Peripheral Nervous System Complications of Infectious Diseases

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Chair: Taylor B. Harrison, MD

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Objectives

Objectives - Participants will acquire skills to discuss the clinical presentation, diagnosis, management, and outcomes of varied peripheral nervous system complications associated with infectious diseases. The course will focus on (1) anterior horn cell disorders, (2) Lyme disease, (3) infectious polyneuropathies, and (4) complications of varicella zoster infection.

Target Audience:

- Neurologists, physical medicine and rehabilitation and other physicians interested in neuromuscular and electrodiagnostic medicine
- Health care professionals involved in the management of patients with neuromuscular diseases
- Researchers who are actively involved in the neuromuscular and/or electrodiagnostic research

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INTRODUCTION

West Nile virus (WNV), a mosquito-borne RNA flavivirus and human neuropathogen, was first isolated from a febrile woman in the West Nile region of Uganda, Africa, in 1937. During the 1940s and 1950s, transmission of WNV by mosquitoes was demonstrated, the close antigenic relationship with flaviviruses was described, and neutralizing antibody was found in many residents of East-Central Africa. The virus also became recognized as a cause of human meningitis or encephalitis in elderly patients during an outbreak in Israel in 1957, although central nervous system (CNS) involvement in middle-aged and younger subjects remained unusual and outcome in the younger age group was generally excellent. During the 1960s to 1970s, birds were identified as a major host, horses were commonly infected, and there were large human epidemics in Africa and the Middle East. Europe also experienced its first WNV outbreak. During the 1980s and 1990s, there were major outbreaks in Africa, the Middle East, Europe, and Russia, although the Romania epidemic in 1996 marked the geographic transition of WNV epidemics from rural areas to urban industrialized areas.¹

The poliovirus has caused paralysis and death for much of human history.² The virus caused major epidemics in Europe in the 1880s and soon after outbreaks appeared in the United States. By 1910, frequent epidemics became regular events throughout the developed world, particularly in cities during the summer months. At its peak in the 1940s and 1950s, polio infected millions of people and paralyzed or killed over half a million people worldwide every year. There are still an estimated 1 million polio survivors in the United States, although the exact incidence and prevalence of postpolio syndrome (PPS) is unknown. Researchers estimate that PPS affects up to 40% of polio survivors.³

West Nile virus gained entry into North America in 1999 in the New York City outbreak.⁴ The viral strain introduced into the United States likely originated from a strain that was circulating in Israel during 1998. In the past decade, WNV has spread and is now widely established from Canada to Venezuela.⁵ In 2011, human cases were reported in Albania, Greece, Israel, Italy, Romania, Russia, and Mexico. Hence, the geographic range of WNV now includes six of seven continents, including Africa, Asia, Europe, Australia (subtype Kunjin), North America, and South America. In contrast, polio cases have decreased by over 99% since 1988, from an estimated 350,000 cases then to 1,352 reported cases in 2010. The reduction is the result of the global effort to eradicate the disease. In 2012, only three countries (Afghanistan, Nigeria, and Pakistan) remain polio-endemic, down from more than 125 in 1988. Persistent pockets of polio transmission in northern Nigeria and the border between Afghanistan and Pakistan are the current focus of the polio eradication initiative. As long as a single child remains infected, children in all countries are at risk of contracting polio. In 2009-2010, 23 previously polio-free countries were reinfected due to imports of the virus.²³

Before 1996, WNV was known to cause high fever, chills, malaise, headache, backache, arthralgia, myalgias, retro-orbital pain, and a maculopapular rash, but neurological symptoms were uncommon. However, since the New York City outbreak, severe neurological illness, including encephalitis and meningitis, has been reported much more frequently, together with neuromuscular manifestations. The diagnosis of WNV infection should be considered in any patient with an unexplained acute febrile or neurological illness during the summer months, particularly if recently exposed to mosquitoes. In such cases serum should be tested for class M immunoglobulin (IgM) antibody to WNV,
which indicates a recent infection. If there are signs of CNS involvement, cerebrospinal fluid (CSF) should be analyzed and also tested for WNV IgM antibody. Cerebrospinal fluid findings typically show increased leukocytes (usually > 200 cells/mm3), increased protein, and normal glucose. Almost half of WNV meningitis patients may have at least 50% neutrophils in their initial CSF specimen, followed by a shift to lymphocytosis. Imaging studies in WNV infection are frequently normal, although they may be useful in excluding other etiologies of acute myelomingingoencephalitis. When abnormal, findings are generally nonspecific and without mass effect. T2-weighted magnetic resonance imaging (MRI) signal abnormalities have been reported in brainstem, deep grey structures (basal ganglia or thalami), and cerebellum. However, other imaging series have found no definite predilection for any specific area of the brain parenchyma. In patients with WNV-associated limb paralysis, abnormal signal intensity may be more pronounced in the spinal cord ventral horns with enhancement around the conus medullaris and cauda equina. However, followup MRIs may show complete resolution of signal abnormalities. Neuromuscular manifestations are now recognized as a prominent feature in patients with WNV neuroinvasive disease (encephalitis, meningitis). In the 1999 New York City outbreak, more than 50% of patients with confirmed WNV encephalitis had severe muscle weakness as a cardinal sign. Weakness was an apparent risk factor predicting death in patients with WNV encephalitis. In the 2002 and 2003 WNV epidemics in the United States, neuromuscular manifestations were a well-recognized feature associated with increased morbidity and mortality. In Colorado, the state with the most reported cases of WNV infection (2,943) and fatalities (63) during the 2003 epidemic, as many as 50% of patients with encephalitis had evidence of acute flaccid paralysis.

NEUROMUSCULAR MANIFESTATIONS OF WEST NILE AND POLIO VIRUS INFECTION

WEST NILE VIRUS POLIOMYELITIS

In the original New York City outbreak, several case series attributed neuromuscular complications, particularly acute flaccid paralysis, to peripheral neural processes, namely Guillain-Barré syndrome (GBS), motor axonopathy, or severe axonal polyneuropathy. In the 2002 epidemic, more cases of WNV-associated acute flaccid paralysis were also seen across the Southern United States. These patients had asymmetric acute flaccid paralysis, absent deep tendon reflexes in affected limbs, preserved sensation, bowel or bladder dysfunction, and respiratory distress. Electrodiagnostic (EDX) studies in these subjects revealed markedly decreased or absent motor responses in the paretic limbs, preserved sensory responses, and widespread asymmetric muscle denervation, without evidence of demyelination or myopathy. The clinical and EDX findings were classic for poliomyelitis and inconsistent with GBS or other peripheral nerve disorders. These cases were first reported in 2002, with clinical, laboratory, and electrophysiologic guidelines to help physicians discern poliomyelitis from GBS (Table 1). Subsequently, clinical, laboratory, and neurophysiologic findings suggested that WNV-associated acute flaccid paralysis was a poliomyelitis syndrome with involvement of anterior horn cells (AHCs) of the spinal cord. Soon thereafter pathologic confirmation of WNV poliomyelitis was obtained (Figure 1, A-C). Indeed, postmortem examinations of patients with WNV infection from the 2002 epidemic showed that poliomyelitis was the major CNS finding in each case. This is in agreement with the neuropathology of experimental or naturally occurring WNV infection in monkeys, horses, and birds. In these vertebrates, WNV shows a pronounced tropism for gray matter of the spinal cord, causing poliomyelitis. In contrast, peripheral nerves are not commonly involved.

Most investigators actively involved in WNV clinical research now accept poliomyelitis to be the most common cause of WNV-associated acute flaccid paralysis in humans. Moreover, the Centers for Disease Control now classifies WNV infection into WNV fever and neuroinvasive disease, with further subdivision of the latter group into encephalitis, meningitis, and poliomyelitis. Patients with the poliomyelitis presentation commonly have associated signs of meningitis, encephalitis, or respiratory distress from involvement of spinal motor neurons supplying the phrenic nerves to the diaphragm, but acute flaccid paralysis also may occur in the absence of fever or meningoencephalitis. Recovery from neurological sequelae of WNV neuroinvasive disease may be slow and incomplete, with a poorer prognosis for recovery of physical function in patients with acute flaccid paralysis. The initial four patients treated by the author in 2002 with acute flaccid paralysis and profound loss of AHCs in paretic limbs, based on EDX studies, remain weak in affected limbs almost a decade after the disease onset.

Table 1. Characteristics in West Nile virus-associated poliomyelitis compared with typical Guillain-Barré syndrome

<table>
<thead>
<tr>
<th></th>
<th>West Nile poliomyelitis</th>
<th>Guillain-Barré syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of onset</td>
<td>Acute phase of infection</td>
<td>Weeks after acute infection</td>
</tr>
<tr>
<td>Fever, leukocytosis</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Weakness distribution</td>
<td>Asymmetric; monoplegia to quadriplegia</td>
<td>Generally symmetric; proximal and distal muscles</td>
</tr>
<tr>
<td>Sensory symptoms</td>
<td>Some myalgias, infrequent numbness, paresthesia, or sensory loss</td>
<td>Sensory loss, painful distal paresthesias</td>
</tr>
<tr>
<td>Bowel and bladder</td>
<td>Often involved</td>
<td>Rarely involved</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Often present</td>
<td>Absent</td>
</tr>
<tr>
<td>CSF profile</td>
<td>Pleocytosis, elevated protein</td>
<td>No pleocytosis, elevated protein (albuminocytologic dissociation)</td>
</tr>
<tr>
<td>Electrodiagnostic features</td>
<td>Anterior horn cell or motor axon loss (reduced/absent CMAPs, preserved SNAPs, asymmetric denervation)</td>
<td>Demyelination (marked slowing of conduction velocity, conduction block, temporal dispersion); reduced SNAPs</td>
</tr>
</tbody>
</table>

CMAP = compound muscle action potential, CSF = cerebrospinal fluid, SNAP = sensory nerve action potential

Modified from Leis and colleagues.
the acute WNV illness. However, each of these patients had needle electromyographic (EMG) evidence of profound denervation in muscles of the most affected limbs with few or no voluntarily recruited motor unit potentials (MUPs) and absent or markedly reduced motor responses with normal sensory responses on nerve conduction studies. Table 2 shows motor and sensory amplitudes in one of these patients, a 50-year-old man with WNV poliomyelitis limited to the right upper limb. Followup nerve conduction studies at 3, 6, and 12 months continued to show markedly reduced motor responses in proximal muscles with normal sensory responses. Followup needle EMG examinations also showed persistent profound denervation in shoulder girdle muscles with only a single voluntarily recruited MUP in deltoid and biceps (Figure 2). This patient never regained the ability to abduct or forward elevate the arm past the horizontal position. In contrast, limbs with lesser degrees of ANC loss, based on the presence of recordable motor responses and preserved innervation on needle EMG, had better recovery of function. Indeed, after performing EDX evaluations on many WNV patients with varying degrees of acute flaccid paralysis observations suggest that prognosis for recovery of function is greatly dependent on the degree of motor neuron loss; limbs with absent motor responses and no voluntary needle EMG activity have a poorer longterm prognosis while those with relatively preserved motor responses and some voluntary activity have a more favorable outcome.

Table 2. Baseline-to-peak amplitudes of motor (m, in mV) and sensory (s, in μV) responses in a 50-year-old man with West Nile poliomyelitis of the right upper limb

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Stimulating site</th>
<th>Recording site</th>
<th>Initial</th>
<th>3-month followup</th>
<th>6-month followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (m)</td>
<td>Wrist</td>
<td>APB</td>
<td>2</td>
<td>11.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Median (s)</td>
<td>Digit II</td>
<td></td>
<td>33.4</td>
<td>35.4</td>
<td>27.2</td>
</tr>
<tr>
<td>Ulnar (m)</td>
<td>Wrist</td>
<td>ADM</td>
<td>1.6</td>
<td>7.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Ulnar (s)</td>
<td>Digit V</td>
<td></td>
<td>28.8</td>
<td>27.6</td>
<td>21.8</td>
</tr>
<tr>
<td>Musculocutaneous (m)</td>
<td>Arm</td>
<td>Forearm</td>
<td>0.2</td>
<td>7.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Musculocutaneous (s)</td>
<td>Erb’s point</td>
<td>Biceps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary (m)</td>
<td>Erb’s point</td>
<td>Forearm</td>
<td>27.1</td>
<td>32.6</td>
<td>21.4</td>
</tr>
<tr>
<td>Radial (s)</td>
<td>Forearm</td>
<td>Dorsum band</td>
<td>31.9</td>
<td>31.8</td>
<td>39.8</td>
</tr>
</tbody>
</table>

ADM = abductor digiti minimi, APB = abductor pollicis brevis, R = right, L = left
Bold data are abnormal.
Modified from Leis and Stokic.16

Figure 2. Needle electromyographic examination in a 50-year-old man with West Nile virus poliomyelitis limited to the right upper limb. Needle examination of the biceps muscle at 1 year followup showed persistent profound denervation with only a single voluntarily recruited rapidly firing motor unit potential. Similar denervation was noted in other shoulder girdle muscles. Clinical followup 5 years later revealed persistent severe weakness in proximal upper limb muscles.

