Neuromuscular Complications of Infectious Disease

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OF INFECTIOUS DISEASE

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Dr. Mitrabhakdi performed her fellowship in neuromuscular disease and electrodiagnosis at Johns Hopkins and is board-certified in Neurology. She is currently an assistant professor of neurology at Chulalongkorn University Hospital in Bangkok and Director of the hospital's EMG laboratory. Dr. Mitrabhakdi's research interests include immune-mediated neuropathies, electrophysiology and rabies pathogenesis, and a variant of chronic inflammatory demyelinating polyneuropathy in Thailand.

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Dr. Lewis is currently Professor and Associate Chairman of Neurology at Wayne State University School of Medicine. He is also Co-Director of the Muscular Dystrophy Association Clinic at the Detroit Medical Center, and Vice Chief of Neurology and Director of Clinical Neurophysiology at Harper Hospital in Detroit. Dr. Lewis is active in many professional societies, including the American Neurological Association, the World Federation of Neurology ALS Consortium, the Peripheral Nerve Society, the American Academy of Neurology, and the AAEM. He is certified by the American Board of Psychiatry and Neurology, the American Board of Electrodiagnostic Medicine, and in 1996 he earned his Certification of Added Qualifications in Clinical Neurophysiology. In addition, Dr. Lewis is on the editorial board of the Journal of Neuropathic Pain and Muscle & Nerve, and is an ad-hoc reviewer for several other journals. He was recently named one of the best doctors in Detroit by Hour Magazine.

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Dr. So is Director of the Neuroscience Clinics and the Neuromuscular and Muscular Dystrophy Association Clinics at Stanford University. He earned his medical degree from Yale University, his PhD from Rockefeller University in New York, and completed his residency in neurology at the University of California at San Francisco. Dr. So was Director of the EMG Laboratory at San Francisco General Hospital in the late 1980s and early 1990s, near the peak of the AIDS epidemic. He has a longstanding interest in the neurologic complications of HIV infections, and has published extensively on the topic. Dr. So’s other clinical and research interests include peripheral neuropathy, nerve injury, and nerve conduction studies.

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Dr. Genge earned her medical degree from the Memorial University of Newfoundland. She went on to complete an internship in neurology at McGill University and a fellowship in neuromuscular disease at Montreal Neurological Institute. She is currently the medical director of the Neurological Day Center at Montreal Neurological Hospital (MNH), as well as MNH’s Director of the Amyotrophic Lateral Sclerosis (ALS) Clinic and a neurologist at MNH’s EMG Clinic. Dr. Genge has won several awards, most recently the Silver Jubilee Medal from the Lieutenant Governor of Quebec. She is also involved in several ongoing research trials involving ALS.

Authors had nothing to disclose.

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OBJECTIVES

This course will provide information on infectious disorders affecting the neuromuscular system. This will include classic and newly recognized agents affecting the motor neuron, peripheral nerve and muscle. Disorders to be discussed include West Nile virus, poliomyelitis, rabies, lyme disease, HIV, leprosy, and viral and parasitic disorders of muscle. After attending this course, the participant will be able to recognize the clinical presentations of these disorders and develop a diagnostic and therapeutic approach consistent with the pathophysiology of these diseases.

PREREQUISITE

This course is designed as an educational opportunity for residents, fellows, and practicing clinical EDX consultants at an early point in their career, or for more senior EDX practitioners who are seeking a pragmatic review of basic clinical and EDX principles. It is open only to persons with an MD, DO, DVM, DDS, or foreign equivalent degree.

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The AAEM designates attendance at this course for a maximum of 3.5 hours in category 1 credit towards the AMA Physician's Recognition Award. This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he/she actually spent in the activity. The American Medical Association has determined that non-US licensed physicians who participate in this CME activity are eligible for AMA PMR category 1 credit.
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**INTRODUCTION**

Poliomyelitis, a medical term, derives from the hybridization of three Greek words, “polio,” “myelo,” and “itis,” which mean gray matter, spinal cord, and inflammation respectively. Thus, the term poliomyelitis can be given to any inflammatory disorder resulting in selective damage of motor neurons at the anterior horn. Prior to the era of polio virus vaccination, paralytic poliomyelitis was caused by the polio virus in more than 98% of the cases where a causative agent was determined. Poliomyelitis was almost equivalent to polio virus infection. With the polio virus vaccination, it has lost its prominence. Causative agents for paralytic poliomyelitis have become more diverse.

West Nile virus (WNV) has been an epidemic in many parts of the world but has spared North America until 1999. The dramatic outbreak of WNV infection in New York City during 1999 heralded the virus reaching North America. Since then, WNV has rapidly spread across the United States. Ten percent of hospitalized patients with WNV infection from the New York City outbreak presented with acute flaccid paralysis (AFP). This author, as well as others, has demonstrated electrophysiological, pathological, and radiological evidence that this paralysis is caused by acute damage of anterior horn motor neurons. Thus, it is reasonable to call WNV-induced paralysis a poliomyelitis. It is these paralytic patients who develop significant disabilities after WNV infection, and are often seen by neurologists and physiatrists. This manuscript will review the epidemiology of WNV infection, clinical, pathological, and electrophysiological features of WNV paralysis, and management issues in these patients.

**WEST NILE VIRUS AND ITS EPIDEMIOLOGY**

West Nile virus is a member of the Flavivirus family (Figure 1) and belongs to the Japanese encephalitis complex subgroup along with several other viruses (including Japanese encephalitis virus, St. Louis encephalitis virus, and Murray Valley virus). It is a ribonucleic acid (RNA) virus with a positive polarity. The virus possesses a spherical shape. It consists of a central core, where nonstructural proteins and the virus genome are located, and an envelope which has capsid, membrane, and envelope proteins. The envelope protein renders the specificity of virus and host-tissue binding.

West Nile virus was first isolated from an African woman in the West Nile district of Uganda during 1937. The virus is maintained in a bird-mosquito-bird cycle. In an appropriate ecological setting, the cycle initiates in the spring and lasts until early fall. Mosquitoes from the genus *Culex* are the main vector, and they bite both humans and birds to transmit the virus. Occasionally, the virus is transmitted by other pathways such as transplacental transmission from mother to fetus, by organ transplantation, or by blood transfusion. The virus has been an epidemic in many parts of the world but did not appear in North America until 1999. Cases from the early outbreaks described a fairly benign clinical presentation with fever, muscle
aches, skin rash, lymphadenopathy, and minimal or no encephalitic signs or symptoms. Later, Flatuea and colleagues reported cases of West Nile encephalitis that were mild with complete recovery. Over several decades, WNV not only continued to spread, but also gained more virulence. Severe encephalitic and paralytic cases have increased in the last several years.

Since the dramatic outbreak of WNV infection in New York City in 1999, WNV has rapidly spread across the continental United States. From 1999 to 2001, there were only 142 documented cases with 18 deaths. The incidence of WNV infection dramatically increased to 4156 cases resulting in about 284 deaths during the summer of 2002, and 5005 cases in 2003.

**CLINICAL FEATURES OF WEST NILE VIRUS PARALYSIS**

Most individuals infected with WNV are asymptomatic. The majority of symptomatic patients present with mild flu-like symptoms—namely West Nile fever. The virus has an incubation period ranging from 2-14 days prior to symptomatic onset. Less than 1% of infected individuals develop severe neurological disorders including encephalitis, meningitis, or AFP. Approximately 10% of the hospitalized patients in the 1999 New York City outbreak had AFP. Subsequently, there have been a few case reports describing patients with WNV infection and a “polio-like” syndrome. During the summer of 2002, there were a significant number of cases of WNV infection, and a group of these patients who presented with AFP were carefully studied. The cardinal clinical feature of these patients was acute asymmetric flaccid paralysis (dark limbs, Figure 2A). Paralysis reached a plateau within hours in most patients and was slightly more frequent in the lower extremities than in the upper extremities. There was minimal or no sensory disturbance. Most patients reported significant muscle aches in the lower back. Bowel and bladder function were infrequently disturbed.

Many patients reported mild flu-like symptoms 1–2 weeks prior to the weakness including headache, fever, malaise, gastrointestinal upset, skin rash, and some patients reported neck rigidity and mental status alteration. However, half of this author’s patients showed no viral prodrome or any meningoencephalitic signs. Many of them were healthy prior to the illness and had no evidence of immunological suppression.

