisms for the development of WNV poliomyelitis are not well understood. WNV likely spreads to the CNS by the hematogenous route. Recent *in vitro* studies have shown that WNV spreads within the CNS by both anterograde and retrograde axonal transport (Samuel *et al*, 2007). These authors have postulated that acute flaccid paralysis may be a stochastic event that reflects viral entry into the peripheral nerves, based on *in vivo* studies in hamsters using peripheral inoculation into the sciatic nerve. Viral dissemination throughout the CNS likely occurs by axonal transport. Morrey *et al* (2008) have shown that a neutralizing monoclonal antibody directed the E16 capsid protein can prevent the development of acute flaccid paralysis in experimentally infected hamsters after the development of infection of spinal cord neurons. This raises the possibility of future therapeutic approaches.

The explanation for the prolonged period between illness onset and weakness, or for the relapse/delayed worsening of weakness in our cases is not clear. Persistent isolation of virus associated with recurrent or relapsing illness has been observed in the setting of infection with the closely related flaviviruses Japanese encephalitis virus and tick-borne encephalitis virus (Kuno, 2001), and viral RNA has been isolated from the synovial tissue of one patient with the arthritogenic arbovirus chikungunya 5 weeks after illness onset (Brighton and Simson, 1984; Carmona *et al*, 2008). Cases of relapsing or recrudescent meningitis and encephalitis from WNV have anecdotally been reported (personal communications to J. J. Sejvar). However, to date, no cases of clinical relapsing illness have been associated with clear evidence of viral persistence. Presence of WNV RNA and WNV antigens have been detected in CSF and brain tissue in a patient with B-cell lymphoma over 70 days after initial infection (Penn *et al*, 2006). Delayed neuroinvasion into the spinal cord with infection of anterior horn neurons is a possibility. This seems most likely in Case 1, where there was delayed-onset limb weakness. However, the mechanisms that might be involved for delayed neuroinvasion are unknown.

Muscle weakness in acute flaccid paralysis may result from direct viral damage to ventral horns cells and/or their neuronal processes. Excitotoxicity has been shown to be important in producing flaccid paralysis in experimental infection in mice with Sindbis virus, an arbovirus in the family Togaviridae (Darman *et al*, 2004; Nargi-Aizenman and Griffin, 2001). Neuronal injury has been suggested to occur in the setting of spinal cord injury (Park *et al*, 2004) and in neurodegenerative diseases, such as amyotrophic lateral sclerosis (Sun *et al*, 2006), on the basis of excitotoxicity. Thus, excitotoxicity-mediated neuronal injury is a potential mechanism in WNV

poliomyelitis, and other mechanisms of injury or death of anterior horn cells or injury to motor nerve roots may play an important role.

Cases 2, 3, and 4 all developed recurrent clinical disease within a period of 3 to 7 weeks after the onset of illness, a time frame consistent with an immune-mediated mechanism for recurrence in these patients. Repeat CSF analyses on Cases 3 and 4 at the time of recurrent limb weakness showed substantial reduction in the CSF pleocytosis compared with the time of the initial illness. The development of cross-reactive antibodies or inflammatory cells is the presumptive mechanism for the development of neurologic disease occurring days or weeks following an antecedent antigenic challenge by infection in the setting of postinfectious inflammatory polyradiculoneuropathies (Hughes and Cornblath, 2005; Van der Meche *et al*, 2001) and acute disseminated encephalomyelitis (Johnson, 1998; Tenembaum *et al*, 2007). A similar mechanism has not been described with specific involvement of ventral horn cells, but an immune-mediated motor axonopathy (acute motor axonal neuropathy; AMAN), resulting in acute flaccid paralysis, has been described (Feasby *et al*, 1986; Heckmann *et al*, 1999). The lack of progression followed by a major relapse occurring within about 3 to 7 weeks, the development of asymmetrical motor weakness with relative preservation of reflexes (particularly in the upper extremities), and the lack of nerve conduction slowing or block argue against Guillain-Barré syndrome (Asbury *et al*, 1990), or subacute inflammatory demyelinating polyneuropathy (Oh *et al*, 2003). However, the timing of the onset and the anatomical distribution of the recurrent limb weakness in our cases suggest the possibility of an immune-mediated mechanism directed against West Nile virus–infected motor neurons and/or ventral nerve roots. Repeat MR imaging and CSF analyses have not provided any direct evidence for a mechanism for recurrent clinical disease in our cases. It is possible that direct viral injury through viral neuroinvasive, excitotoxic, immune-mediated, or other mechanisms, or a combination of these might play a role in the recurrent limb weakness with involvement of ventral horn cells and/or nerve roots.