OTHER SPINAL CORD NEUROPATHOLOGY IN WEST NILE VIRUS INFECTION

Although the anterior horns are the major site of spinal cord pathology, autopsy series show that pathologic changes may extend beyond the spinal cord gray matter with focal inflammatory changes involving the adjacent white matter.13 This may explain the infrequent occurrence of WNV-associated transverse myelitis with clinical involvement of spinal sensory and motor pathways (Leis, personal observation). In addition, neuronophagia, neuronal disappearance, and pathologic alterations have been described in dorsal root ganglia and sympathetic ganglia.13 Involvement of dorsal root ganglia may explain some of the sensory deficits and reduced sensory nerve action potentials on EDX testing that occasionally are reported in patients with WNV infection.7 However, sensory loss attributed to WNV has not been a prominent clinical finding. Another often overlooked finding is
the disappearance of neurons in the sympathetic ganglia (Figure 1, D), which offers a plausible explanation for the autonomic instability observed in some patients, including labile vital signs, hypotension, and potentially lethal cardiac arrhythmias. Such data suggest that autonomic instability may play a role in the morbidity and mortality of human WNV infection.

**WEST NILE VIRUS SPINAL NERVE ROOT INVOLVEMENT**

Inflammatory changes in spinal cord gray matter also may extend into the spinal nerve roots to cause a myeloradiculitis. Involvement of ventral spinal roots may contribute to the asymmetric acute flaccid paralysis seen in many patients with WNV infection. Magnetic resonance imaging findings showing apparent enhancement of ventral nerve roots support the concept that anterior radiculopathy should be considered, in addition to AHC pathology, when assessing patients with WNV-associated acute flaccid paralysis. However, acute isolated radiculopathy as the sole neuromuscular manifestation of WNV infection is not common, although confusion may arise when acute flaccid paralysis due to poliomyelitis is limited to one limb (monoparesis). In one series that included 10 patients with WNV poliomyelitis, four patients had monoparesis. The author has also encountered several patients with WNV and asymmetric weakness in the arms or legs who initially were thought to have cervical or lumbosacral radiculopathies.

**WEST NILE VIRUS PERIPHERAL NERVE INVOLVEMENT**

West Nile virus can involve peripheral nerves although this manifestation is much less frequent than originally assumed during the 1999 outbreak, when weakness and acute flaccid paralysis were attributed to GBS or axonal polyneuropathy. In one series of 64 patients with WNV infection, three patients had mixed axonal degenerating and demyelinating processes and one had a pure demyelinating neuropathy. In addition, there are case reports of patients with true GBS, unilateral brachial plexopathy, and bilateral diaphragmatic paralysis attributed to loss of motor neurons or motor axons supplying the phrenic nerves. Lymphocytic infiltration of nerves and occasional degenerating axons also has been described, suggesting that WNV may reach the CNS via peripheral nerves. Indeed, recent evidence suggests that axonal transport may mediate WNV entry into the CNS to induce acute flaccid paralysis. However, most autopsy series do not suggest that WNV exhibits a predilection for peripheral nerves. Similarly, WNV infection in monkeys, horses, and birds does not commonly involve peripheral nerves. In addition, it should be recognized that prolonged critical illness can be associated with an axonal sensorimotor polyneuropathy, termed critical illness polyneuropathy, which can confound the interpretation of WNV-associated polyneuropathy.

**NEUROMUSCULAR JUNCTION AND SKELETAL MUSCLE IN WEST NILE VIRUS INFECTION**

West Nile virus has been reported to be linked to a defect in neuromuscular transmission. The author has described six cases of myasthenia gravis (MG) that developed after acute WNV infection. All patients had serologically confirmed WNV infection that manifested as neuroinvasive disease with poliomyelitis. None had clinical evidence of MG prior to WNV. In all cases, classic MG symptoms (intermittent ptosis, diplopia, dysarthria, dysphagia, fatigue, generalized weakness, and respiratory distress) either began or worsened within several months (range 3-7 months) of WNV infection. However, residual deficits (disabling fatigue and persistent asymmetric weakness) from neuroinvasive WNV often confounded or delayed the diagnosis of MG. All patients had markedly elevated antibodies against the acetylcholine receptor and one had a thymoma. Treatment varied; one patient was managed with only acetylcholinesterase inhibitors (pyridostigmine), one with pyridostigmine and prednisone, and four with pyridostigmine, multiple immunosuppressive drugs, and intravenous immunoglobulin (IVIg) or plasmapheresis for recurrent MG crises. Myopathy also is an uncommon manifestation of WNV infection, although there are several reports of rhabdomyolysis with creatine kinase (CK) levels as high as 45,000 U/L (normal < 220 U/L). However, in one of these reports, postmortem examination confirmed poliomyelitis with striking loss of motor neurons in the anterior horn and brainstem, and only mild inflammation without necrosis in skeletal muscle. In one series, muscle biopsies on four patients with WNV with acute asymmetric paralysis showed scattered necrotic muscle fibers invaded by macrophages (two patients), normal muscle fibers with inflammatory cells surrounding small blood vessels (one patient), and a normal muscle biopsy (one patient). In one of the patients with scattered necrotic muscle fibers, immunohistochemistry with polyclonal antibodies against flaviviruses did not detect WNV on biopsied muscle. These investigators acknowledged that the scattered necrotic muscle fibers were an unlikely explanation for the severe paralysis observed. In the most comprehensive series of rhabdomyolysis in patients with WNV neuroinvasive disease, nine of 244 hospitalized patients had rhabdomyolysis (median age 70 years, CK levels ranged from 1 to 42K IU). However, six of nine patients had history of recent falls prior to admission. The authors concluded that although the temporal relationship of rhabdomyolysis and WNV illness suggested a common etiology, these patients presented with complex clinical conditions that may have led to development of rhabdomyolysis from other causes. In addition, it is now commonly recognized that critical illness can be associated with a diffuse myopathy, termed critical illness myopathy, which can cause generalized weakness, respiratory failure, and inability to wean from the respirator. Accordingly, the role played by direct WNV invasion of muscles and the clinical significance of WNV-associated myositis remains to be elucidated.

West Nile virus has also been reported to cause myocarditis, and cardiomyopathy, which can predispose to fatal arrhythmia. However, cardiac arrhythmias have also been reported to occur across the spectrum of WNV disease, including in cases of WNV fever not associated with myocarditis. Since statistics on the incidence of WNV myocarditis as the cause of cardiac arrhythmias are lacking, it is possible that autonomic instability caused by direct WNV infection of neurons controlling cardiac function may also have precipitated cardiac arrhythmias.
WEST NILE VIRUS AND AUTOIMMUNE DISEASE

An unresolved issue that may have important neuromuscular implications is whether WNV infection can induce autoimmune disease. Support for this contention arises from the numerous reports of WNV patients with various neuromuscular diseases that have a presumed autoimmune mechanism, including GBS, other demyelinating neuropathies, myasthenia gravis, brachial plexopathies, and stiff-person syndrome. In the latter case, stiff-person syndrome with antibodies to glutamic acid decarboxylase developed several weeks after WNV fever. However, longterm followup of patients with WNV infection should clarify whether there is an increased incidence of autoimmune diseases.

SPECTRUM OF NEUROMUSCULAR SYMPTOMS AND SIGNS IN WEST NILE VIRUS INFECTION

In the author’s initial series of 54 WNV patients who had extensive EDX evaluation and a few autopsies, neuromuscular manifestations included: acute flaccid paralysis with electrophysiologic or pathologic features of poliomyelitis (n = 19), clinical findings of autonomic instability (cardiac dysrhythmias, marked fluctuations in blood pressure, gastrointestinal complications including gastroparesis) or pathologic alterations in sympathetic ganglia (n = 7), brainstem dysfunction (n = 4) including three cases of seventh nerve palsies (two delayed several weeks after acute illness and one with acute illness), myopathy (n = 3, in two attributed to critical illness myopathy and one case of rhabdomyolysis with acute renal failure), diffuse axonal polynuropathy (n = 2, one attributed to critical illness polynuropathy and one to acute polynuropathy associated with WNV), new onset myasthenia gravis (n = 2), transverse myelitis with involvement of sensory and motor pathways (n = 1), gait apraxia (n = 1), and optic nerve involvement (n = 1). In the latter case, full-field pattern reversal visual evoked potential studies showed a monoclonal abnormality that suggested a conduction defect in the visual pathways anterior to the optic chiasm. In nine patients, the chief complaint was severe or disabling fatigue without objective muscle weakness on clinical examination or abnormalities on neurophysiologic studies. The specific physiologic mechanism for WNV fatigue remains unknown. In the PPS, poliovirus-induced lesions in the reticular activating system are thought to contribute to the subjective fatigue. In patients with WNV infection, prolonged fatigue is common after the acute illness, affecting nearly two-thirds of patients. At 1 year followup, fatigue was the most common persistent symptom in patients hospitalized from the 1999 New York outbreak, affecting 67% of patients whereas muscle weakness was found in 44% of patients. Thus, physicians should be aware that fatigue and subjective weakness may be the major complaint in patients with WNV infection, particularly in those with WNV fever. In addition, the author observed two patients that developed severe, but reversible, muscle weakness that recovered completely within weeks. Both patients were hospitalized for their weakness. Weakness involved both lower limbs in one patient (paraparesis) and one upper limb in the other (monoparesis). Their neurophysiologic studies were unremarkable after recovery of function, in agreement with the clinical examination. The reversible muscle weakness likely reflects transient AHC dysfunction during the phase of acute WNV illness, with full recovery of function occurring within several weeks. Although rapid reversal of paralysis has rarely been reported with WNV infection, this phenomenon is not new and was first observed in patients with poliomyelitis caused by the poliovirus. Jacob von Heine (1799-1878) recognized the transitory nature of some attacks of paralysis early in the 19th century, and he attributed the rapid improvement to fluid exudate and edema in the spinal cord that was reabsorbed. Therefore, in acute WNV infection, as in acute poliovirus infection, reversible paralysis may reflect transient AHC dysfunction. In two other patients, the author observed that WNV infection caused exaggerated weakness in previously weak limbs (from lumbar spinal stenosis) suggesting that preexisting dysfunction may predispose AHCs to additional injury during acute WNV infection. It is speculated that AHCs that have survived an initial insult, or incorporated too many muscle fibers from denervated motor units beyond the metabolic capability, may be especially prone to injury.

WEST NILE VIRUS IMMUNITY AND PATHOGENESIS

Although postmortem examinations have confirmed WNV poliomyelitis and encephalitis, the precise mechanisms that underlie destruction of neurons remain to be fully elucidated. The increased risk of severe WNV infection in immunosuppressed and elderly patients suggests that an intact immune system is essential for control of WNV. West Nile virus-specific antibodies are responsible for reducing viremia and preventing development of severe disease, while different T-lymphocyte populations play an important role in clearing infection from tissues and preventing viral persistence. However, the possible pathologic effect of the immune system in WNV neuroinvasive disease cannot be overlooked. There is evidence that bystander neuronal death may occur as a result of a cascade of immunobiological events in the spinal cord that impaired glutamate transport and allowed excess glutamate to accumulate extracellulary around motor neurons. West Nile virus neuroinvasive disease is also characterized by increased production of proinflammatory cytokines derived from infected cells and upregulation of other proinflammatory genes. These cytokines and other proinflammatory factors are either neurotoxic or attract leukocytes into the affected area, which further contribute to WNV-induced neurotoxicity. Hence, WNV-induced inflammation is now recognized as a major contributor of neuropathogenesis. The concept of a pathologic effect of the immune system in WNV neuroinvasive disease provides a framework for the development of anti-inflammatory drugs as much needed interventions to limit the cascade of immunobiological events leading to neurotoxicity.