On neurological examination, patients may have fever, mental status alteration, and neck rigidity. As mentioned, these abnormalities may be absent in some patients. Most cranial nerves are usually normal; however, facial weakness may be present in more than half of these patients. Flaccid limb weakness is conspicuous. Muscular atrophy develops in the late phase of the illness. Sensory examination is normal or minimally affected. Deep tendon reflex (DTR) can be diminished in severely paralyzed limbs. However, DTR is frequently exaggerated in the late phase of the disease.

To further illustrate the clinical features of WNV paralysis, two typical cases will be presented below.

**Case 1**

A 36-year-old woman was healthy until 1 week prior to presentation when she developed mild flu-like symptoms, including headache, malaise, and gastrointestinal upset. One day prior to admission to the hospital, she noted lower back pain. On the morning of admission, she awoke to find her left leg paralyzed. At no time did she have confusion, neck stiffness, or other meningoencephalitic symptoms or signs. She denied bowel and bladder dysfunction or muscle pain.

Examination revealed a temperature of 100.9° F and a flaccid left leg without movement except for minimal ankle dorsal and plantar flexion. There were absent left knee and ankle deep tendon reflexes. All other reflexes were well preserved and the rest of her examination was normal.

She received a course of intravenous immunoglobulin (IVIg) treatment (1 g/kg/day for 2 days) with no significant improvement. Recovery will be discussed later.

**Case 2**

A 44-year-old man who was previously healthy developed a tingling sensation in his back that lasted about 8 hours. He felt tired, experienced a headache, a fever of 102° F, and neck stiffness. Four days later, his legs were paralyzed, followed by left arm paralysis 10 days later, and right arm paralysis 24 hours after that. His left facial muscles were also paralyzed and he could not close his eyelids. He was transferred into the intensive care unit and although there was respiratory distress, he was able to be managed without intubation.
This patient was seen by the author 6 weeks after hospitalization. His examination at that time showed significant bilateral facial weakness. There was severe asymmetric limb weakness. Most muscles in the left limbs were not able to move against gravity, whereas muscles in the right limbs were a 4 on the Medical Research Council scale. Sensory examination was normal. Deep tendon reflex were very brisk in all joints, and toes were down-going.

RECOVERY OF PARALYSIS

Data on WNV paralysis recovery are scanty. Among patients hospitalized in New York and New Jersey in 2000, only one-third regained ambulation within a year.40 Three paralytic patients from another study required the use of a wheelchair after an 8-month follow-up.40 Although no detailed quantitative assessment of motor function was described in these studies, they seem to suggest an unfavorable outcome. However, a study in patients infected with WNV in 2002 showed a remarkable variation of recovery.24 Some of these patients recovered completely within weeks.

The author and colleagues have followed eight patients with WNV paralysis and assessed their motor function quantitatively by obtaining Amyotrophic Lateral Sclerosis Functional Rating Scores (ALSFRS) (Figure 2B). Among these eight patients, highly variable recoveries were noticed. The ALSFRS is a questionnaire used to assess overall motor function and includes 10 questions related to patient motor function. Total ALSFRS range from 40 (normal) to 0 (no motor function). Improvement in ALSFRS occurred mainly over the first 6 months. Patients with single limb paralysis (Figure 2A, patients D and G) had flat curves, but achieved relatively high scores, suggesting that unaffected limbs provided much of the motor function associated with activities of daily living. At this time, it is unknown whether patients with WNV paralysis will develop “post-WNV syndrome” similar to post-polio syndrome.

Of interest is that initial severity of the illness did not predict the final outcome. One can use Cases 1 and 2 (Figure 2B, patients G and F) described previously as examples. The second case had more systemic symptoms and severe four limb paralysis initially. His condition appeared much worse than that in Case 1 upon presentation. Yet, his strength recovered completely, whereas paralysis in the left leg of Case 1 improved minimally after 20-month follow-up.

LABORATORY FEATURES

A definitive diagnosis of WNV meningoencephalitis or poliomyelitis requires pertinent neurological symptoms and positive immunoglobin M (IgM) antibodies to WNV detected by enzyme-linked immunosorbent assay on the cerebrospinal fluid (CSF). Presence of IgM antibodies in the serum is no longer considered reliable because the United States population has been exposed to the virus in the last several years and many asymptomatic individuals may carry antibodies in their serum.50 Other abnormal findings in CSF include elevated lymphocytes and protein levels. Occasionally, neutrophils may be dominant in the early phase of the illness, but lymphocytosis usually develops within a few days. This author has also seen patients with elevated serum creatine kinase (CK) ranging from several hundreds up to 20,000 mg/dl. This elevated CK may have originated from necrotized muscle fibers as shown in this author’s muscle pathology study (Figure 4) the results of which will be discussed later under Pathological Findings and Pathogenesis.

Magnetic resonance imaging (MRI) studies in most cases are usually normal. However, abnormalities have also been described,18,25 such as focal white matter and thalamic lesions with increased signal intensity on the T2-weighted image. An important MRI finding is the focal abnormal signal intensity within the anterior horns (Figure 3, A and B). The level of abnormal spinal MRI findings corresponds to the weakness. This observation provides strong evidence for the selective damage of the anterior horn of the spinal cord. Root enhancement is rarely seen (Figure 3, C and D).

Electrophysiological study is helpful for the diagnosis of WNV paralysis.9,18,24,25 Motor nerve conduction studies (NCSs) may reveal severely reduced amplitudes of compound muscle action potentials (CMAPS) in symptomatic limbs. However, if the NCS is performed in the early phase of the illness, CMAPs can be normal since Wallerian degeneration may take 7-10 days to complete. Nerve conduction velocities are usually preserved, and sensory NCSs are normal. Needle electromyography (EMG) shows severe denervation in muscles of weak limbs and the corresponding paraspinal muscles. Taken together, these abnormalities in the paralyzed limbs localize the lesions to the anterior horn motor neurons or their ventral nerve roots. The localization is consistent with the aforementioned MRI findings.

DIAGNOSIS

The diagnosis of WNV paralysis should be considered whenever the clinical presentation of acute asymmetric paralysis with normal sensory examination occurs during the seasons when mosquito-borne diseases might occur. Weakness may involve a single limb or multiple limbs, but is usually not confined to the distribution of individual nerves. Absence of viral prodrome does not exclude the diagnosis. Electrophysiological studies and neuroimaging can be helpful as has been discussed. A definitive diagnosis requires a positive IgM antibody test or PCR detection of WNV in CSF. (See Laboratory Features section).
Figure 2  Clinical features and motor function recoveries of West Nile virus-induced paralysis:
The cardinal clinical features of this author’s patients are illustrated in figure 1A. Weak limbs (at plateau) are darkened. Degree of darkness corresponds to the severity of weakness. Age, sex, and duration of nadir are listed below each patient. Figure 1B summarizes the ALSFRS changes in these patients.

ALS = amyotrophic lateral sclerosis; ALSFRS = amyotrophic lateral sclerosis functional rating score.
The differential diagnosis may include Guillain-Barré syndrome (GBS), myopathy, neuromuscular junction disorders (NMJ), and other virus-related motor neuron diseases. Sensory disturbance and slowed conduction velocities in NCSs of most GBS patients may be sufficient to differentiate WNV paralysis. Acute motor axonal neuropathy (AMAN) as a subtype of GBS could closely imitate WNV paralysis, but is less problematic in the United States since AMAN is extremely rare in this country. If the issue does arise, one may have to rely on a WNV IgM antibody test of CSF. Myopathy and NMJ disorders usually have quite different clinical presentations; their differential diagnoses will not be discussed in this manuscript.

All flaviviruses of the Japanese and tick-borne encephalitis complex are known to affect lower motor neurons. Flaccid weakness and needle EMG abnormalities consistent with lower motor neuron damage have been documented in St. Louis encephalitis, Japanese encephalitis, Murray Valley encephalitis, and Powassan encephalitis. Pathological studies have shown specific inflammatory involvement in the anterior horns in Japanese encephalitis, nearly identical to that seen in polio virus-induced myelitis. Similar pathology was also shown in Russian Spring Summer encephalitis (Far eastern tick-borne). However, its clinical presentation is unique and is characterized by cervical cord motor neuron involvement and conspicuous head-drop due to neck flexor denervation. Based on the above information, one should consider these infectious agents when dealing with a patient with an acute lower motor neuron disorder. It is usually difficult to discern among these diseases clinically. Epidemiological data may be critical for the diagnostic consideration. Specific serology or PCR tests are often necessary.