Further clinical and pathophysiologic studies are needed to better understand the clinical and virologic underpinnings of WNV poliomyelitis in general, and the phenomenon of delayed-onset or recurrent worsening of clinical weakness in particular. Clinicians should be aware of these clinical patterns and closely follow patients with WNV poliomyelitis over the days and weeks following illness onset.

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References

Ahmed S, Libman R, Wesson K, Ahmed F, Einberg K (2000). Guillain-Barré syndrome: an unusual presentation of West Nile virus infection. *Neurology* **55:** 144–146.

Al-Shekhlee A, Katirji B (2004). Electrodiagnostic features of acute paralytic poliomyelitis associated with West Nile virus infection. *Muscle Nerve* **29:** 376–380.

Asbury AK, Cornblath DR (1990). Assessment of current diagnostic criteria for Guillain-éBarré syndrome. *Ann Neurol* **27(Suppl):** S21–S24.

Bendz P (1954). Pain associated with acute poliomyelitis; neurologic and therapeutic considerations. *AMA Am J Dis Child* **88:** 141–147.

Brighton SW, Simson IW (1984). A destructive arthropathy following Chikungunya virus arthritis—a possible association. *Clin Rheumatol* **3:** 253–258.

Carmona RJ, Shaikh S, Khalidi NA (2008). Chikungunya viral polyarthritis. *J Rheumatol* **35:** 935–936.

Darman J, Backovic S, Dike S, Maragakis NJ, Krishnan C, Rothstein JD, Irani DN, Kerr DA (2004). Viral-induced spinal motor neuron death is non-cell-autonomous and involves glutamate excitotoxicity. *J Neurosci* **24:** 7566–7575.

Feasby TE, Gilbert JJ, Brown WF, Bolton CF, Hahn AF, Koopman WF, Zochodne DW (1986). An acute axonal form of Guillain-Barré polyneuropathy. *Brain* **109(Pt 6):** 1115–1126.

Flaherty ML, Wijdicks EF, Stevens JC, Daube JR, Chenworth EC, Helou EF, Sohail MR (2003). Clinical and electrophysiologic patterns of flaccid paralysis due to West Nile virus. *Mayo Clin Proc* **78:** 1245–1248.

Glass JD, Samuels O, Rich MM (2002). Poliomyelitis due to West Nile virus. *N Engl J Med* **347:** 1280–1281.

Hayes EB (2005). Virology, pathology, and clinical manifestations of West Nile virus disease. *Emerg Infect Dis* **11:** 1174–1179.

Heckmann JG, Sommer JB, Druschky A, Erbguth FJ, Steck AJ, Neundorfer B (1999). Acute motor axonal neuropathy associated with IgM anti-GM1 following Mycoplasma pneumoniae infection. *Eur Neurol* **41:** 175–176.

Hughes RA, Cornblath DR (2005). Guillain-Barré syndrome. *Lancet* **366:** 1653–1666.

Johnson R (ed) (1998). Postinfectious demyelinating disease. Philadelphia, New York: Lippincott-Raven.

Kraushaar G, Patel R, Stoneham GW (2005). West Nile virus: a case report with flaccid paralysis and cervical spinal cord: MR imaging findings. *AJNR Am J Neuroradiol* **26:** 26–29.

Kuno G (2001). Persistence of arboviruses and antiviral antibodies in vertebrate hosts: its occurrence and impacts. *Rev Med Virol* **11:** 165–190.

Leis AA, Stokic DS (2005). Neuromuscular manifestations of human West Nile virus infection. *Curr Treat Options Neurol* **7:** 15–22.

Leis AA, Stokic DS, Polk JL, Dostrow V, Winkelmann M (2002). A poliomyelitis-like syndrome from West Nile virus infection. *N Engl J Med* **347:** 1279–1280.

Leis AA, Stokic DS, Webb RM, Slavinski SA, Fratkin J (2003). Clinical spectrum of muscle weakness in human West Nile virus infection. *Muscle Nerve* **28:** 302–308.