TREATMENT FOR NEUROINVASIVE WEST NILE INFECTION

At present, no specific therapy has been approved for human use in WNV infection. However, the merging knowledge about the pathogenesis of WNV infection has direct therapeutic implications. Treatment strategies that control the previously described cascade of events leading to neuronal death may prove beneficial. Promising therapies include the use of interferon and
interferons, which have been shown to reduce mortality in mice infected by subcutaneous injection of WNV. Other potential therapies include ribavirin, nucleic acids, RNA interference, antisense oligomers, peptides, imino sugars, and mycophenolic acid (for a review, see Diamond). These agents act through distinct mechanisms and are moving through various stages of preclinical development.

The role of corticosteroids in WNV neuroinvasive disease is controversial, with concern that immunosuppressive effects may worsen outcome. However, high-dose steroids have been used successfully in anecdotal reports to treat WNV-associated acute flaccid paralysis and to shorten the acute phase of WNV meningoencephalitis. The author also has administered high-dose intravenous steroids to two patients with acute flaccid paralysis and brainstem involvement, including progressive seventh nerve palsies, who showed clear improvement in brainstem symptoms and facial paralysis within 24 hours of treatment. However, both cases were characterized by an atypical temporal pattern of progressive symptoms or new deficits occurring several weeks after the onset of the acute illness. In most cases, WNV is thought to be cleared by an effective immune response after only several days of viremia. Accordingly, this relatively delayed progression of symptoms is more likely to reflect secondary injury from the downstream cascade of excitotoxic events and a secondary wave of inflammation. In cases where the temporal course suggests that indirect immune-mediated mechanisms may be contributing to neuronal injury, a trial of high-dose corticosteroids seems justified. There also has been great interest in passive immunization with IVIg for the treatment of patients with acute WNV infection. Immune serum frequently was used in the pre-antibiotic era to treat infectious diseases, and animal data indicate an important role for humoral immunity in controlling WNV infection. Given the endemic nature of WNV in the Middle East, IVIg obtained from Israeli blood donors that contains WNV-specific antibodies provides clear-cut protection to animals treated before or shortly after infectious challenge with WNV. In contrast, IVIg obtained from blood donors from the United States without WNV-specific antibodies has no similar protective effect. Hence, neutralizing antibody therapeutics show promise in inhibiting WNV infection and preventing acute flaccid paralysis in vivo, which justifies phase I and II studies using humanized or human monoclonal antibodies.

**DIFFERENTIAL DIAGNOSIS OF NEUROINVASIVE WEST NILE INFECTION**

The differential diagnoses of WNV infection include other arbovirus encephalitides (e.g., St. Louis encephalitis virus; Japanese encephalitis virus; Eastern, Western, and Venezuelan equine encephalitis viruses; tick borne encephalitis virus), other viral meningoencephalitides (La Crosse virus, Murray Valley virus, coxsackievirus, echovirus, enterovirus), bacterial meningitis or encephalitis (including Lyme disease and Leptospirosis), tick paralysis, and noninfectious conditions that affect brain or spinal cord (e.g., stroke, brain or spinal cord tumors, spinal cord compression). Guillian-Barré syndrome and other immune-mediated neuropathies are also diagnostic considerations, since in some cases WNV poliomyelitis may mimic these disorders (Table 1). Poliovirus poliomyelitis should also be considered in the differential diagnosis if the patient resides in or travels to a polio-endemic region. However, in 2012 only three countries (Afghanistan, Nigeria, and Pakistan) remain polio-endemic.

In addition, poliovirus infection mainly affects infants or young children whereas WNV primarily affects middle-aged to elderly adults.

The author’s observations and literature review suggest that patients with WNV infection who have muscle weakness or other neuromuscular signs and symptoms often are given erroneous diagnoses and may receive inappropriate, potentially injurious treatments. Among patients referred to the author’s rehabilitation center with WNV neuroinvasive disease, initial diagnoses that ultimately proved to be erroneous included evolving stroke, GBS, myopathy, food poisoning, endocarditis, sepsis, heat stroke, malingering, gastroenteritis, drug reaction, spinal cord compression, diabetic myopathy, and myocardial infarction. Diagnostic studies and therapies directed at these erroneous diagnoses are typically ineffective and can produce significant morbidity. Hence, physicians should consider a diagnosis of WNV infection in any patient who presents with a febrile illness that progresses over several days associated with neurological signs or symptoms, especially during the summer months (i.e., “summer flu” plus neurological symptoms). Healthcare providers also need to be aware that the spectrum of neuromuscular manifestations may range from a poliomyelitis syndrome in the absence of overt fever or meningoencephalitis to subjective weakness and disabling fatigue. This awareness will help to avoid less tenable diagnoses and inappropriate treatment.

**CONCLUSION**

Although anterior horns are the major site of spinal cord pathology in WNV infection, inflammatory changes may also involve muscle fibers, peripheral nerves, spinal roots, and spinal sympathetic neurons and ganglia, contributing to the wide spectrum of neuromuscular manifestations of WNV infection. Although there is no specific treatment or vaccine approved for human WNV infection, several drugs that can alter the cascade of immunobiochemical events leading to neuronal death may be potentially useful. Treatment of PPS is also supportive and includes physical, occupational, and speech therapy, and medications to control pain and lessen fatigue.
REFERENCES

Peripheral Nervous System Complications of Neuroborreliosis

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INTRODUCTION

On September 26, 1922, almost precisely 90 years ago, two French physicians, Charles Garin, an intern at the time, and A. Bujadoux, about whom we know nothing more, evaluated a 56-year-old sheep farmer with an illness dating to June 14 when he had removed an attached tick from his left buttock. Three weeks following the bite he developed a painful red ring the size of a “5 franc coin” around the bite site, with severe local pain and left sided sciatica. The ring then enlarged to involve both buttocks, the abdomen, and the left thigh to the knee. He also developed excruciating pain unresponsive to morphine involving both lower extremities and the right brachial plexus and arm. When first seen by the authors in September, he had right deltoid paralysis and atrophy but an otherwise normal neurologic examination. Cerebrospinal fluid (CSF) showed a polymorphonuclear-predominant pleocytosis (75 cells); a Wassermann test was slightly positive. The authors concluded he had non-syphilis spirochetosis and treated him with neoarsphenamine. His pain disappeared almost immediately. They argued that this was a case of tick bite paralysis, noting that false-positive Wassermann tests were seen in tick borne relapsing fever and Rocky Mountain spotted fever (RMSF).

This discussion will consider how this vignette relates to a pediatric rheumatologic disorder first characterized in Lyme, Connecticut, and how vivid imaginations have led some to argue for pathophysiologic linkages even more misguided than that initial presumption of tick bite paralysis.

HISTORY

The disorder now referred to as Lyme disease has two distinct historical threads, joined in the early 1980s with the recognition that both were caused by a closely related family of tick-transmitted spirochetes, known collectively as Borrelia burgdorferi sensu lato. In the mid-1970s, parents in Lyme and Old Lyme, Connecticut, became concerned that a surprising number of children in a very small area were being diagnosed with juvenile rheumatoid arthritis. This resulted in a series of detailed studies culminating in the observations that many of the affected children had preceding tick bites and an unusual rash. More specifically, the disease was linked exclusively to bites of small hard-shelled Ixodes ticks. The rash was noted to begin with some latency following the tick bite, be relatively asymptomatic, and gradually (over days to a number of weeks) enlarge to at least 5 cm in diameter but often many times that size. As physicians dealing with what was originally termed Lyme arthritis became more cognizant of these dermatologic presentations they realized that the rash was identical to that described in the U.S. literature in 1970, and in the European literature in the early 20th century.
With the assessment of ever more patients with Lyme disease, it became clear that this was in fact a multisystem disease, with a number of specific organotropisms. Skin is clearly involved most frequently. Although the site of inoculation in all patients, an observed rash is estimated to occur in about 50% of adults but 90% of children 2 (presumably as children’s skin is more likely to be monitored by concerned outside observers). During its prolonged feeding the tick ingests blood which triggers proliferation of spirochetes in the tick’s gut. Spirochetes then circulate throughout the tick, ultimately invading its salivary glands, from which they are injected into the host—a process that typically requires up to about 48 hours—making it highly unlikely that bites of shorter duration will result in infection. Infection initially remains localized to the skin. Spirochetes slowly multiply locally and migrate centrifugally from the inoculation site. The advancing edge of migration triggers an inflammatory reaction, causing the expanding ring-like erythoderm, known as erythema migrans (EM; previously erythema chronicum migrans). Ultimately, spirochetes may disseminate systemically, causing the expected inflammatory response to a bacteremia—a febrile illness, often with nonspecific widespread achiness, headache, fatigue, and loss of mental agility—comparable to that seen in virtually any systemic inflammatory disorder. Although termed flu-like, patients do not develop upper respiratory or gastrointestinal symptoms.

With systemic dissemination, other organ systems can become targets of involvement. With the strain of B. burgdorferi responsible for all U.S. cases of Lyme disease (known as B. burgdorferi sensu stricto) the most common secondary site is again the skin. Up to a quarter of infected individuals develop multifocal EM,3 with each new EM representing a nidus of metastatic infection, and each recapitulating the slowly expanding pattern. In Europe, infection is caused primarily by this strain plus two closely related borrelias: B. garinii and B. afzelii. Presumably because of strain differences, multifocal EM is reported in a far smaller percentage of European patients. Conversely, two of the earliest reported European cutaneous manifestations, acrodermatitis chronica atrophica and borrelia lymphocytoma, are rarely if ever reported in the United States.

In early series, approximately 5% of patients first presented with unexplained heart block, on occasion third degree, requiring a temporary pacemaker. An additional 15% presented with various neurologic manifestations.4 An usual form of arthritis, affecting single large joints in a relapsing fashion (termed a relapsing large joint oligoarthritis), was the manifestation of systemic involvement that led to the initial identification of the disease. Notably, small joints (fingers and toes) and the spine are not typically involved. Individual joints spontaneously become inflamed, swollen, and painful for days to weeks, and then subside spontaneously or with either anti-inflammatory or antimicrobial therapy. Joint involvement is usually considered one of the later manifestations, occurring months or years after initial infection, although on occasion it can occur soon after initial dissemination. Importantly, the face of this disease has changed over the decades since its earliest descriptions. Many of the originally described phenomena occurred in individuals who had experienced early manifestations, were not diagnosed or treated with antimicrobials, and then went on to develop signs and symptoms of disseminated infection. With widespread recognition of the signs of early infection, and even more widespread early treatment, the frequency of many of these phenomena has likely decreased substantially.

The European thread of the story is somewhat different. Again, EM and other cutaneous manifestations were the first described.2 However, the first appreciation of systemic involvement was the report by Garin and Bujadoux.1 Hence, systemic involvement has been viewed as a primarily neurologic disorder from the outset. The neurologic triad described early on—meningitis, radiculoneuritis, and cranial neuritis—was for many years the sine qua non for diagnosing this disease. From the time of Garin and Bujadoux going forward, this was always viewed as a nervous system infection and treated accordingly, including using penicillin as early as the 1950s.9 Perhaps as a result of these divergent histories there has long been an emphasis on the differences between European and U.S. Lyme disease, emphasizing the prominent nervous system involvement in Europe and joint involvement in the United States. However, current epidemiologic studies suggest that about 15% of infected individuals have nervous system involvement on both continents, with forms of involvement that are qualitatively remarkably similar.10 Although joint involvement may be more prominent in the United States there is a significant ascertainment bias, with the seminal U.S. literature on Lyme disease written by rheumatologists. Regardless, it is likely safe to assume that nervous system involvement is sufficiently similar so that insights into neurologic disease gained in Europe and North America should be generally applicable in both regions.

Given that this disorder has been known for over a century, that the basic neurologic manifestations were characterized 9 decades ago, that treatment with penicillin was shown to be effective 6 decades ago, and that the causative organism was identified 30 years ago, it is perhaps surprising that so much controversy still surrounds this illness. The controversy has centered on several key misunderstandings regarding diagnosis in general, diagnosis of nervous system disease in particular, and the efficacy of standard antimicrobial therapy. In all three areas, the scientific data are quite clear, yet some continue to insist on alternative hypotheses based not on fact but on pseudoscientific misconceptions.