**PATHOLOGICAL FINDINGS AND PATHOGENESIS**

The selective destruction of anterior horn motor neurons with inflammatory infiltration has been confirmed in several autopsy studies, and WNV antigens were found localized in the anterior horn. This localization is consistent with early pathological studies as well as the findings from human subjects inoculated with WNV intramuscularly. Moreover, almost all flaviviruses have been documented to cause motor neuron damage at the anterior horns. Taken together, based on clinical presentation, neuroimaging, and pathological

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Figure 3 MRI findings in patients with West Nile virus infection:
A: A sagittal T2 weighted MRI image of the lumbar spinal cord. Abnormal signal intensity (arrows) is conspicuous within the cord. B: A transverse view of the cord at the mid-lumbar level. Abnormal signal intensity (arrows) is confined to the anterior horns. C. MRI from another case shows lumbar/sacral roots that are enhanced by GAD. D. No signal abnormality in these roots when GAD is not given.

MRI = magnetic resonance imaging, GAD = gadolinium
findings, motor neuron damage at the anterior horn of the spinal cord is likely the major contributor to the WNV-induced paralysis. The anterior horn cell damage is not uniformly distributed but rather occurs in segments of the spinal cord (Figure 4). These findings may explain the asymmetry and variable degrees of weakness among limbs. However, this also raises an important question concerning how this segmental damage is produced. A simple hematological viral spreading may not satisfactorily explain the segmental nature of these lesions in the spinal cord. Alternatively, WNV may invade peripheral nerve terminals via a receptor and reach motor neurons by retrograde axonal transporting. Thus, whichever limb is invaded by the virus will be affected first and develop more limb weakness. This is an attractive hypothesis, but remains to be proven. This hypothesis is indirectly supported by the pathological finding that motor nerve terminals were damaged and infiltrated by inflammatory cells (Figure 4C). These cells are CD8 predominant over CD4 lymphocytes, with minimal or no macrophages. The cellular profile is suggestive of an inflammatory reaction to the viral invasion.

Although there was a case report that described a patient with GBS with conduction velocities below 35 m/s, demyelinating neuropathy was extremely unusual among patients in the United States reported from 1999 to present. Creatine kinase (CK) elevation has been observed in some of this author’s patients which suggests muscle involvement in the disease. However, this

Figure 4 Pathological evidence of anterior horn cell damage and motor nerve terminal involvement in West Nile virus infection:

Figure A and B: Hematoxylin and eosin (H&E) stained sections of the spinal cord from an autopsy at 250x the original magnification. Motor neurons at the anterior horn are almost depleted (Figure A). In contrast, most motor neurons (arrowheads) in another segment of the spinal cord are well preserved (Figure B). A few motor neurons appear swollen (arrow, figure B). In addition, conspicuous inflammatory cells infiltrate diffusely in both segments of the cord. Figure C is a left rectus femoris muscle biopsy that includes intramuscular nerve twig showing inflammation of endo- and perineurial blood vessels (small and large arrows) and scattered degenerating myelinated nerve fibers (small arrows). There are also mononuclear inflammatory cells infiltrating in the nerve fiber bundle. Frozen section, H&E stain, 500x original magnification. Figure D: muscle biopsy from another case shows several scattered necrotized muscle fibers. However, most muscle fibers appear normal. Frozen section, H&E stain, 250x original magnification.
author believes this is not a major contributor to WNV paralysis since the vast majority of muscle fibers appeared intact in muscle biopsy (Figure 4D).

As has been discussed, recovery among paralyzed patients is remarkably variable. The reason for this variation is still unclear. The preliminary data suggests that the variation may be caused by different degrees of motor neuron or motor unit loss.20,35 Many of the experiences from polio virus infection might be applicable to WNV paralysis. Acute asymmetric weakness with normal sensory function is the most prominent symptom in both diseases. Selective spinal motor neuron destruction with inflammatory infiltration in the anterior horn is the main pathological feature present in both disorders. These features are also seen in some patients infected by other mosquito-borne flaviviruses. Therefore, it is reasonable to speculate that these viruses may share a similar pathophysiological mechanism that allows them to invade and damage motor neurons selectively.

TREATMENT AND PREVENTION

To date, there is no controlled study showing effective measures to combat WNV, nor is any vaccine available. Thus, treatment is mainly supportive.20,35 Many of the experiences from polio virus infection might be applicable to WNV paralysis.

A broad spectrum of antiviral medication like ribavirin effectively inhibited viral replication in vitro in mice.21 Its efficacy in human subjects remains to be determined. Intravenous immunoglobulin protected mice from WNV infection and was claimed to be effective in a few case reports.3,13,42 There is an ongoing controlled trial of IVIg treatment which will compare IVIg with high titers of anti-WNV IgG (obtained from Israel) and IVIg with low titers (obtained from American donors). The results are not available at this time. Four patients were treated with Unite States-made IVIg in 2002 and observed no significant effect.

Rehabilitation is an important part of management in this disease including physical therapy, occupational therapy, and speech therapy when dysphagia is present. Patients with long-lasting paralysis require frequent joint stretching to prevent contracture. When lower limbs are involved, bracing appears quite helpful to maximize ambulatory capability, particularly in patients with single-limb paralysis. In weak limbs, superficially located peripheral nerves, such as the peroneal nerve at the fibular head and ulnar nerve across the elbow, are subject to compression. Careful cushion protection at these sites is necessary.

SUMMARY

West Nile virus causes acute paralysis primarily by damaging motor neurons at the anterior horn of the spinal cord. Patients present with pure motor deficits similar to patients with polio virus infection. Recovery from paralysis is highly variable among these patients, and probably depends on the severity and quantity of motor neuron damage or motor unit loss. Based on observations in the last several years, WNV is likely to continue to spread. This demands more knowledge about the disorder, particularly in the following aspects: (1) development of an effective and safe vaccine and specific antiviral drugs; (2) delineation of paralysis recovery which will be critical for evaluating vaccines or future therapeutic trials; and (3) pathogenesis of viral invasion into the nervous system and selective neuronal damage.

REFERENCES

8. Chu JF, Ng ML. Characterization of a 105-kDa plasma membrane associated glycoprotein that is involved in West Nile virus binding and infection. Virology 2003;312:458-469.
INTRODUCTION

Rabies is an acute encephalitis caused by viruses of genus *Lyssavirus*, of seven putative genotypes. The disease is inevitably fatal and presents a horrifying clinical picture. Although rabies kills more people each year than dengue virus, yellow fever, and Japanese encephalitis combined, it receives little attention and is ranked low in the World Health Organization priority list. Human rabies can manifest in either encephalitic (furious) or dumb (paralytic) forms. While encephalitic rabies is a well-recognized clinical disorder, the paralytic form is not as easily identified. Paralytic rabies continues to be confused with Guillain-Barré syndrome (GBS) and other treatable autoimmune diseases of peripheral nerves. Misdiagnoses of rabies has led to human-to-human transmission through corneal, liver, and kidney transplants from donors who were thought to have GBS or stroke. Many rabies patients misdiagnosed as having GBS have undergone plasma exchange.

Survival time in paralytic rabies is longer than in furious rabies. The mechanisms responsible for motor weakness and a longer survival period have not been clearly identified. Several hypotheses have been proposed including rabies virus variants associated with the particular vector, location of the wound, incubation period, prior rabies vaccination, and virus localization in the central nervous system (CNS). However, none of these have been substantiated. This author has also demonstrated that dysfunction of peripheral nerves, not anterior horn cells, is responsible for weakness in paralytic rabies (submitted for publication).

In order to improve the diagnosis of human rabies, there is a need to better recognize paralytic rabies patients. This manuscript summarizes the distinct clinical features associated with paralytic rabies as compared to GBS and furious rabies. Data on the electrophysiological and pathological features are also reviewed.

CLINICAL FEATURES

Clinical features can be divided into five stages: the incubation period; the prodrome, the acute neurological phase, coma, and death. Because of the clinical diversity during the acute neurological phase, rabies can be distinguished as classic (encephalitic/furious and paralytic/dumb forms) and nonclassic forms. Classic rabies is almost always associated with true rabies virus (genotype 1). Nonclassic rabies patterns can be found in...
patients exposed to bats and lately, in Thai patients infected by dogs. Atypical presentations are also seen in rare rabies survivors.