Li J, Loeb JA, Shy ME, Shah AK, Tselis AC, Kupski WJ, Lewis RA (2003). Asymmetric flaccid paralysis: a neuromuscular presentation of West Nile virus infection. *Ann Neurol* **53:** 703–710.

Malzberg MS, Rogg JM, Tate CA, Zayas V, Easton JD (1993). Poliomyelitis: hyperintensity of the anterior horn cells on MR images of the spinal cord. *AJR Am J Roentgenol* **161:** 863–865.

Morrey JD, Siddharthan V, Wang H, Hall JO, Skirpstunas RT, Olsen AL, Nordstrom JL, Koenig S, Johnson S, Diamond MS (2008). West Nile virus-induced acute flaccid paralysis is prevented by monoclonal antibody treatment when administered after infection of spinal cord neurons. *J NeuroVirol* **14:** 152–163.

Nargi-Aizenman JL, Griffin DE (2001). Sindbis virus-induced neuronal death is both necrotic and apoptotic and is ameliorated by N-methyl-D-aspartate receptor antagonists. *J Virol* **75:** 7114–7121.

Oh SJ, Kurokawa K, de Almeida DF, Ryan HF Jr, Claussen GC (2003). Subacute inflammatory demyelinating polyneuropathy. *Neurology* **61:** 1507–1512.

Park E, Velumian AA, Fehlings MG (2004). The role of excitotoxicity in secondary mechanisms of spinal cord injury: a review with an emphasis on the implications for white matter degeneration. *J Neurotrauma* **21:** 754–754.

Park M, Hui JS, Bartt RE (2003). Acute anterior radiculitis associated with West Nile virus infection. *J Neurol Neurosurg Psychiatry* **74:** 823–825.

Penn RG, Guarner J, Sejvar JJ, Hartman H, McComb RD, Nevins DL, Bhatnagar J, Zaki SR (2006). Persistent neuroinvasive West Nile virus infection in an immunocompromised patient. *Clin Infect Dis* **42:** 680–683.

Saad M, Youssef S, Kirschke D, Shubair M, Haddadin D, Myers J, Moorman J (2005). Acute flaccid paralysis: the spectrum of a newly recognized complication of West Nile virus infection. *J Infect* **51:** 120–127.

Samuel MA, Wang H, Siddharthan V, Morrey JD, Diamond MS (2007). Axonal transport mediates West Nile virus entry into the central nervous system and induces acute flaccid paralysis. *Proc Natl Acad Sci U S A* **104:** 17140–17145.

Sejvar JJ, Bode AV, Marfin AA, Campbell GL, Ewing D, Mazowiecki M, Pavot PV, Schmitt J, Pape J, Biggerstaff BJ, Petersen LR (2005). West Nile virus-associated flaccid paralysis. *Emerg Infect Dis* **11:** 1021–1027.

Sejvar JJ, Bode AV, Marfin AA, Campbell GL, Pape J, Biggerstaff BJ, Petersen LR (2006). West Nile Virus-associated flaccid paralysis outcome. *Emerg Infect Dis* **12:** 514–516.

Sejvar JJ, Leis AA, Stokic DS, Van Gerpen JA, Marfin AA, Webb R, Haddad MB, Tierney BC, Slavinski SA, Polk JL, Dostrow V, Winkelmann M, Petersen LR (2003). Acute flaccid paralysis and West Nile virus infection. *Emerg Infect Dis* **9:** 788–793.

Sumner N, Jones L (2008). Multifocal neuropathy associated with West Nile virus infection. *Neurology* **71:** 1123.

Sun H, Kawahara Y, Ito K, Kanazawa I, Kwak S (2006). Slow and selective death of spinal motor neurons in vivo by intrathecal infusion of kainic acid: implications for AMPA receptor-mediated excitotoxicity in ALS. *J Neurochem* **98:** 782–791.

Tenembaum S, Chitnis T, Ness J, Hahn JS (2007). Acute disseminated encephalomyelitis. *Neurology* **68:** S23–S36.

Tyler KL, Pape J, Goody RJ, Corkill M, Kleinschmidt-DeMasters BK (2006). CSF findings in 250 patients with serologically confirmed West Nile virus meningitis and encephalitis. *Neurology* **66:** 361–365.

Van der Meche FG, Van Doorn PA, Meulstee J, Jennekens FG (2001). Diagnostic and classification criteria for the Guillain-Barré syndrome. *Eur Neurol* **45:** 133–139.

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