**DIAGNOSIS**

Diagnosis of infectious diseases typically relies on isolation of the responsible organism from affected patients. In Lyme disease, this can be easily performed in patients with EM, a lesion that, much like the analogous chancre in syphilis, contains innumerable spirochetes that are clearly demonstrable on biopsy. However, EM is such a characteristic lesion that, in the appropriate setting, the diagnosis should be made presumptively based on its appearance, with treatment instituted.11 In all other circumstances, laboratory confirmation of the diagnosis is required.

Microbiological confirmation is often difficult for a number of reasons. The organism will only grow in specific media, something not available in most microbiology laboratories. Incubation must be at a lower temperature than for most human pathogens and, given the slow dividing time, cultures must be...
maintained for weeks before judged positive or negative. Likely most significant though is that the number of organisms present in readily available samples (serum, CSF, etc.) is so low that even using polymerase chain reaction type technologies has very low diagnostic sensitivity; there often simply are no organisms present in the tested sample.12

As a result, as in many other infections, diagnosis has relied primarily on demonstration of the host antibody response to the causative organism. While early serologic assays had a number of technical limitations, those available today have as good sensitivity and specificity as those available for most other infections. However, the way in which they are used rather than how they perform has been frequently misinterpreted as evidence of their inadequacy. With virtually all other serologic tests, one measures both acute and convalescent titers, using the evolution in the antibody response as evidence of acute infection. In Lyme disease (perhaps by analogy to the Venerable Disease Research Laboratory [VDRL] and related assays in syphilis) it has been customary to use just a one-time titer. However, the VDRL is a measure of nonspecific anticardiolipin antibodies arising as part of a broader and misdirected immune response, not as a targeted response to the causative organism. Use of a one-time measure of specific antibody concentration has two important limitations. Very early in any infection, the amount of specific antibody in serum is minimal and undetectable. The patient is said to be seronegative, not because the infection is not present, but because the antibody response is not yet measurable against background seroreactivity. In Lyme disease, this initial seronegativity typically last up to 4-6 weeks (as opposed to as long as 6 months in human immunodeficiency virus). Serologies in this setting, which includes many patients with EM, will often be negative. This is not because the test is inadequate but because normal biology dictates that there is not yet a measurable response. Conversely, a single positive titer could be cross-reactive, could be due to past infection, or could be due to current disease.

Although the best approach would still be to obtain acute and convalescent titers, two recommendations serve to limit the impact of these issues. First, in patients with pathognomonic early disease (i.e., EM) treatment should be initiated without even drawing a serologic test and certainly regardless of its result.11 Second, to minimize the likelihood of a false-positive result due to cross-reactive epitopes, testing should use a two-tier assay.11,13 Sera should be screened with a quantitative assay such as an enzyme-linked immunosorbent assay (ELISA), which measures total reactive antibody. If, and only if, this produces results interpreted as positive or borderline, a second test, a Western blot, should be performed to determine if the antibodies detected in the ELISA are relevant or cross-reactive. Western blot criteria were developed in, and applicable to, patients with positive and borderline serologies only, and are based on statistical observations.

In acute disease (< 1-2 months duration), the response is typically primarily immunoglobulin M (IgM). Three IgM bands were identified as informative; individuals with acute Lyme disease usually have at least two of these (Table 1). Importantly though, by the end of the first or at most second month of infection, the immune system converts the predominant response to immunoglobulin G (IgG). If a patient with more than a month’s symptoms only has IgM bands on Western blot, this almost certainly is a false-positive result. Similarly, in patients with disease of more than a month or two duration, 10 IgG bands have been identified as informative, such that patients who have any five of the 10 almost certainly have, or have had, Lyme disease (Table 1). These bands are not selected because any of them are unique to Lyme disease (none are) but rather to maximize positive and negative predictive values. A patient with fewer than five of these bands is highly unlikely to have infection. Although some laboratories have established their own lists of interpretive criteria, none of these are based on any systematic analysis of data; such alternatives that do not have demonstrated accuracy should not be used.

Unfortunately, some early studies described patients with presumed Lyme disease of long duration who appeared to be seronegative.14 Looking back, there are many potential explanations for these observations but the simplest is that the diagnostic technology then available was inadequate. However, observations such as these, as well as the literature prior to the identification of the organism and development of serologic techniques, led to the notion that “Lyme disease is a clinical diagnosis.” While this assertion still has validity, it cannot be interpreted to mean that any clinician can simply assert that something is Lyme disease because (s)he thinks that is what it is. Rather, as in any analogous context, clinical diagnosis requires an appropriate synthesis of clinical observations with laboratory, epidemiological, and other scientifically-validated data to come to an appropriate conclusion. Finally, as the evidence in support of standard diagnostic technologies has become more compelling, some have started to invoke “coinfections”—the notion that patients’ symptoms relate to infection with other tick-borne pathogens—most commonly babesia, ehrlichia, and anaplasma, and occasionally bartonella. All cause acute febrile illnesses, some with potentially serious consequences. None cause prolonged more indolent symptoms and none have been associated with prolonged nervous system involvement.

One other laboratory technique that can be useful in central (but not peripheral) nervous system infection with B. burgdorferi is the demonstration of intrathecal production of specific antibody.15-18 Because the central nervous system (CNS) acts as an independent immunologic compartment, and since

<table>
<thead>
<tr>
<th>Bands</th>
<th>IgM</th>
<th>IgG</th>
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<td>23, 39, 41 kD</td>
<td>18, 23, 28, 31, 39, 41, 45, 58, 66, 93 kD</td>
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These are to be used as the second step in two-tier testing and are applicable only if enzyme-linked immunosorbent assay is positive or borderline.

Table 1. Western blots criteria in Lyme disease.
infection with B. burgdorferi (as in other infections) leads to migration of targeted B cells into the CNS with subsequent local proliferation, measuring concentrations of specific antibodies in CSF, comparing this to serum antibodies after correcting for blood brain barrier function, can produce a relative index indicative of local production of antibodies in the CNS. When positive, this allows the inference that at some time there was active B. burgdorferi infection in the CNS. Unfortunately, just as with serum antibodies, this measure can remain elevated long after active infection has resolved. Fortunately, active infection is almost always accompanied by a CSF pleocytosis, elevated protein, and other evidence of antibody production such as oligoclonal bands or increased IgG synthesis rate.

**Neurologic Manifestations**

Although the focus of this discussion is on peripheral nervous system (PNS) manifestations, a brief mention of concerns about CNS symptoms in Lyme disease is essential to understand the purported controversy. The single most egregious misconception is that individuals who perceive difficulties with memory and cognition should be assumed to have nervous system Lyme disease. As every practicing neuromuscular medicine specialist knows, virtually any state with a systemic inflammatory response (urinary or respiratory tract infections in older individuals, sepsis, flu, active rheumatoid arthritis to name a few) can induce a toxic metabolic encephalopathy. Somewhat similar symptoms occur in individuals who are sleep deprived, stressed, depressed, or have other neuropsychiatric disorders. Without minimizing the impact or importance of these symptoms, it is critical to recognize that they are not indicative of CNS disease and have no more specificity for Lyme disease than for depression, systemic lupus, or the flu. The notion that the diagnosis of Lyme disease can be made based primarily on such symptoms is not only illogical but actually harmful, particularly when coupled with the incorrect notion that it reflects a purportedly difficult to treat infection of the brain, as the diagnosis of any brain infection is rightly terrifying to most rational people.

Actual parenchymal brain infection with B. burgdorferi is remarkably rare, estimates years ago were of about 1 case per million population at risk per year. Current incidence, with more widespread early treatment, is undoubtedly even lower. When this does occur, it is typically a form of meningoencephalitis with inflammatory CSF and focal abnormalities on neurologic examination and magnetic resonance imaging (MRI) of the appropriate part of the neuraxis. Affected individuals almost always have intrathecal antibody production. Single photon emission computed tomography scans have been suggested to assess neuroborreliosis; they are generally uninformative. In instances in which the MRI demonstrates focal inflammation, positron emission tomography scans demonstrate locally-increased metabolic activity.

How then does Lyme disease affect the PNS? The most common form of nervous system involvement, occurring in up to 15% of infected individuals, consists of one or more of three elements: meningitis, cranial neuritis, and radiculoneuritis. All most commonly occur in the early disseminated phase of infection, typically within one or a few months of infection onset. Often, patients with more severe symptoms present earlier, those with more subtle or indolent symptoms later, suggesting a dose-response effect related either to inoculum size or the nature of the individual’s inflammatory response to the particular spirochete strain.

Meningitis, which often co-occurs with PNS manifestations but is likely not responsible for them, presents with typical headaches, photosensitivity, neck stiffness, and systemic symptoms. Symptom severity is highly variable and bears only a weak relationship to degree of the pleocytosis. Compared to enteroviral meningitis, onset tends to be over days (rather than a few hours or less with enterovirus) and less severe overall. Cerebrospinal fluid usually demonstrates a lymphocytic pleocytosis, mildly elevated protein, and often intrathecal antibody production or other evidence of heightened antibody production such as oligoclonal bands.

As in the case described by Garin and Bujadoux, PNS symptoms can be pleomorphic. Cranial neuropathies likely are the most common presentation, particularly with seventh nerve palsies, which represent about 80% of Lyme disease associated cranial neuropathies. Facial palsy can be bilateral in up to 20%. Other commonly affected nerves include those to the extraocular muscles, and occasionally either the trigeminal or the vestibuloacoustic. Although involvement of the lowest cranial nerves has been reported in rare anecdotes, this is truly unusual. Involvement of the optic nerve is as rare as is involvement of other parts of the parenchymal CNS. A range of PNS manifestation associated with Lyme disease are presented in Table 2.

The patient described by Garin and Bujadoux was quite typical of individuals with Lyme radiculoneuritis. Pain is radicular in character, and is often confused with a mechanical radiculopathy. It tends to involve the limb that was the site of the tick bite, is quite severe, and though somewhat dermatomal, typically spreads beyond a single dermatome. It likely is the most frequently misdiagnosed form of nervous system Lyme disease. Clues often include the absence of relevant abnormalities on spine imaging, the involvement of multiple dermatomes clinically and on neurophysiologic testing, and a CSF pleocytosis.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Details</th>
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<tr>
<td>Radiculopathy</td>
<td>Motor, sensory, mixed</td>
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<tr>
<td>Plexopathy</td>
<td>Lumbosacral, brachial</td>
</tr>
<tr>
<td>Mononeuropathy</td>
<td>One or several</td>
</tr>
<tr>
<td>Mononeuropathy multiplex</td>
<td>Large or small nerves, and confluent</td>
</tr>
<tr>
<td>Cranial neuropathies</td>
<td>VII, III-VI, occasionally VIII; rarely IX-XII</td>
</tr>
<tr>
<td>Diffuse polyneuropathies</td>
<td>Diffuse: acute, subacute or indolent Rarely demyelinating</td>
</tr>
<tr>
<td>Entrapment</td>
<td>Carpal tunnel</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td>???</td>
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</tbody>
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Table 2. Range of peripheral nervous system manifestations associated with Lyme disease
It appears likely that both the cranial neuropathies and the radiculoneuritis are manifestations of a Lyme disease-related mononeuropathy multiplex.24 Patients can present with more typical mononeuropathies, or with lumbosacral or brachial plexopathies. Some patients, particularly those with more longstanding infection, can present with more of a stocking glove-type picture. Neuropsychologically, these patients appear to have a confluent mononeuropathy multiplex. In fact, looking neuropathologically at a broad cross section of patients with Lyme disease-related PNS involvement, it appears that all represent various presentations of the same pathophysiologic process.

The few available neuropathologic studies25,26 demonstrate perivascular inflammatory infiltrates (without true vasculitis) and patchy nerve damage. Although there have been rare case reports and small series of Guillain-Barré syndrome-like patients27 with apparent Lyme disease, this must be considered either very rare or coincidental, given the low frequency with which it is observed. Pathophysiology is unclear. In the only animal model of neuroborreliosis, the experimentally infected rhesus macaque monkey,28 neuropathologic and histopathologic findings are identical to those described above. In no animal or human material has there ever been evidence of intact spirochetes, immune complex deposition, vasculitis, or other compelling evidence of a specific mechanism. In both humans and experimental animals, PNS changes resolve fairly rapidly after antimicrobial therapy.