**Incubation Period**

The incubation period of rabies is the most variable among viral infections of the CNS; the most common period is 1-2 months, but it can range from less than 7 days to more than 6 years. Unusually long incubation periods have been found in persons who emigrate to the United States from southeast Asia. An incubation period of less than a week has been seen with direct inoculation of the virus into the nervous system, as in patients who sustain brachial plexus injury from dog bites.

The absence of history of exposure to rabid animals, however, cannot exclude rabies, particularly in rabies-endemic areas where trivial exposures are common.

**Prodrome**

The prodromal stage begins when the virus moves centripetally from the periphery to the dorsal root ganglia (causing neuropathic pain) and the CNS. These developments mark the end of the incubation period, and most patients die within the next 2 weeks. As many as a third of patients with a dog-related infection (equally common in furious and paralytic rabies) and three-quarters of those with bat-related disease experience local symptoms or neuropathic pain at the bite site. This is presumably due to ganglioneuritis, described as burning, itching, tingling, or pruritus. An intense and progressive local reaction, starting at the bite site and spreading to involve the whole limb in a nonradicular pattern, or the ipsilateral side of the face, is a reliable indicator of rabies. Pruritus commonly results in extensive excoriations. Prodromal symptoms last a few days, generally not exceeding a week.

**Acute Neurological Phase**

Within hours or a few days after the prodrome, rabies patients enter an acute neurological phase. Two-thirds of patients suffer from the furious form of rabies and the remaining present with the paralytic form. Furious rabies patients generally die within 7 days (average 5 days) after the clinical onset, although the survival may be as long as 2-3 weeks. The average length of survival is 13 days in paralytic cases.

In furious rabies, the earliest neurological abnormality is fever and hyperactivity brought on by internal (thirst, fear, nervousness, etc.) or external (light, noise, etc.) stimuli. This is followed by typical furious features consisting of fluctuating consciousness, aero- and hydrophobia, and spontaneously occurred inspiratory spasms. Autonomic dysfunctions (hypersalivation, nonreactive pupils, piloerection, etc.) are usually observed. Seizures and hallucinations are rare, but may occasionally be seen in patients with fully developed disease, often at the preterminal stage.

In paralytic rabies, the diagnosis is extremely difficult due to the lack of aggression. Cardinal features of furious rabies appear late and are usually mild. Phobic spasms, seen in all furious rabies patients, occur in only 50% of paralytic patients. Inspiratory spasms are less evident because of weakness; they generally start in the bitten limb but progress to all limbs and bulbar, facial, and respiratory muscles. Facial diaphoresis is as common in paralytic rabies as it is in sporadic GBS. The following features suggest paralytic rabies and serve to differentiate this disorder from GBS: persistent fever from the onset of limb weakness; intact sensory function of all modalities except at the bitten region; percussion myoedema; and bladder dysfunction. Percussion myoedema is most readily elicited on the chest, deltoid, and thigh regions. It consists of mounding of the muscle at the percussion site, which then disappears over a few seconds. The reason why percussion myoedema is found in paralytic rabies is unknown, but this sign is not observed in GBS or furious rabies. Nevertheless, it should be interpreted with caution, because it can be seen in hypotension, hypothyroidism, renal failure, and in syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

**Coma**

Inspiratory spasms may aid in diagnosis at coma stage, but they are difficult to detect in paralytic rabies due to weakness. Various forms of cardiac arrhythmia may occur presumably due to viral involvement at the sinus or atrioventricular node(s) and myocarditis. Coma precedes circulatory insufficiency, a major cause of death in almost all cases.

**FURIOUS AND PARALYTIC RABIES**

Clinical data from 115 Thai rabies patients (furious 80, paralytic 35) were examined and compiled from this author and colleagues published reports between 1988 and 2004. These data revealed longer survival periods in the paralytic rabies group (11 days versus 5.7 days in furious group). Cardinal features of furious rabies—fluctuating consciousness, hydro- or aerophobia and inspiratory spasms, signs of autonomic dysfunction—were seen in all Thai furious rabies patients. In noncanine rabies endemic areas, such as in North America where bats are the principle vector of rabies, clinical expression may be variable.

Only one or two classic signs of rabies, or perhaps none, may be seen during the whole clinical course in paralytic rabies. Consciousness was preserved until the preterminal phase. Phobic spasms were reported in only half of the confirmed paralytic rabies patients. (Hemachudha and Rupprecht, 2004, personal communication). Weakness was the initial manifestation.
PARALYTIC RABIES AND GUILLAIN-BARRÉ SYNDROME

Some clinical features associated with GBS and paralytic rabies can overlap, almost to the extent that they may be clinically distinguishable (Table 1).9,12

All three main subtypes of GBS, in which weakness is predominant, result from an immune mediated process directed against Schwann cells and myelin or axolemma of motor and sensory fibers (Table 1).5,7,8,21 Similarities observed in GBS and paralytic rabies are not seen in paralysis associated with other viral infections such as flaviviruses, poliovirus, and West Nile virus where anterior horn cell involvement has been documented by electrophysiologic and magnetic resonance imaging (MRI) studies.4,18,19,20 Clinical similarities between GBS and paralytic rabies raise questions whether both share the same neuroanatomical involvement and whether mechanisms responsible for weakness in paralytic rabies are immunologic in nature as has been reported for GBS in association with Campylobacter jejuni, Mycoplasma pneumoniae, cytomegalovirus, and Epstein-Barr virus.24

PATHOPHYSIOLOGY OF PARALYTIC RABIES

Neuroanatomical Basis for Weakness

Symptoms and signs in paralytic and furious rabies are indicative of derangement of the spinal cord (anterior horn cell) or peripheral nerves in the former and cerebral functions in the latter. Although MRI is useful in aiding diagnosis, MRI fails to explain the clinical diversity in human rabies.17 This is also true in the case of distribution of rabies virus antigen and inflammatory reactions in the CNS.21 Evidence supporting peripheral nerve dysfunction is based on electrophysiologic studies, the results of which are in accord with peripheral nerve pathology.

ELECTROPHYSIOLOGIC FEATURES IN PARALYTIC RABIES

In a study of three paralytic rabies patients by the author and colleagues, electrophysiologic studies showed evidence of peripheral nerve dysfunction in all three with findings indistinguishable from demyelinating and axonal GBS variants. (Submitted for publication.) Dysfunction of peripheral nerves was suggested by findings of multifocal demyelination along with length-dependent sensory neuropathy in one patient, a severe reduction in conduction velocities and marked prolongation of distal latencies in another patient, and progressive decline in of motor and sensory amplitudes without abnormal spontaneous activities on needle electromyography (EMG) examination in the third patient. This last patient also had early and progressive prolongation in late latencies, suggesting involvement of the proximal nerve segments, during sequential examinations on days 3, 4, 6, and 8 after the onset of clinical symptoms.

Local prodromal neuropathic pain is also likely to be due to dorsal root ganglionopathy. This is based on the presence of typical pain characteristics, the progressive decline in sensory nerve action potential (SNAP) amplitudes in the bitten segment (not in a length-dependent fashion), and pathological findings of dorsal root ganglionitis.

As opposed to the electrodiagnostic findings in paralytic rabies, the sensory and motor nerve conduction studies, including late responses in three furious rabies patients studied by the author and colleagues, were normal. Abundant denervation potentials were evident primarily in the bitten limb even before clinical weakness appeared. This suggests an acute motor fiber loss, probably at the anterior horn cell level. Recent studies also have shown that rabies-infected rat spinal cord motoneurons resist cytolysis, and the apoptotic process is delayed in these neurons as in paralytic rabies whereas this was noted only when furious rabies patients approached coma.
compared to hippocampus cells. Hence, all of these suggest that peripheral nerve dysfunction is responsible for weakness in paralytic rabies.

**PATHOLOGY**

Histopathological study performed on 11 paralytic rabies patients suggested peripheral nerve demyelination as the prime pathological change. Mild to moderate loss of myelinated nerve fibers was reported in 11 of 17 nerves examined; segmental demyelination and remyelination in 16 teased nerve preparations; axonal loss of a variable degree was present in 4 cases; and Wallerian-like degeneration in teased single fibers was noted in 6 nerves. In nine nerves, the primary abnormality was segmental demyelination and remyelination or myelinated nerve fiber loss, either singly or in combination. In none of these cases was Wallerian-like degeneration seen as the only pathological feature. All spinal nerve studies showed evidence of Wallerian-like degeneration as well as segmental demyelination. Such demyelination was absent in the case of furious rabies.