Finally, particularly in light of the preceding discussion, a consideration of motor neuron disease, a subject of controversy for 2 decades, is useful. Several anecdotes described patients who appeared to have motor neuron disease,29,30 were treated for Lyme disease, and recovered. One epidemiologic study in an endemic area raised the possibility of an association between motor neuron disease and positive Lyme serologies, but showed no compelling response to treatment.31 Most data suggest that an association is unlikely. That said, it is important to recognize that B. burgdorferi infection is associated with a polymyelopathy, that occasionally motor symptoms can be more prominent than sensory, and that, in some patients with radiculoneuropathy, there can be associated involvement of the spinal cord at the affected level, potentially resulting in upper motor neuron signs. Consequently, in individuals with potential exposure and a predominantly lower motor neuron picture, perhaps with mild myelopathic features, the diagnosis should be considered, just as one considers cervical compressive myelopathies and other alternative diagnoses in the appropriate setting.

### Treatment

In vitro, B. burgdorferi is highly sensitive to a broad range of simple antimicrobials. Although not studied systematically in the United States, the European literature is quite clear that meningitis, radiculoneuritis, and cranial neuritis are equally effectively treated (cured in 90-95%) by oral doxycycline and intravenous cephalosporins such as ceftriaxone or cefotaxime.32 Common practice is to treat patients with PNS Lyme disease with 3-4 weeks of oral doxycycline. If they do not start to show improvement within 2-3 months (or if they worsen significantly after treatment) retreatment with 2-4 weeks of intravenous ceftriaxone is usually curative (Table 3).

The role of a CSF examination is unclear. Given that meningitis is typically cured by oral antibiotics, one can make a strong case for simply treating orally, regardless of the CSF findings, rendering the CSF information irrelevant. On the other hand, one might argue that in a patient who fails to respond, CSF examination may be informative, and in this setting knowledge of the pre-treatment findings would be helpful. However, given the small number of patients who require retreatment, the role of pretreatment CSF assessment remains highly unclear.

### Summary

Peripheral nervous system involvement occurs in up to 10-15% of patients with Lyme disease, most commonly manifesting as facial nerve palsy, but occasionally involving other cranial nerve roots or peripheral nerves. Most often missed is the originally-described syndrome of acute, severely painful, mono- or oligoradiculal involvement. Virtually all manifestations appear to be attributable to a mononeuropathy multiplex. Although immune mechanisms may play a role in the pathophysiology of PNS involvement, antimicrobial therapy is generally highly effective in rapidly ending progression of disease, indicating a required role of active infection. Currently available serologic testing is highly accurate in nervous system Lyme disease, with the single exception that occasionally symptoms may occur so early in infection that serologic responses may not yet be demonstrable. In this setting, a followup titer in several weeks will usually be diagnostic. Two to 4 week courses of simple antibiotics such as oral doxycycline, or occasionally parenteral cephalosporins, are highly effective.
REFERENCES

An estimated 7% of the adult population is afflicted by polyneuropathy (PN). In approximately 75% of cases a detailed history and focused laboratory evaluation will identify a proximate cause. Although not routinely considered in the initial differential diagnosis of PN, infectious diseases are important contributors to multiple PN syndromes and, conversely, PN may be associated with many infectious diseases. Infection-related PNs are, in most cases, indirect consequences of immune activation rather than a direct result of peripheral nerve infection or toxin production. Polyneuropathies may present with prototypical sensorimotor axonal PN, acquired demyelinating PN, or mononeuritis multiplex. This discussion will provide a general overview of the presentation, diagnosis, and management of the more common PN syndromes associated with selected infectious diseases: human immunodeficiency virus (HIV) and viral hepatitis (hepatitis B virus [HBV] and hepatitis C virus [HCV]). The bacterial and viral infections associated with Guillain-Barré syndrome (GBS) will be reviewed. Diphtheria and leprosy, although rare in industrialized countries, will also be discussed given that these conditions remain relevant for the neuromuscular practitioner given the ease of international travel and migration.

**HUMAN IMMUNODEFICIENCY VIRUS**

More than 34 million people currently live with HIV/acquired immune deficiency syndrome (AIDS), with approximately 7,000 new infections per day in 2010. In North America, approximately 1.3 million are infected. The most common neurological complication of HIV infection is PN. Polyneuropathy in this clinical population is generally related to chronic HIV infection with moderate-to-severe immunodeficiency, HIV-associated distal sensory PN (HIV-PN), or a treatment-related toxicity related to select antiretroviral drugs, known as antiretroviral toxic neuropathy (ATN). Less common PN syndromes include autonomic neuropathy, PN associated with diffuse infiltrative lymphomatosis syndrome (DILS), peripheral nervous system (PNS) vasculitis, and inflammatory demyelinating PNs.

Human immunodeficiency virus-associated distal sensory PN and ATN are the most common PN syndromes and are clinically important primarily due to neuropathic pain and measurable impact on quality of life, function, and disability. Early in the era of combination antiretroviral therapy (cART) approximately 35% of patients with moderate-to-severe immunodeficiency (CD4 T cell count < 300) had symptomatic PN. Asymptomatic neuropathy signs may be observed in another 20% and, morphological data from autopsy specimens suggest that neuropathy is nearly ubiquitous with severe end-stage AIDS. The most consistent risk factor for HIV-PN across multiple studies is age. Recent data suggest symptomatic PN impacts a smaller percentage (10%) of the HIV-infected population than previously described. Trends in earlier HIV diagnosis and earlier initiation of effective non-neurotoxic cART likely contribute to these observations. While the pathophysiology is not precisely known, HIV-PN is likely a consequence of chronic immune activation as opposed to direct viral infection of peripheral nerves, dorsal root ganglia (DRG), or Schwann cells.

The dideoxynucleoside nucleoside reverse transcriptase inhibitors (NRTIs) didanosine (ddI), zalcitabine (ddC), and stavudine (d4T)—the so-called “d-drugs”—have all been associated with the development of ATN. While the frequency of ATN has
decreased markedly with increased availability of non-neurotoxic cART options, ATN remains important in resource-limited regions where d4T in particular is a common cART component. D-drug neurotoxicity stems from inhibition of the mitochondrial DNA (mtDNA) gamma polymerase, a key enzyme for mtDNA replication and repair.16 Typically, ATN occurs within 1 year of treatment initiation and most commonly within the first 3 months,17,18.

Human immunodeficiency virus-associated PN typically presents with stocking-distribution sensory symptoms, numbness, and neuropathic pain being most frequent. Examination reveals minimal distal extensor weakness with decreased or absent ankle reflexes.19 Polyneuropathy may also be symptom-predominant with a normal examination, consistent with small fiber pathology. Nerve conduction studies (NCSs) typically show generalized length-dependent sensorimotor axonal PN, but may be normal. Needle electromyography (EMG) may show distal-to-proximal gradient of chronic reinnervation changes, though it is typically normal if NCSs show no large myelinated fiber involvement. Classic pathological findings of HIV-PN include distal axonal degeneration with reduced unmyelinated fiber density and lesser reductions in small and large myelinated fiber densities.20 Skin biopsy is more sensitive than NCSs, showing reduced epidermal nerve fiber density.21-23 Antiretroviral toxic neuropathy shares similar clinical and electrophysiological features with HIV-PN, the clinical distinction based on the timing of symptom onset or worsening related to drug exposure and the patient’s response to dosage reduction or drug withdrawal.12 At times the neuropathic symptoms of ATN may continue to progress for weeks after drug withdrawal, a phenomenon commonly referred to as “coasting.”

Attention to the prevailing state of immunodeficiency during the onset and evolution of PN symptoms is paramount when approaching the diagnostic workup. When PN onset coincides with severe immunodeficiency in a cART-naïve patient, the high prevalence of HIV-PN makes alternative causes unlikely. Conversely, if PN symptoms commence with only mild immunodeficiency (e.g., CD4 > 500), HIV-PN is unlikely and other etiologies should be investigated, with testing as recommended by American Association of Neuromuscular and Electrodiagnostic Medicine-endorsed laboratory testing guidelines.2 Worsening neuropathic pain in the setting of stable HIV disease (suppressed viral load, only mildly or moderately immunosuppressed) on non-neurotoxic cART with suppressed viral load should also prompt thorough evaluation. Commonly used medications which may contribute to PN include dapsone, metronidazole, trimethoprim/sulfamethoxazole, and isoniazid. Alcohol or intravenous drug (e.g., heroin) abuse, malnutrition, vitamin (e.g., thiamine, B12) deficiency, renal insufficiency, and disorders of glucose metabolism may all significantly contribute to PN risk in the setting of HIV.

Efficacy for neuroregenerative therapy has not been established.24-28 Though limited data suggest cART initiation may improve HIV-PN, no large scale trial documents significant improvement.29,30 Management has therefore focused on symptomatic pain relief. Unfortunately, trials evaluating multiple agents from different drug classes have failed to show clinically meaningful efficacy: amitriptyline,31,32 gabapentinoids,33,34 mexiletine,31,35 topical lidocaine gel,36 low-dose topical capsaicin,37 and Peptide T (an in vivo gp120 inhibitor).38 There is no evidence in support of acupuncture.12 Improvement in neuropathic pain has been described with lamotrigine (specifically in ATN), high-dose (8%) topical capsacin, recombinant nerve growth factor, and smoked marijuana.39-42

**Autonomic Neuropathy**

The prevalence of HIV-associated autonomic neuropathy is not known; autonomic symptoms, however, are frequent and particularly so with severe immunodeficiency.51-53 Autonomic neuropathy is important due to its association with cardiac morbidity.46 Resting tachycardia, orthostatic hypotension, impotence and urinary dysfunction, early satiety, constipation and/or diarrhea, and disorders of sweating may be present. Study of sympathetic ganglia shows neuronal degeneration coupled with perivascular mononuclear cell infiltration with T cells and macrophages.47

Bedside evaluation may reveal a > 20 mmHg drop in systolic or > 10 mmHg drop in diastolic blood pressure without an adequate increase in heart rate. In the absence of a dedicated autonomic laboratory or quantitative sensory testing, electrophysiological evaluation of suspected autonomic neuropathy is unfortunately limited. Sympathetic skin response, which evaluates small fiber sudomotor function, and may be available on standard needle EMG equipment but is insensitive. Heart rate variability with the Valsalva maneuver or deep breathing may also be evaluated with some standard needle EMG equipment. Important considerations with suspected autonomic dysfunction are the contributions of anemia, hypovolemia, cardiomyopathy, and adrenal insufficiency, the latter which may be suggested by orthostatic hypotension with generalized fatigue, myalgia, weakness, and hyponatremia and/or hyperkalemia. Adrenal insufficiency may be diagnosed with a random cortisol or a cosyntropin stimulation test. Treatment of orthostatic hypotension with autonomic dysfunction may include salt (sodium chloride, NaCl) supplementation, thigh-high compression stockings, the mineralocorticoid fludrocortisones, midodrine, or erythropoietin.

**Diffuse Infiltrative Lymphomatosis Syndrome**

Diffuse infiltrative lymphomatosis syndrome is rare, estimated in 3-4%, and characterized by multisystem CD8 lymphocytic visceral infiltration involving primarily salivary glands and lungs.48 Peripheral nerve, kidney, and gastrointestinal involvement are also seen. Clinical presentation is of parotid enlargement, sicca symptoms and CD8 hyperlymphocytosis (generally defined as CD8 counts > 1,500). Diagnosis is based on the presence of xerostomia, chronic (> 6 months) submandibular enlargement, and lymphocytic infiltration on either salivary biopsy or gallium scintigraphy.

Patients with peripheral nerve involvement typically present with acute or subacute painful sensorimotor axonal PN.49 The pathological hallmark consists of angiocentric peripheral nerve infiltration of T lymphocytes, mimicking that seen with T-cell lymphoma.50 It is important to recognize this PN syndrome as management includes initiation of cART with or without low-to-moderate doses of systemic corticosteroids. Analgesic
management may be considered contingent upon pain severity and its impact on function.

Inflammatory Demyelinating Polyneuropathies

Acute and chronic inflammatory demyelinating PNs (AIDP and CIDP, respectively) are relatively rare conditions in the setting of HIV infection, with descriptions limited to small case series, and are classically associated with mild-to-moderate immunosuppression. Early published reports emphasized these syndromes as neurological presentations prompting to the diagnosis of HIV infection: AIDP in particular has been described with the HIV seroconversion syndrome, which may occur between 3-9 weeks after initial virus exposure. The symptoms of an HIV seroconversion syndrome, which is estimated to occur subsequent to one-third to one-half of acute HIV infection, are typically indistinctive “viral” complaints of fever, headache, myalgia, arthralgia, rash, or diarrhea. However, AIDP may also occur with severe immunodeficiency, though CD4 counts are rarely < 50.