This author's recent histopathological examination of two paralytic and one furious rabies patients agrees with previous reports (submitted for publication) (Table 2). All of these patients had local neuropathic symptoms. In the two paralytic cases, a moderate to severe degree of lymphocytic infiltrations, mainly of CD3-positive T cells, was evident in dorsal and spinal nerve roots. The degree of inflammation appeared to be greater at the level of the bitten segment. A lesser degree of inflammation was also noted in spinal cord gray matter. Anterior horn cells appeared intact in one and depleted in another, but no central chromatolysis was observed in the remaining cells. In a furious rabies case where the patient had been bitten at the right ankle, only scant inflammatory cells were observed along the spinal nerve roots at all levels. Moderate mononuclear inflammatory cell infiltrates were present in the spinal gray matter of thoracic and lumbar levels and, to a lesser extent, in the cervical cord. Some of the anterior horn cells demonstrated central chromatolysis. Dorsal root ganglionitis was found in all cases.

Inflammation and demyelination of the spinal nerve roots and peripheral nerve, therefore, are characteristic findings in paralytic rabies. Although inflammation was also evident in spinal cords of these patients, this may not be a constant finding. As mentioned previously, spinal cord inflammation was scant in all four furious and in three paralytic rabies patients in relation to viral antigen and survival time. It was also not limited to the spinal cord in paralytic cases.

**DIAGNOSIS**

Establishment of a definitive clinical diagnosis of human rabies is difficult and requires the presence of major cardinal signs in
the furious forms. Such a requirement may not be helpful in noncanine rabies endemic areas, such as North America, since these clinical expressions may be variable. However, either phobic spasms alone or the presence of three or more of the following—agitation, confusion, seizures or dysphagia, hypersalivation, limb pain, paresthesia, limb weakness, or ataxia—appeared to be significantly associated with ante-mortem diagnosis.22 These clinical features, however, may overlap with those found in Nipah virus and enterovirus-71 encephalitis.3,13 Examination of brain tissue obtained with a liver-biopsy needle aspiration via the transorbital approach should be required in all patients with encephalitis or paralyis who later progress to coma. Fluorescent examination of brain impression for rabies-virus antigen is inexpensive, sensitive, and reliable.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes encephalitis caused by arboviruses such as Japanese, eastern equine, and West Nile viruses, and enterovirus-71 and Nipah-virus infection. Diffuse flaccid paralysis such as Japanese, eastern equine, and West Nile viruses, and encephalitis, may mimic rabies. Although fluctuation of consciousness is observed in both disorders, phobic and inspiratory spasms are seen only in rabies. Tetanus resembles rabies only in the form of reflex spasm. All patients with tetanus have a clear mental state. Rabies patients do not have persistent rigidity or sustained contraction of axial musculature as seen in tetanus. Spasms in rabies predominantly affect accessory respiratory muscles and the diaphragm, whereas in tetanus, spasms occur in axial muscles. Opisthotonos is extremely rare in rabies.

Acute hepatic porphyria with neuropsychiatric disturbances, autonomic dysfunction, and ascending paralysis with facial aparesis, may mimic rabies. Although fluctuation of consciousness is observed in both disorders, phobic and inspiratory spasms are seen only in rabies. Tetanus resembles rabies only in the form of reflex spasm. All patients with tetanus have a clear mental state. Rabies patients do not have persistent rigidity or sustained contraction of axial musculature as seen in tetanus. Spasms in rabies predominantly affect accessory respiratory muscles and the diaphragm, whereas in tetanus, spasms occur in axial muscles. Opisthotonos is extremely rare in rabies.

The axonal form of GBS, acute motor axonal neuropathy, shares several clinical features with rabies.11 Inspiratory spasms and abnormal sensorium may appear late in the course and may be masked by generalized muscle weakness. Nerve conduction studies do not differentiate rabies from GBS (submitted for publication).

Ante-mortem Diagnostic Approach

During life, routine laboratory studies are nondiagnostic. Hyponatremia is present in most cases due to SIADH. Cerebrospinal fluid (CSF) may appear normal. Alternatively, CSF pleocytosis in GBS-like patients, who have negative human immunodeficiency virus-serology, should alert the clinicians, particularly when fever, hyponatremia, and bladder dysfunction occur early in the course.

MANAGEMENT

Treatment is purely symptomatic and consists of reducing the degree of agitation in the patient, and to comfort the patient and family. Fear of rabies is universal among health-care personnel, resulting in poor nursing care. Attending physicians and nurses who routinely care for patients with rabies may need pre-exposure vaccination. Past efforts to prevent a fatal outcome have failed. Attempted treatment including interferon, antiviral drugs, intrathecal and systemic high-dose administration of human rabies immunoglobulin, steroids, and antithymocyte globuline, have been unsuccessful.

CONCLUSION

With the increased number of Southeast Asians emigrating to the United States, the importance of recognizing rabies will become even greater. It is essential that physicians understand the different clinical features and manage patients appropriately.

REFERENCES


INTRODUCTION

While there are many infections that affect peripheral nerve function by toxic mechanisms (botulism, diphtheria, and tetanus) or immune mechanisms (post-viral Guillain-Barré syndrome (GBS)), this manuscript will focus on disorders in which the infectious agent directly involves the peripheral nerve.

HERPES VIRUS INFECTION

Herpes virus infections are some of the most common viral infections in humans, particularly in relationship to recurrent infections. The peripheral nervous system manifestations of these infections are of particular interest.

After an initial infection, both herpes simplex virus (HSV) and herpes varicella zoster (VZV) may lay dormant in spinal dorsal root and cranial sensory ganglia. An autopsy study of cranial nerve ganglia from 18 cadavers found HSV deoxyribose nucleic acid (DNA) in 42% of all cranial nerve (CN) ganglia studied and VZV DNA in 44% with at least 1 of the 2 viruses found in 65% of the ganglia. This supports the concept that most, if not all adults, carry latent herpes virus in at least some ganglia.

Herpes Zoster

One of the most common peripheral nerve infections is herpes zoster. In virtually all people, after an initial exposure to the VZV, which typically causes chickenpox, the virus will become persistently latent in the peripheral nervous system ganglia including cranial and spinal dorsal root ganglia. The loss of immune control allows for reactivation of the virus by mechanisms that remain unclear. In otherwise immune competent individuals, the reactivation is confined to segmental ganglia, but in immune compromised patients the reactivation can be generalized leading to serious systemic infection. The likelihood of reactivation increases in the elderly, but it is not uncommon in young adults.

The skin rash known as shingles occurs when the virus reaches the skin. Axoplasmic flow of the virus from the nerve ganglion along the fibers, followed by transaxonal flow to the subcutaneous tissue and skin produces local tissue damage and inflammation with resultant sensitization of secondary nociceptors responsible for local pain and hyperalgesia. The development of post-herpetic neuralgia is complicated and includes changes in both peripheral and central pain pathways.

The most common manifestation of VZV reactivation is zoster sensory radiculopathy which manifests primarily as severe radicular pain along a dermatome. This is then associated with the development of local edema and maculopapular rash, followed usually within 36 hours by vesicles that eventually dry and crust over. There may be pruritis and dysesthesias, as well as decreased sensation and allodynia in the involved dermatome. Involvement is usually unilateral, most often in thoracic segments (55%), and less often the CNs (20%). The clinical involvement...
Peripheral Nerve I: Herpes Zoster, Herpes Simplex, Leprosy, and Lyme Disease

is purely sensory, although motor involvement may occur. This is less noticeable when the thoracic regions are involved but can be disabling if cervical or lumbosacral segments are affected.

Zoster cranial neuropathy usually involves the trigeminal (CN V) and facial (CN VII) nerves. Vesicular rash may appear on the areas of sensory distribution by these nerves: first division of CN V (herpes zoster ophthalmicus); hard palate, and external ear innervation of CN VII (herpes zoster oticus). When there is motor involvement, weakness of involved muscles results, e.g., Ramsay-Hunt syndrome (RHS) of ipsilateral facial palsy with VIII, IX palsies following herpes zoster oticus. Herpes zoster ophthalmicus is particularly concerning because of the potential visual loss from sclerokeratitis and uveitis. In addition, intracranial carotid vasculitis causing ischemic strokes has been reported.

**Varicella Zoster and Bell’s Palsy**

The causes of acute facial nerve palsy include trauma, inflammatory/immune mediated disorders, and infections. Idiopathic facial nerve palsy has been classically called Bell’s Palsy (BP). The infectious etiologies of BP are noted in Table 1. The strongest evidence that BP is induced by viral infections comes from the recognition of VZV in patients with RHS, in which the BP is associated with mucocutaneous vesicles in the tympanic membrane, external auditory canal, pinna, or base of the tongue. In these cases VZV has been found in a majority of cases. The question remains as to whether VZV causes BP in those cases without mucocutaneous manifestations (zoster sine herpete). Polymerase chain reaction studies of saliva as well as serologic studies have shown that VZV viral reactivation may account for 8-25% of idiopathic cases.5,14

**Motor Involvement With Varicella Zoster**

Motor involvement from cervical zoster may manifest as diaphragmatic paralysis or arm weakness (zoster paresis); from lumbosacral zoster as leg weakness, with or without bowel and bladder dysfunction. It can also present as long-standing radicular pain, similar to typical pain from lumbar spine degenerative disease. Finally, herpes infection may result in generalized sensory-motor demyelinating polyneuropathy, as seen in GBS. This presents as ascending paralysis, with areflexia and sensory complaints developing from several days to a few weeks. Involvement of respiratory muscles and cranial nerves frequently occur. This most likely represents an immune mediated neuropathy rather than a direct infectious neuropathy.

Zoster sine herpetae is thought to be rare, but it is probably under-diagnosed. It is frequently considered in patients with segmental pain and paresthesias without clear etiology. It most likely results from reactivation of latent VZV in the dorsal root ganglion that fails to reach the skin, so that there is no visible rash.

Neurologists and physiatrists do not frequently see patients with acute VZV reactivation and are more likely to be involved with patients with post-herpetic neuralgia.

**Electrophysiologic findings.** In zoster motor radiculopathy, needle electromyography (EMG) abnormalities in involved muscles include abnormal spontaneous activity and decreased number of motor units, indicative of denervation. In zoster-associated generalized inflammatory polyneuropathy, nerve conduction studies (NCSs) show evidence of primary demyelinating neuropathy.

**Diagnosis.** The diagnosis of zoster neuropathy is established largely by clinical history and thorough physical and neurological examination. Cerebrospinal fluid (CSF) analysis reveals mild lymphocytic pleocytosis and elevated protein concentration but typically lumbar puncture is not required for segmental zoster. There is a rise in VZV titers coincident with the onset of the neurological findings, and determination of this (paired serum and CSF titers) may often be necessary, especially in cases of motor neuropathy or CN palsies of unclear etiology and zoster sine herpetae. Amplification of DNA of the virus in the CSF by PCR may be used to confirm diagnosis.

**Treatment.** Antiviral agents given for zoster infection, such as acyclovir, valacyclovir, and famciclovir may reduce the duration of an acute attack, decrease the formation of new lesions, and

<table>
<thead>
<tr>
<th>Table 1 Infections associated with Bell’s palsy</th>
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<tbody>
<tr>
<td><strong>Bacteria</strong></td>
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<tr>
<td>Tetanus, brucellosis, typhoid fever, leptospirosis, diphtheria, leprosy</td>
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<tr>
<td><strong>Spirochete</strong></td>
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<tr>
<td>Lyme Disease</td>
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<tr>
<td><strong>Viral</strong></td>
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<tr>
<td>Herpes Family</td>
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<tr>
<td>Herpes Simplex-1; Varicella Zoster; Human herpes virus-type 6; Epstein Barr;</td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Non-Herpes viruses</td>
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<tr>
<td>Measles; Mumps; Rubella; Rabies; Hepatitis; Human Immunodeficiency Virus</td>
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reduce acute pain. Analgesic treatment includes the nonsteroidal anti-inflammatory agents (NSAIDs), tricyclic antidepressants, anticonvulsants, and topical anesthetics. Table 2 includes a list of agents that have been studied and used for postherpetic neuralgia.

**Herpes Simplex and Bell’s Palsy**

Recurrent HSV primarily causes skin and mucocutaneous infections, but there is increasing evidence of HSV mononeuropathies. In particular, the role of HSV in BP has recently been emphasized. The data supporting this remains controversial and is not as strong as evidence for VZV infection. Nevertheless, the recent use of PCR on saliva, endoneurial fluid, and posterior auricular muscle suggests that a significant number of patients with “idiopathic Bell’s Palsy” may have activated or reactivated HSV infection. In one series, 40% of BP patients without VZV reactivation had PCR+ HSV-1 in saliva obtained within 5 days of onset whereas only 7% of patients with RHS had + HSV-1. Only 19% of healthy seropositive (have latent HSV-1 but no BP) shed HSV-1 in saliva. HSV-2 was not detected in any patient. In another small series, HSV-1 viral DNA was detected in endoneurial fluid or posterior auricular muscle (from peripheral spread of the virus from CN VII sensory ganglia to the distal site) in 79% of BP patients (11/14) but in 0/9 patients with RHS or 12 control subjects. EBV was not detected in any subject and eight out of nine RHS patients were PCR + for VZV. Other studies have also shown an association of HSV-1 and BP. Whether HSV accounts for a majority of cases remains unclear and the mechanism of neural damage remains unknown. However, the evidence is increasingly compelling that HSV reactivation may cause BP without skin manifestations.

The increasing awareness of the relationship of HSV and VZV to BP raises the question of therapy. Many clinicians are now adding anti-herpes medication to prednisone for the acute treatment of BP, irrespective of identification of viral involvement. However, the data supporting this practice is not striking. Whether the addition of acyclovir to prednisone improves outcomes in BP remains controversial. A Cochrane review in 2001 identified only two articles that addressed this issue with a randomized trial and the conclusions were inconsistent. An American Academy of Neurology practice parameter also stated that “For patients with Bell’s palsy, a benefit from steroids, acyclovir, or facial nerve decompression has not been definitively established. However, available evidence suggests that steroids are probably effective and acyclovir (combined with prednisone) is possibly effective in improving facial functional outcomes.” Since then a few studies have been published either being retrospective or prospective with retrospective control subjects. These have all tended to show better outcomes with anti-viral agents plus corticosteroids than with no treatment or with corticosteroids alone. However, no definitive statement about efficacy can be made. One of the interesting considerations of HSV infection is its potential role as a vector for gene therapy. When applied to the skin, HSV is transported to the sensory ganglia via retrograde transport. Studies are underway to utilize this approach to deliver targeted therapy to the dorsal root ganglia. Encouraging reports in animal models of the delivery of neurotrophins to prevent cis-platinum and pyridoxine neuropathy and enkephalins to treat pain have been published.

**Mycobacterial Infection**

**Leprosy**

Leprosy is an important cause of neuropathy worldwide. In the United States, it is a relatively rare condition, but with the immigration of increasing numbers of people from all over the world, it is being encountered more frequently. Leprosy or Hansen’s disease is a chronic infection of the skin and peripheral nerves. The mode of transmission is believed to be droplet spread and direct contact with ulcerated skin lesions. The organism, in the proper conditions, can live in the soil for over a month. The risk of disease contraction, however, is low. For example, there is only a 5% conjugal disease rate. Humans, armadillos, and primates are the only known hosts and reservoirs. Endemic in Europe during the Middle Ages, it virtually disappeared in Europe except for Norway where it remained into the 20th century and it was a Norwegian, Gerhard Henrick Armhauer Hansen who discovered the bacillus in 1873.

Leprosy is primarily a cutaneous and peripheral nerve disorder with the loss of sensation causing the mutilations and ulcerations that have become the historical hallmarks of the disease.