Clinical, electrophysiological, and pathological findings do not differ from that observed in non-HIV infected patients. An important unique clinical feature of AIDPs in the setting of HIV infection is the presence of a mild lymphocytic pleocytosis in cerebrospinal fluid (CSF), which contrasts with the traditional CSF profile of the relatively acellular albuminocytologic dissociation. Differential diagnosis of HIV-associated AIDP may include cytomegalovirus (CMV) polyradiculopathy or HIV-associated neuromuscular weakness syndrome (HANWS). While CMV has been associated with AIDP in the setting of severe immunodeficiency, it is more commonly associated with ascending weakness due to polyradiculopathy. Early bladder (urinary retention) or bowel (obstipation) involvement are important clinical signs that help distinguish this syndrome from AIDP. Cerebrospinal fluid reveals a polymorphonuclear pleocytosis (average cell count of 500-600/ml) with elevated protein and decreased glucose, although may be normal. A positive CMV polymerase chain reaction in CSF confirms the diagnosis.

Prefered therapy of CMV polyradiculopathy is a combination of gancyclovir with initiation of cART. Without antiviral therapy, survival is on the order of weeks.

Human immunodeficiency virus-associated neuromuscular weakness syndrome is an acute (1-2 weeks) or subacute (> 2 weeks) syndrome of rapidly progressive neuromuscular weakness associated with lactic acidosis and possibly hepatic steatosis. Most patients with HANWS present with nausea, vomiting, abdominal pain, and a sensorimotor axonal PN, though some patients have been noted to have mixed features of demyelination and/or concomitant myopathy. While the cause is not clear, mitochondrial dysfunction is the leading hypothesis. This condition has been linked mostly to stavudine (d4T) and there exist little evidence-based management options outside of NRTI withdrawal and supportive care.

Management consists of plasma exchange (PE) or intravenous immunoglobulin (IVIg) for AIDP and oral immunosuppressants with or without IVIg or PE for CIDP, essentially unchanged from that recommended for non-HIV infected patients. There exist few data describing outcomes of acquired inflammatory demyelinating PNs in the setting of HIV outside of one small study documenting that intensive care unit length of stay and number of days on ventilation does not differ between HIV and non-HIV infected patients.

Peripheral Nervous System Vasculitis

Peripheral nervous system vasculitis has a low incidence in HIV (< 1%), but it is important to recognize as it is a severe condition that is treatable. Peripheral nervous system vasculitis may be observed at any stage of infection, though generally observed early after initial infection or late in the setting of severe immunodeficiency. Whereas an underlying state of immune activation may be at play early in the infection, CMV reactivation or another infectious phenomenon is the major consideration in late stages of infection. A painful mononeuropathy multiplex (MM) is the classic presentation with asymmetrical non-length–dependent signs and symptoms. Nerve conduction studies document an asymmetric sensorimotor axonal PN; overlapping mononeuropathies, however, may at times obscure the multifocal nature and the condition presents as a prototypical length-dependent sensorimotor axonal PN. Needle EMG shows non-length–dependent and/or asymmetric active denervation coupled with variable acute, subacute, or chronic reinnervation changes. In some cases concomitant irritably myopathy is noted. When nerve biopsy is performed (generally sural, superficial peroneal, or radial), concomitant muscle biopsy (gastrocnemius, peroneus brevis, or deltoid) may increase diagnostic sensitivity. The pathological hallmark is necrotizing thrombosis or inflammatory infiltration of vessels on nerve biopsy. Small, medium, and large vessel vasculitis have all been reported.

When vasculitis occurs relatively early in HIV with mild-to-moderate immunosuppression, it may be associated with immune complex deposition or infiltrating CD8 T cells. These inflammatory processes may reflect a reaction to HIV infection of endothelial cells or, in some cases, neoplasm. Other potential causes for a similar clinical picture are related to HBV or HCV co-infection, cryoglobulinemia, immune complex disease, or drug reaction. Serum autoantibodies must be interpreted with caution in HIV/AIDS due to the high frequency of polyclonal B-cell activation in the setting of abnormal T cell regulation. With severe immunodeficiency, CMV is the classic pathogen and particularly so with a history of prior or current CMV infection (e.g, retinitis, gastroenteritis, or pneumonia). Vasculitis has also been reported with mycobacterium tuberculosis, and pneumocystis jirovecii. Management depends mostly on the severity of prevailing immunodeficiency: early HIV-associated vasculitis may be treated with ARVs whereas in later stages therapy is directed towards the underlying co-infection. For those with advanced disease and evidence of CMV, gancyclovir with or without foscarinet is preferred.

POLYNEUROPATHY ASSOCIATED WITH VIRAL HEPATITIS

Hepatitis B

Hepatitis B causes chronic infection in approximately 10% of infected patients, and the global burden of chronic HBV is considerable given that approximately 350 million people are
of HCV virus in the late 1980s, it was realized that > 80% of mixed cryoglobulinemia could be ascribed to HCV infection. The pathogenic IgM generally feature rheumatoid factor (RF) activity. Hepatitis C virus PN may present as a generalized sensorimotor PN or MM. Pathologically, cryoglobulinemia may be associated with vasculitis affecting small arteries, arterioles, capillaries, and venules. Nerve tissue shows axonal loss with fascicular variability, demyelination, and perivascular mononuclear infiltrates. Palpable purpura with underlying leukocytoclastic vasculitis is common, as are Raynaud’s disease, glomerulonephritis, and gastrointestinal pain. Strict attention to collection and laboratory processing are paramount when assessing for cryoglobulins (reviewed in Ramos-Casals and colleagues65). Additional laboratory findings which may support a diagnosis of cryoglobulinemia included low complement (C4 and CH50, with C3 levels typically normal) and presence of rheumatoid factor activity.

Treatment of HCV-associated PN is based on therapy directed towards the underlying infection, which currently includes ribavirin and pegylated interferon-α. Antiviral therapy combined with high-dose corticosteroids have been used with severe vasculitis in spite of negative trials, as the effect of antiretroviral therapy is relatively delayed.68,69 Severe cryoglobulinemic vasculitis may also be treated with rituximab, a monoclonal antibody against the CD20 antigen expressed on B cells.70

INFECTIONS ASSOCIATED WITH GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome is the most common cause of neuromuscular paralysis in nonpolio afflicted industrialized countries, with a incidence of 0.62-2.66/100,000 person years.71 A detailed description of the clinical presentation, electrophysiologic and clinical variants, as well as therapeutic options are beyond the scope of this discussion, the details of which are reviewed elsewhere (see Hughes and Cornblath72). While there is little doubt that GBS is immune mediated, it is atypical for an autoimmune disease given that it is monophasic, demonstrates male predominance, and incidence increases with older age. Guillain-Barré syndrome is commonly considered to be a postinfectious neurological syndrome given that up to two-thirds of patients report an illness in the preceding 6 weeks (generally the previous 1-4 weeks) before neurological symptoms. In most cases, the antecedent infectious cause cannot be definitively identified. Respiratory and gastrointestinal syndromes are most frequently reported.

The infectious pathogen most commonly associated with GBS is Campylobacter jejuni, a gram negative rod which is the most common cause of bacterial gastroenteritis in developed countries. C. jejuni has been implicated in up to 32% of GBS cases in prospective series.73,74 Gastroenteritis from C. jejuni is generally a febrile illness with abdominal pain and non-bloody diarrhea. Epidemics of acute motor axonal neuropathy (AMAN) related to C. jejuni have been reported in Northern China, while seasonal gastroenteritis associated with AMAN has been described in Mexico.75,76 Such has also been described in Japan. C. jejuni infection may portend more severe GBS, typically in setting of AMAN and acute motor and sensory axonal neuropathy (AMSAN), and a poorer prognosis.73,77 The vast majority of patients with C. jejuni gastroenteritis, however, do not develop GBS, and GBS with asymptomatic C. jejuni infection have also
been reported; these findings suggest important host determinants exist which contribute to the GBS development. Apart from AMAN, C. jejuni has also been associated with AIDP, AMSAN, and the Miller-Fisher variant of GBS.

C. jejuni triggers GBS through a mechanism coined “molecular mimicry,” wherein cross-reactivity between bacterial cell wall epitopes and nonprotein gangliosides of human peripheral nerve leads to immune-mediated nerve damage. C. jejuni polymorphisms of the gene involved in production of ganglioside epitopes (cst-II) is associated with both host antibody production and clinical phenotypes (e.g., Miller-Fisher variant, with gangliosides QG1b, GM1, and GD1a, with weakness).78 C. jejuni gastroenteritis is associated with generation of IgG against the GM1 ganglioside, the presence of which may predict a more severe case for GBS with worse recovery. Although other ganglioside antibodies have also been identified against GD1a, GM1b, and GalNac-GD1a in the setting of C. jejuni, these antibodies are not consistently associated with neither a particular infectious agent nor a particular electrophysiological GBS phenotype.

The second most common bacterial infection preceding GBS is mycoplasma pneumonia, associated with up to 5% of GBS, typically in younger patients.79,80 The most common presentation of M. pneumoniae infection, which causes an atypical or walking pneumonia, is low grade fever, dry or nonproductive cough, diffuse arthralgia, and headache. Sputum gram stain and cultures are negative. Diagnosis is made by presence of cold agglutinins or though collection of acute and convalescent antibody titers. M. pneumoniae may be associated with glactocerebroside (Gal-C) antibodies.81

The most common virus associated with GBS is CMV, followed by Epstein-Barr virus (EBV).73,74 Both of these viruses may be more common in younger GBS patients. Although transaminase elevations have been believed to suggest potential CMV or EBV infection in GBS, the majority of transaminase elevations with GBS are idiopathic.82 Atypical lymphocytes in peripheral blood, cold agglutinins, or the presence of polymorphonuclear cells in spinal fluid may suggest CMV infection. Cytomegalovirus has been estimated to precede neurological symptoms in approximately 17% of GBS.73 Clinically, CMV infection is associated with a nonspecific upper respiratory viral syndrome with lymphadenopathy and diagnosis can be made through collection of acute and convalescent sera. Cytomegalovirus is associated with generation of IgM targeting the ganglioside GM2. Cytomegalovirus has been reported to cause more sensory symptoms, cranial nerve involvement, and may be associated with delayed recovery. Epstein-Barr virus also causes a nonspecific viral syndrome with fever, pharyngitis, lymphadenopathy, and atypical lymphocytes lasting 1-4 weeks. Rarely, it may involve splenic enlargement of liver involvement. Epstein-Barr virus may be diagnosed with either a Monospot test (Paul-Bunnell heterophile IgM) or acute and convalescent antibody titres. It has been suggested that EBV infection may be associated with less milder form of GBS (e.g., capable of ambulating at nadir).80 At this time neither the identification of a specific pathogen nor a particular autoantibody influences GBS treatment decisions.

Diptheria

Corynebacterium diptheria is a toxogenic gram positive bacterium that causes local infection of the upper respiratory tract or skin. Diptheria is currently rare given longstanding immunization programs, with the last confirmed U.S. case in 2003.83 C. diptheria persists in resource-poor settings, which in the Americas includes Haiti and the Dominican Republic and in nonimmunized individuals and, when associated with neurological symptoms, is an important consideration in the differential diagnosis of GBS.

Diptheria typically begins as an exudative pharyngitis, with a greyish-white membranous exudate. In severe cases a “bull neck” due to cervical lymphadenopathy and local tissue swelling may be observed. Neurological symptoms begin after acute infection in up to 20% of patients, typically in a biphasic pattern.84 In classic diptheric PN, bulbar symptoms develop between 3-6 weeks after pharyngitis. Common symptoms and signs include weakness of the soft palate, impaired pharyngeal sensation, and paralysis of pupillary accommodation (which causes blurring of near vision). A more generalized demyelinating sensorimotor PN, which when severe may cause diaphragmatic weakness, may follow after 8 weeks. Cardiovascular complications may be observed, with loss of vagal tone and tachycardia secondary to involvement of large myelinated parasympathetic fibers. Cutaneous infection, which is less common than the classic pharyngitis, may cause local neuropathic symptoms and signs, the distribution of which is dependent upon the proximity of selected nerves to the skin lesion(s).