*Mycobacterium leprae* (*M. leprae*), the etiologic agent of leprosy, is a remarkable organism unlike most other bacteria. The

<table>
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<tr>
<th>Table 2</th>
<th>Therapy for post-herpetic neuralgia</th>
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<tr>
<td><strong>Tricyclic Antidepressants</strong></td>
<td></td>
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<tr>
<td>Amitriptyline</td>
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<tr>
<td>Nortriptyline HCL</td>
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<td>Doxepin HCL</td>
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<tr>
<td><strong>Anticonvulsants</strong></td>
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<tr>
<td>Carbamazepine</td>
<td>Phenytoin</td>
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<tr>
<td>Gabapentin</td>
<td>Topiramate</td>
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<td>Lamotrigine</td>
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<tr>
<td>Capsaicin Ointment</td>
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<tr>
<td>Lidocaine Patches</td>
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<td>Corticosteroids</td>
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structure is similar to other mycobacteria and its lipid capsule protects it from lysosomal enzymes and allows it to survive inside cells. The survival temperature of the organism is low—27-30° C, which accounts for the localization of many of the lesions and also explains the infections of internal organs of the armadillo, which keeps a relatively low core temperature. It has a predilection for Schwann cells and macrophages with occasional involvement of axons. Research in the last few years has shed some light on the molecular mechanisms behind this neurrotropism. The neural targets in the Schwann cell have been identified, and the mechanism by which *M. leprae* attaches to them elucidated. These cells can act as a sanctuary site for the microbe, and a source of infection and relapse. Infiltration of the nerve is not the only pathogenetic mechanism leading to neuropathy. Indirect or secondary damage to the nerve by the inflammation leading to production of cytotoxic enzymes, mechanical pressure on the nerve by edema, and nerve infarction from vasculitis, can result in neuropathy.

**Clinical Manifestations**

Leprosy manifests as a spectrum of different types (Table 3). The type of disorder is primarily dependent on the patient’s immune system. The tuberculoid form of leprosy occurs in patients with relatively well-preserved cell-mediated immunity, resulting in a well-contained and localized infection. Pathology shows few, if any, organisms in the lesion (paucibacillary), with granuloma formation and inflammatory cells expressing Th1 cytokines. The lepromatous form occurs in patients who are anergic to *M. leprae*, resulting in a more diffuse and aggressive process. Pathology in this form shows numerous organisms (multibacillary), with the tissue staining for Th2 cytokines. Intermediate syndromes exist between the two ends of the spectrum. These are borderline forms, with features of both types (midborderline) that could easily change from one to the other (borderline tuberculoid or borderline lepromatous), coincident with fluctuations in the status of the immune system.

Fluctuations in clinical manifestations may occur due to inflammatory reaction syndromes that punctuate the chronic course of leprosy. Type 1, or reversal reaction, is believed to be secondary to an increase in cell-mediated immunity against the presence of *M. leprae* in specific areas. This manifests as new or increased inflammation of surrounding skin and nearby nerve trunks in previously involved areas or pre-existing lesions. Type 2 reaction or erythema nodosum leprosum is believed to be a systemic inflammatory response against large amounts of antibody-antigen complexes deposited extravascularly. Skin lesions (often with subcutaneous nodules that are tender and erythematous), may appear acutely, and ulcerations may occur.

There is often a considerable delay in the diagnosis of leprosy, mainly due to variable clinical features and poor familiarity with the disease. Leprosy should be suspected in individuals from endemic areas or immigrants from endemic countries who present with neuropathy and skin changes. The most common

<table>
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<tr>
<th>Skin Smear</th>
<th>Tuberculoid</th>
<th>Lepromatous</th>
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<tbody>
<tr>
<td>Immune Response</td>
<td>Paucibacillary</td>
<td>Multibacillary</td>
</tr>
<tr>
<td>Evolution</td>
<td>Cell Mediated</td>
<td>Humoral</td>
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<tr>
<td></td>
<td>Th-1; CD 4 (helper)</td>
<td>Th-2 (suppressor)</td>
</tr>
<tr>
<td>Localization</td>
<td>Rapid but can be self-limited</td>
<td>Slow but unrelenting</td>
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<tr>
<td>Skin</td>
<td>Cool regions</td>
<td>Cool regions</td>
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<tr>
<td></td>
<td>Face, trunk extensor limb surfaces</td>
<td>Nasal cartilage and mucosa</td>
</tr>
<tr>
<td>Skin</td>
<td>Localized; Sharply demarcated</td>
<td>Multifocal</td>
</tr>
<tr>
<td></td>
<td>Erythematous plaques</td>
<td>Macules;Papules;Bullae</td>
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<tr>
<td></td>
<td>Spontaneous healing</td>
<td>Nodules;Ulcers</td>
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<tr>
<td></td>
<td>Hairless dry skin</td>
<td>Thick (Leonine facies)</td>
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<tr>
<td>Nerve</td>
<td>Mononeuropathy</td>
<td>Mono or polyneuropathy</td>
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<tr>
<td></td>
<td>Indirect nerve damage</td>
<td>Direct infiltration</td>
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<tr>
<td></td>
<td>from immune/inflammatory response</td>
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<tr>
<td>Nerve Pathology</td>
<td>Granuloma; CD 4 in center; CD 8 (killer) in rim</td>
<td>Macrophages</td>
</tr>
<tr>
<td></td>
<td>Few bacilli</td>
<td>Many bacilli</td>
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neurologic symptom of leprosy is hypoesthesia or sensory loss. A syndrome of superficial neuropathy is uniquely associated with leprosy. This refers to initial involvement of the most superficial nerves, the cutaneous and superficial portions of peripheral nerve trunks. This results in diminution of pain, temperature, touch, and pressure sensation. Sensory loss can be so severe that repeated trauma to the site might not be felt, resulting in mutilation. There is sparing of the deeper and “warmer” nerves resulting in preserved proprioception and vibration sensation, and deep tendon reflexes until late in the course of the disease. While temperature predilection may account for the superficial sensory signs, there is also evidence that Schwann cells of unmyelinated and small diameter fibers may be more involved than those of large diameter fibers.

Two features of the disorder are typical and strongly point to the diagnosis. One is the hypo- or analgesia of hypopigmented lesions. The other is the nerve thickening which can be quite striking, to a much greater extent than seen in inherited neuropathies.

Mononeuropathy occurs when a segment of a peripheral nerve trunk is damaged in the area of inflammation. This may happen in all forms of leprosy. There are certain sites of predilection and nerves commonly affected: the distal forearm segment of the median nerve (proximal to the carpal tunnel), the medial epicondyle segment of the ulnar nerve, the fibular and ankle segments of the peroneal nerve, the ankle segment of posterior tibial nerve, the wrist segment of superficial radial nerve, sural nerve, facial nerve, and the greater auricular nerve. These sites are commonly thickened. Development of skin lesions within the vicinity of focal pain and paresthesias may herald the mononeuropathy.

There are instances when no overt signs or accompanying skin lesions are present, and a silent neuropathy or quiet nerve paralysis develops insidiously. In tuberculoid and borderline tuberculoid forms, a pure neuritic form has been reported. There are no skin lesions found, and a thickened palpable nerve or nerve segment may be the only clue. In lepromatous forms, a slowly progressive, more diffuse nerve involvement, in a stocking and glove distribution, may occur.

**Electrophysiology**

Electrophysiologic studies in leprosy show abnormalities consistent with mononeuropathy simplex or multiplex. Both demyelinating and axonal features are seen. Focal slowing is noted in nerve segments of predilection (as mentioned earlier). Nerve conduction velocities correlate with nerve enlargement and weakness. Peripheral nerves that are superficial or closest to the skin are more likely to yield abnormal results. Sensory studies are more frequently abnormal as compared to motor studies.

**Diagnosis**

The diagnosis of leprosy is established by skin biopsy, with or without nerve biopsy. Demonstration of acid-fast organisms in granulomatous skin lesions confirms the diagnosis. In tuberculoid forms, where no organism may be found, the presence of granulomas with asymmetric destruction of nerve fascicles may be enough to point to the diagnosis. In pure neuritic form, an excision skin biopsy including subcutaneous fat, and a nerve biopsy, may be required.

**Treatment**

Multidrug therapy (MDT) was recommended in 1982 by the World Health Organization (WHO), mainly due to reports of increasing resistance to dapsone, a drug initially used as monotherapy. Multidrug therapy consists of rifampin, dapsone, and clofazimine. For the multibacillary disease (lepromatous leprosy), all three drugs are given for 2 years or longer until the skin smear is negative. For paucibacillary form (tuberculoid), dapsone and rifampin are given for 6-12 months.

For Type 1 or reversal reaction, prolonged anti-inflammatory treatment is necessary. Immunosuppressants, including high-dose corticosteroids, azathioprine, and cyclosporine are effective. For Type 2 or erythema nodosum leprosum, thalidomide is the drug of choice. Thalidomide lowers tumor necrosis factor levels and decreases IgM synthesis. It has a rapid onset of action and reduces the need for corticosteroids. Pentoxifylline and colchicines may also be used for mild cases. Systemic corticosteroids may be needed for neuritis.