C. diptheria produces a protein exotoxin which causes segmental demyelination of nerve roots and peripheral nerves. Most pathologic changes are seen at the level of the roots and DRG, due to the presence of fenestrated capillaries which produce an ineffective blood-nerve barrier. While bulbar symptoms are believed to reflect local effects of exotoxin, the generalized sensorimotor PN follows hematogenous dissemination of exotoxin. Electrophysiology and CSF findings are similar to that observed with AIDP.

Management includes intravenous penicillin and early treatment with diptheritic horse serum antitoxin.84 Antitoxin may prevent or lessen the PN severity, but treatment decisions are necessary generally prior to confirmation of diagnosis for antitoxin to be effective. Administration of antitoxin may be associated with serum sickness, which has been reported in up to 10% of those receiving treatment. Cultures from the pharynx or skin swabs are confirmatory, but specific culture conditions are required. Acute and convalescent serum titres can also be supportive for infection. Treatment of the subsequent neurological complications is supportive and, given the cardiac morbidity, cardiac monitoring is warranted.

LEPROSY

Mycobacterium leprae was first identified as the pathogen responsible for chronic granulomatous infection of skin and peripheral nerve in the late 1800s by Dr. Gerhard Hansen, hence the moniker Hansen’s disease, but recognition of the syndrome dates back over 2,000 years. Generally considered in the current
era as a disease of poverty, leprosy remains an important cause of PN worldwide and is the leading infectious cause of disability. Overall, an estimated 2-3 million people are currently living with leprosy-related disability and, although prevalence has dropped substantially due to global eradication efforts, approximately 250,000 new cases are reported annually. The disease is predominately found in tropic and subtropic regions, with the most cases currently reported in Brazil, India, and Indonesia. The recorded prevalence and incidence of leprosy are considered low given the stigma associated with the condition contributing to reluctance of patients to seek care. Pockets of endemism in the United States occur in Texas, Louisiana, Hawaii, and California with most cases being identified in immigrant populations.

Humans are the principle reservoir, though some primates carry M. leprae and in the Americas armadillo-derived strains account for up to two-thirds of isolates. Infection is intracellular, involving macrophages in skin and Schwann cells in nerve. Transmission is believed to be via respiratory or nasal droplets, though cutaneous transmission cannot be entirely excluded. M. leprae is slow growing, and there is a long interval between infection and clinical symptoms, spanning around 5-7 years. The majority of M. leprae-infected individuals do not develop clinical disease; the exact proportion, however, is not known as no diagnostic test reliably identifies subclinical infection.

Familiarity with the signs of leprosy is important as there exists no confirmatory point-of-care diagnostic test and prompt treatment prevents the development of disability. Clinical diagnosis is made by the presence of typical skin lesions, enlarged nerves, and skin smear or biopsy documenting acid-fast bacilli. Skin lesions include macules (< 10 mm) or plaques (> 10 mm) located over the trunk or abdomen, but may occur anywhere. Skin lesions are generally hypopigmented, have a raised edge, and are accompanied by sensory loss. Based on skin lesions, the disease may be classified as paucibacillary (up to five skin lesions) or multibacillary (over five skin lesions), a schema which helps guide treatment decisions (discussed later). In an estimated 10% of patients, rash may be absent and with PN being the only symptom. Leprosy is further classified as being either tuberculoid or lepromatous, with the type of disease determined by the host’s cell-mediated immune response: tuberculoid leprosy is characterized by a good cell-mediated immune response with few skin lesions and no detectable mycobacteria; lepromatous leprosy, by contrast, features a poor immune response (anergy) with multiple skin lesions and high mycobacterial burden. Tuberculoid leprosy is generally paucibacillary while lepromatous disease is typically multibacillary. Many patients lie in the middle of these extremes, a condition referred to as borderline leprosy. Infectivity is generally limited to lepromatous leprosy.

Leprosy-related PN stems from either M. leprae’s direct infection of Schwann cells or may be a consequence of the immune response to mycobacterial antigens. On average, approximately 20-30% of leprosy patients have PN signs and symptoms at time of diagnosis, though estimates vary significantly amongst different studies. In patients with PN, sensory symptoms are more common than motor symptoms, and “negative symptoms” or loss of function predominates. Loss of autonomic function results in anhidrosis in the distribution of involved nerves with cool, dry skin. Pain, when present, usually occurs with nerve inflammation and edema. An asymmetrical, non-length dependent MM is the most common PN pattern. Generalized PN, however, may also be seen.

In tuberculoid leprosy nerve involvement is typically in close proximity to skin lesions. Common nerves involved in disease include the sural, fibular, posterior tibial, median, ulnar, posterior auricular, and superficial radial sensory nerves. Nerve swelling is typically proximal to the skin lesion. In lepromatous disease PN is more prominent, with more diffusely enlarged nerves, and pathology frequently involves cooler regions of the body, including the nose, ears, and the tips of fingers and toes, reflecting both diffuse disease and M. leprae’s predilection for replicating in cooler temperatures.

The host immune response is an important mediator of nerve damage. Generally speaking there exist two types of immune responses, or reactions: (1) a type I, or reversal reaction (RR); and (2) a type II reaction, or erythema nodosum leprosum (EHL). These reactions can occur before, during, or after introduction of multidrug therapy and may lead to the patient’s initial neurologic presentation. Type I RR’s represent an increase in cell-mediated immunity and is recognized clinically by erythematous skin lesions and peripheral nerve swelling (particularly the ulnar nerve at the elbow and tibial nerve behind the malleolus). Type I RR reactions generally occur with borderline leprosy and during the first year of therapy. Type II EHL reactions present with painful erythematous skin nodules (panniculitis), acute mononeuropathies, as well as orchitis, arthritis, and fevers. Type II EHL reactions are typically seen with lepromatous leprosy though may also occur with borderline disease.

The World Health Organization currently recommends 6 months of multidrug therapy with dapsone and rifampicin for paucibacillary disease or 12 months of dapsone, rifampicin, and clofazimine for multibacillary disease. Steroids are a mainstay of therapy to improve neurologic outcome of RR s, with current recommendations endorsing prednisolone 40 mg daily, generally for about 12 weeks. Recognizing that patients with pre-existing neuropathy are at higher risk for worsened neuropathy after treatment initiation, however, there is no conclusive evidence that steroids can prevent neuropathy. Shorter courses of steroids are generally used for EHL, but for severe and/or recurrent reactions thalidomide may be considered.

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Varicella Zoster Virus and Postherpetic Neuralgia: A New Era?

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INTRODUCTION

Varicella zoster virus (VZV) is a stable, highly neurotropic, human alpha herpesvirus that causes chickenpox (varicella). After primary infection, VZV becomes latent in cranial nerve, dorsal root, and autonomic ganglia along the entire neuraxis.\(^1,2\) Decades later, viral reactivation produces herpes zoster (shingles), characterized by dermatomal pain and rash.\(^3,4\) Pain usually lasts 4-6 weeks but may persist for months or years, a condition known as postherpetic neuralgia (PHN). Postherpetic neuralgia is the most common neurological complication of zoster, and most clinicians agree to define it as pain lasting 3 months or longer after resolution of rash. In addition to PHN, zoster may also be complicated by sensorimotor deficits due to associated meningoradiculitis, unilateral segmental motor neuronitis, and degeneration of related motor and sensory spinal roots. These neuromuscular sequelae of VZV infection are challenging to treat and have important implications for quality of life and utilization of healthcare resources.

ZOSTER AND ITS COMPLICATIONS

Herpes zoster has the highest incidence of all neurological diseases, affecting about 1 million people each year in the United States,\(^5\) with millions more worldwide. Zoster skin lesions typically resolve within 7-10 days, but pain during this period may be intense. In cases with more severe inflammatory damage to structures beyond sensory ganglia, numbness and weakness in corresponding dermatomes and myotomes cause lasting functional impairments. In some cases, the diagnosis of zoster-induced neurological dysfunction is confounded by the absence of rash, a condition known as zoster sine herpete.\(^6\)

Zoster results from latent VZV reactivation and transport to basal epidermis of skin. Initially, infected cells down-regulate interferon-α and lymphocyte adhesion molecules, favoring virus spread.\(^7\) As infected cells die, interferon-α is induced in neighboring cells, slowing the spread of VZV and enhancing T-cell clearance of the infection.\(^8,9\) The frequency of zoster is proportionally related to the incidence of chickenpox, which is independent of socioeconomic status, population density, gender, or ethnic origin.\(^10\) No genetic predisposition has been identified.\(^11\)

Most cases of zoster resolve without incident, but a minority of patients go on to develop PHN, the most common neurological complication of zoster. Pain is usually aching, burning, or lancinating. Other features include allodynia (pain with normally innocuous tactile stimuli) and hyperalgesia (hypersensitivity to mildly painful stimuli). Estimates of the incidence and prevalence of PHN vary depending on the definition used and the age and immune system function of the population under study. Older age, presence of prodromal pain, greater rash severity, and greater acute pain severity are all clear risk factors.\(^12-15\)

Older individuals are especially vulnerable to zoster and PHN because of decreased cell-mediated immunity.\(^16\) A retrospective review of 916 zoster patients found that nearly 40% of those over age 60 continued to have pain for months or years after resolution of rash compared to 4.2% in those younger than age 20.\(^17\) In a prospective study of patients older than 60, a similar PHN prevalence of 35% was observed 6 months after zoster onset.\(^18\) Using a more stringent criterion of pain ≥ 3 on a 0 (“no pain”) to 10 (“pain as bad as you can imagine”) scale, a large herpes zoster vaccine trial in individuals over age 60 demonstrated a
lower PHN prevalence of 12.5% among placebo-treated patients who developed zoster. Overall, zoster and PHN may be viewed in the context of a continuum of immunodeficiency, ranging from a natural decline in VZV-specific cell mediated immunity (CMI) with age to more serious immune deficits seen in cancer patients and transplant recipients, and ultimately in patients with acquired immune deficiency syndrome.

The exact cause of PHN is uncertain, but data suggest several possible mechanisms. One is that decreased VZV-specific cellular immunity in elderly patients may contribute to low-level ganglionitis, which in turn may sustain pain and even contribute to alteration of neural circuitry involved in pain perception. The hypothesis that viral ganglionitis contributes to PHN is compatible with other concepts of pain generation in this condition. Rowbotham and Fields have suggested that PHN is not a homogeneous disorder and that multiple pathophysiological mechanisms are likely responsible for pain. These include abnormal sensitivity of damaged cutaneous afferents to stimuli, destruction of sensory nerves or cell bodies resulting in altered central nervous system processing of normally innocuous tactile stimuli, and deafferentation due to destruction of large and small diameter sensory fibers and accompanying sensitization of central pain transmitting neurons. Ongoing nerve or ganglionic inflammation due to persistent viral activity may further amplify pain by increasing input along these central and peripheral pathways.

The impact of PHN on quality of life may be severe and long-lasting. Due to unrelenting pain, patients can develop a wide array of disturbances in psychosocial and physical functioning, including depression, impaired sleep and appetite, diminished energy, as well as physical, occupational, and social disability. Changes in mood, personality, activity level, and social interactions are common. The cost of incompletely effective drugs and increased utilization of primary care physicians, specialists, and other services are a significant public health problem that may consume substantial healthcare resources.

VARICELLA ZOSTER VIRUS VACCINES

The chickenpox vaccine was developed by passaging VZV isolated from a 3-year-old boy 11 times in human embryonic lung cells, six to seven times in guinea pig embryo (GPE) cells, and two to six times in human diploid WI-38 cells. Merck laboratories further passaged the virus though different cell lines to produce the commercial varicella vaccine (Varivax®) which contains 1,350 plaque-forming units (PFUs) in 0.5 ml of sterile water. Like wild-type virus, Oka/Merck vaccine virus becomes latent in ganglia and can reactivate to produce zoster. To date, the rate of zoster in vaccinated children is comparable to that in healthy children after natural varicella.

The attenuated Oka/Merck-VZV vaccine containing 18,700-60,000 PFUs of virus was tested in a large-scale double-blind, placebo-controlled, multi-center Shingles Prevention Study (SPS) to determine the effect of VZV vaccination in preventing zoster. More than 38,000 recipients of the zoster vaccine were followed closely for 3 years. The incidence of zoster in the placebo group was 11.1 per 1,000-person years. This figure approximates the results of an epidemiological survey performed a decade ago, which revealed zoster exceeding 10 cases per 1,000-person years among individuals older than 75 years. Overall, the vaccine reduced zoster incidence by about 50% but did not prevent the disease in everyone. The incidence of PHN was reduced by 66%. The zoster vaccine was introduced in 2006, and vaccination is now recommended for immunocompetent adults aged 60 or older. Studies are ongoing to evaluate the use of vaccine in younger adults and immunocompromised individuals.

IMPACT OF VACCINATION

While the varicella and shingles vaccines represent impressive steps in the prevention of VZV-related disease, they will not eliminate chickenpox, zoster, or PHN, because not all individuals who would benefit get vaccinated, and not all vaccinated individuals develop adequate immunity. Even if all older adults in the United States were vaccinated in the next few years, many would still develop zoster, PHN, or other complications. Furthermore, childhood varicella vaccine will not eliminate PHN. The precise longterm effect of childhood immunization on the incidence of zoster and PHN is unknown. While VZV vaccination protects most children from chickenpox, less exposure of adults to infected children may reduce periodic immune boosts, resulting in lower cell-mediated immunity to VZV. Thus, vaccination of children may actually place today’s adults at higher risk for zoster and PHN later in life.

By the year 2050, 20.2% of Americans (88.5 million people) will be 65 years or older. The population over 85 will increase by more than 100% to 19 million, greatly increasing the number of people at risk for zoster and PHN. There are also likely to be more patients with cancer, human immunodeficiency virus infection, organ transplants, and other sources of pharmacological immunosuppression who will be susceptible to the serious complications of VZV reactivation. Despite recent progress in disease prevention, zoster and PHN will continue to be important clinical problems for many decades to come.

COST EFFECTIVENESS OF ZOSTER VACCINATION

Numerous analyses have examined the cost effectiveness of zoster vaccination in different countries, and most have found the vaccine to be cost effective. Data from the United States predicts a similar favorable outcome for society and payers. In a 2007 analysis, Pellisier and colleagues modeled the effect that vaccination would have on a cohort of 1 million people older than age 60 compared to an unvaccinated group. The age-specific incidence, health-care resource use, costs, and quality-adjusted life years (QALYs) were examined. Costs and outcomes were presented over the lifetime of vaccinees. The analysis assumed a vaccine cost of $150, and healthcare resource utilization and costs associated with the diagnosis of herpes zoster and PHN were calculated from the Medstat database. The cost calculation included inpatient admissions, outpatient doctors’ visits, emergency visits, diagnostic procedures, and outpatient pharmacy prescription. Using PHN
CURRENT TREATMENT OF ZOSTER AND ITS COMPLICATIONS

Oral antiviral medication for 7-10 days is standard treatment for herpes zoster that is within 72 hours of onset. Early aggressive treatment of pain may also be beneficial to reduce the chances of developing PHN. The Federal Drug Administration has approved lidoderm, gabapentin, and pregabalin for treatment of PHN. A new long acting 8% capsaicin patch was also recently approved for this indication.41 Other generic medications including oral narcotics, tricyclic antidepressants, and numerous other anti-epileptic medications are also routinely used off-label in clinical care. American Academy of Neurology practice guidelines give a level A recommendation (class I and II evidence) for tricyclic antidepressants, gabapentin, pregabalin, opioids, topical lidocaine, capsaicin cream, and preservative-free intrathecal methylprednisolone. Other modalities have less evidence to support their use.42 Unfortunately, most treatments are associated with significant potential side effects, especially in the elderly population that suffers the most from PHN.

SUMMARY

Varicella zoster virus causing zoster and its related complications is a common cause of neuromuscular dysfunction. Postherpetic neuralgia is the most common problem but meningealculitis, segmental motor neuronitis, and ganglionitis may also occur. Varicella and herpes zoster vaccination are major steps toward the reduction of these complications, but the vaccines do not provide complete protection. The socioeconomic impact of zoster complications remains substantial and will remain so in the decades to come due to increases in the populations at risk. Antiviral treatment reduces the length and severity of acute zoster symptoms and may help prevent PHN. Data also suggest acute pain management may reduce the risk of PHN.18,43 However, current treatments are incompletely effective and better options are needed.

REFERENCES

Peripheral Nervous System Complications of Infectious Diseases

CME Questions:

1. Electrodiagnostic (EDX) studies in patients with West Nile virus (WNV) poliomyelitis show which of the following?
   1. Markedly decreased or absent motor responses in the paretic limbs
   2. Preserved sensory responses
   3. Widespread asymmetric muscle denervation
   4. No evidence of demyelination or myopathy

   A. Only 1, 2, and 3 are correct.
   B. Only 1 and 3 are correct.
   C. Only 2 and 4 are correct.
   D. All are correct.

2. Clinical and laboratory features of poliomyelitis, which help physicians discern it from Guillain-Barré syndrome (GBS), include which of the following?
   1. Fever and leukocytosis
   2. Sensory loss and painful distal paresthesias
   3. Asymmetric distribution of weakness
   4. Lack of pleocytosis in cerebrospinal fluid with elevated protein (albuminocytologic dissociation)

   A. Only 1, 2, and 3 are correct.
   B. Only 1 and 3 are correct.
   C. Only 2 and 4 are correct.
   D. All are correct.

3. Common neuromuscular manifestations of WNV infection include each of the following EXCEPT:
   A. Disabling fatigue.
   B. Poliomyelitis.
   C. Demyelinating polyneuropathy.
   D. Involvement of brainstem motor neurons.

   A. Only 1, 2, and 3 are correct.
   B. Only 1 and 3 are correct.
   C. Only 2 and 4 are correct.
   D. All are correct.

4. All of the following statements regarding poliovirus infection are correct EXCEPT:
   A. Poliovirus continues to infect millions of people and paralyze or kill over half a million people worldwide every year.
   B. There are still 1 million polio survivors in the United States and hundreds of thousands of cases of postpolio syndrome.
   C. Poliovirus cases have decreased by over 99% since the late 1980s.
   D. Previously polio-free countries are reinfected due to imports of the virus.

5. The Centers for Disease Control now classifies WNV infection into WNV fever and neuroinvasive disease, with further subdivision of the latter group into which of the following?
   1. Meningitis
   2. Poliomyelitis
   3. Encephalitis
   4. Myositis

   A. Only 1, 2, and 3 are correct.
   B. Only 1 and 3 are correct.
   C. Only 2 and 4 are correct.
   D. All are correct.

6. Perceptions of the predominant extracutaneous manifestations of Lyme disease have been important in the development of the understanding of this infection. Which of the following statements are TRUE?
   1. In Europe, the major emphasis has been on nervous system involvement
   2. In Europe, the major emphasis has been on rheumatologic involvement
   3. In the United States, the major emphasis has been on rheumatologic involvement
   4. In the United States, the major emphasis has been on nervous system involvement

   A. Only 1, 2, and 3 are correct.
   B. Only 1 and 3 are correct.
   C. Only 2 and 4 are correct.
   D. All are correct.
7. Which of the following disorders might be seen in a patient with peripheral nervous system (PNS) Lyme disease?
   1. Unilateral facial nerve palsy
   2. Brachial plexitis
   3. Radial nerve palsy
   4. Acute painful L4 radiculopathy
   
   A. Only 1, 2, and 3 are correct.
   B. Only 1 and 3 are correct.
   C. Only 2 and 4 are correct.
   D. All are correct.

8. A patient presents in summer in an area endemic for Lyme disease and recalls a tick bite 6 weeks previously. Which of the following would be compelling evidence of Lyme disease?
   1. History of a 3 cm diameter target shaped rash that began within hours of the tick bite, attained its full diameter in 2 hours, and faded over the next 2 days
   2. History of a 3 cm diameter target shaped rash that began 3 days after the tick bite, enlarged to 20 cm in diameter over the course of 14 days, then gradually faded
   3. New onset of right facial nerve palsy this morning, negative serum Lyme enzyme-linked immunosorbent assay (ELISA) and Western blot
   4. New onset of right facial nerve palsy this morning, strongly positive Lyme ELISA and Western blot
   
   A. Only 1, 2, and 3 are correct.
   B. Only 1 and 3 are correct.
   C. Only 2 and 4 are correct.
   D. All are correct.

9. In a patient with likely exposure to Lyme disease 5 years ago and a positive Lyme ELISA and immunoglobulin G Western blot currently, which of the following disorders would MOST LIKELY be causally related to Lyme disease?
   1. History of bilateral facial nerve palsy 4½ years ago
   2. History of spontaneous onset of severe radicular-type pain in the right arm 4½ years ago, resolving over 6 months, with residual deltoid atrophy
   3. History of aseptic meningitis 4½ years ago
   4. History of typical amyotrophic lateral sclerosis beginning 4½ years ago, with the patient now on a ventilator
   
   A. Only 1, 2, and 3 are correct.
   B. Only 1 and 3 are correct.
   C. Only 2 and 4 are correct.
   D. All are correct.

10. Which one of the following test results would be indicative of Lyme disease in a patient with symptoms of 3 months duration?
    A. Negative ELISA; Western blot with two IgM bands, two IgG bands.
    B. Negative ELISA; Western blot with two IgM bands, five IgG bands.
    C. Positive ELISA; Western blot with two IgM bands, two IgG bands.
    D. Positive ELISA; Western blot with one IgM band, five IgG bands.

11. GBS has been associated with infections related to which of the following?
    1. Campylobacter jejuni
    2. Mycoplasma pneumoniae
    3. Cytomegalovirus
    4. Salmonella enteritidis
    
    A. Only 1, 2, and 3 are correct.
    B. Only 1 and 3 are correct.
    C. Only 2 and 4 are correct.
    D. All are correct.

12. PNS vasculitides related to hepatitis infection:
    1. Are always associated with mixed cryoglobulins
    2. Are generally associated with systemic symptoms
    3. Are generally only seen with chronic active hepatitis
    4. May be treated with combination antiviral and immunosuppressant medication
    
    A. Only 1, 2, and 3 are correct.
    B. Only 1 and 3 are correct.
    C. Only 2 and 4 are correct.
    D. All are correct.

13. Clinical features of diphtheric polyneuropathy include which of the following?
    1. Autonomic dysfunction
    2. A progressive, monophasic clinical course
    3. Impairment in near vision
    4. Early onset of areflexia
    
    A. Only 1, 2, and 3 are correct.
    B. Only 1 and 3 are correct.
    C. Only 2 and 4 are correct.
    D. All are correct.
14. An human immunodeficiency virus (HIV)-positive female is referred to the clinic for bilateral stocking-distribution lower extremity dysesthesia and allodynia, which have evolved over the past 6 months. Her CD4 count is currently 400 cells/mm³ with a nadir CD4 of 273 2 years prior. Current CD8 count is 900 cells/mm³. Her antiretroviral regimen includes emtricitabine and tenofovir coupled with atazanavir boosted with ritonavir, which she has been on for 2 years. What is the MOST LIKELY cause of this neuropathic pain syndrome in this patient?
A. Diffuse interstitial lymphomatosis syndrome.
B. Antiretroviral toxic neuropathy.
C. HIV-associated distal sensory polyneuropathy.
D. It is likely related to alternative causes and further workup is necessary.

15. All of the following statements regarding leprosy are correct EXCEPT:
A. Duration and type of therapy can be determined by skin findings.
B. Reversal reactions are important mechanisms of peripheral nerve injury.
C. Hypopigmented skin lesions with a raised edge and sensory loss are prototypical clinical findings.
D. Mycobacterium leprae infects skin macrophages, schwann cells, and dorsal root ganglia.

16. Pick the TRUE statement.
A. Postherpetic neuralgia is an uncommon neurological condition.
B. Varicella zoster virus is a zoonotic infection.
C. Varicella zoster virus is a herpes virus.
D. Zoster only affects sensory nerves.

17. Which of the following is the MOST important risk factor for developing postherpetic neuralgia?
A. Sex.
B. Age at time of zoster outbreak.
C. Age at time of chicken pox infection.
D. Severity of chicken pox rash.

18. Which statement is TRUE regarding commercially-available zoster vaccine?
A. It works in 90% of people who receive it.
B. It comes in killed and live attenuated forms.
C. The virus used in zoster vaccine is different from the virus used in chicken pox vaccine.
D. It works better in younger people.

19. Which of the following medications is considered first line treatment for postherpetic neuralgia?
A. Mexilitine.
B. Serotonin-norepinephrine reuptake inhibitors.
C. Carbamazepine.
D. Opioids.