**Prognosis**

Disease control with therapy is good although relapses, particularly from lepromatous leprosy can occur. However, WHO data from a 9-year follow-up showed relapse rates of under 1%. Longer follow-up is necessary because late relapses are possible given the slow replication rate of the bacteria. Immune/inflammatory reactions have been noted in some patients, usually within the first 3 years after treatment. Unfortunately, the recovery of sensation has not been shown to be very good. As such, even after treatment ulcerations, infectious complications and amputations remain a concern.

**LYME DISEASE**

Between 1972 and 1976 over 50 individuals from the area of Lyme, Connecticut developed an arthritis that waxed and waned and one-quarter of these patients had a prior skin rash called erythema migrans (EM). In 1981 spirochetes were found in Ixodes scapularis ticks harvested from Lyme-endemic regions.
These spirochetes named *Borrelia burgdorferi* (*B. burgdorferia*) after their discoverer, were subsequently cultured from blood, CSF, and skin of Lyme disease patients. In retrospect, clinical cases most likely due to Lyme disease were noted in the 1980s and PCR of tissue samples dating back to the late 1800s have detected *B. burgdorferi* in both North America and Europe. The clinical picture of Lyme disease was recognized in Europe since the early 1900s with patients with EM and lymphocytic meningoradiculitis being called Bannwarth’s syndrome. It is now clear that Lyme disease and Bannwarth’s syndrome are synonymous, both caused by tick-borne spirochetal infection.

**Epidemiology**

In the United States, Lyme disease is the consequence of infection with the spirochete *B. burgdorferi*. In Europe, *B. garinii* and *B. afzelii*-associated geno-species are more commonly responsible. While 48 states have reported cases, over 90% of cases come from 8 states: Connecticut, Delaware, Maryland, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin. Only certain counties are involved within these states. In Europe, Germany, Austria, Sweden, and Switzerland are particularly involved, and in Asia, Russia, northeast China, and Japan have significant occurrences.

The number of cases of Lyme disease appears to continue to increase although Center for Disease Control reporting is inconsistent. In endemic areas, the incidence can be as high as 1% per year. All ages can be affected and the major risk factor is time spent outdoors where exposure to ticks is possible. There is a 20-30% asymptomatic infection rate most likely related to non-pathogenic strains, too small an inoculum, or effective host immune response.

An individual acquires the organism after being bitten by a variety of Ixodes ticks (*I. scapularis* [deer tick], or *I. pacificus* [western black legged tick] in North America, and *I. ricinus* [sheep tick] in Europe). Immature ticks live on small rodents, and inhabit deer and bears when more mature. In many patients, the tick bite may not be recalled. The tick probably needs to reside on the skin for greater than 24 hours to enable effective transfer of the spirochete.

**Borrelia Burgdorferi**

*Borrelia burgdorferi* is a gram negative bacterial spirochete with 7–12 flagella surrounded by a cellular membrane and covered by a carbohydrate-containing outer layer. It contains 105 lipoproteins, some of which are shared with other pathogens. This accounts for some of the false positive antibody tests that may confuse clinicians. Positive Lyme serology may be seen in as high as 25% of patients with bacteremia.

**Clinical Manifestations**

There are three stages to Lyme disease, with the first developing after an incubation period of 3-30 days. There is local infection, consisting of the typical rash, a non-pruritic bull’s-eye with central clearing. This lesion, known as EM, develops at the site of the tick bite and is seen in 80% of patients with Lyme disease. Typically seen within 10 days of infection, the lesion can enlarge over several days. Skin biopsies have identified *B. burgdorferi* at the leading edge of the EM lesion. Fatigue, myalgias, arthralgias, and headache may be seen, but unlike “the flu,” respiratory and gastrointestinal symptoms are uncommon. Ten percent of patients with only EM and no neurologic manifestations have had positive blood and CSF cultures suggesting early dissemination of the disease.

The second phase is characterized by early disseminated infection with meningitis, lymphadenopathy, malar rash, conjunctivitis facial nerve, or other CN palsies, painful radiculoneuritis, and elevated liver enzymes. Cardiac involvement, particularly atrioventricular block, occurs in up to 10% of patients. Neurologic involvement occurs in 15% of patients and can wax and wane over 6 months. Late stage infection occurs months to years after inoculation. Migratory arthritis, particularly of the knees and temporomandibular joint, skin conditions, uveitis encephalomyelitis, and chronic polyradiculoneuropathy are the most common manifestations. Acrodermatitis chronica atrophicans is seen primarily in infected elderly European women. Extensor surfaces of the legs and distal arms become thin and sclerotic over infected areas.

**Neurologic Manifestations—the Central Nervous System**

In the second phase of the disease, aseptic meningitis/encephalitis is common and can last 4-8 weeks. It can manifest solely as headache, but facial nerve palsy or spinal radiculitis strongly suggests the diagnosis. Cerebral spinal fluid pleocytosis, typically of 100-200 cells/µl but as high as 4000 cell/µl is seen, with primarily mononuclear cells. Cerebral spinal fluid glucose is normal and protein may be increased. Oligoclonal bands are seen in 10% of cases in the United States, but are reportedly higher in Europe. More severe cases will have an encephalitic component including confusion, movement disorders, and behavioral changes. Transverse myelitis has been reported.

In the third stage, mild chronic encephalopathy with memory loss and difficulty concentrating is the most common symptom
Peripheral Nervous System Manifestations

Cranial Neuritis

Facial nerve palsies are seen in a majority of cases during the second stage. Bilateral palsies can be seen in 30% of cases and is so striking that Lyme disease should immediately come to mind. They frequently come on days to weeks apart and are asymmetric. The weakness usually begins about 3 weeks after EM and evolves over 1-2 days. Ipsilateral paresthesias and ear and jaw pain are not uncommon. Taste is usually spared suggesting a distal localization, but CSF and magnetic resonance imaging (MRI) abnormalities also point to more proximal localization. Most patients have complete palsies, but recovery in 4-8 weeks is seen in many. This would suggest that conduction block is playing a role. Other CNs, notably the optic, oculomotor, abducens, trigeminal, and vestibulocochlear nerves have been involved, but much less commonly than the facial nerve. The optic nerve disorders have included optic neuritis, papilledema, and ischemic optic neuropathy. Cranial nerve involvement suggests meningeal involvement, so it is not surprising that CSF abnormalities are seen in these cases.

Painful Radiculoneuritis

Painful radiculoneuritis occurs in 40% of Lyme disease patients, normally occurring within 2 months of the tick bite, but sometimes after an interval of 6 months. Lumbar disease is more common than cervical disease. Pain is often worse at night. Multilevel radiculopathy, lumbosacral and brachial plexitis, and mononeuritis multiplex also occur. This clinical manifestation tends to be associated with severe CSF inflammatory changes, and cranial neuropathy is seen coincidentally in a majority of cases. The pain typically lasts for 2-16 weeks and resolves spontaneously. Weakness occurs days or weeks after the pain and is focal or multifocal. There is usually good recovery over a few months. The electrophysiologic findings appear to be suggestive of a primary axonal disorder with reduced sensory and motor amplitudes, evidence of denervation on needle EMG, but relatively normal conduction velocities. F-wave latency prolongation is not uncommon, most likely reflecting nerve root inflammatory involvement.7 There are some reports of multifocal conduction block and possible demyelinating features. The overall picture has similarities to the lumbosacral plexitis seen in diabetics which has a similar clinical onset and recovery. The physiologic explanation for the recovery over a few months in a primary axonal disorder is not entirely clear.

Myositis

Myositis has been reported in a series of eight patients.13 Myalgias, cramps, and elevated CK are seen in patients with early disease, but weakness is unusual. Needle EMG findings include spontaneous fibrillations and positive sharp waves as well as myopathic motor unit action potentials. Muscle biopsies have shown interstitial inflammatory changes and spirochetes have been seen between muscle fibers.

Polyneuropathy

Polyneuropathy occurs in 40-60% of patients in stage III of the disease. The neuropathy is distal, symmetrical, and predominantly sensory in two-thirds of untreated patients. The chief complaints are pain and intermittent paresthesias in distal extremities. Less than 25% of patients report a glove and stocking sensory disturbance. Weakness is rare, deep tendon reflexes are often preserved, and physical signs may be minimal. The neuropathy typically persists for weeks to months. Cerebral spinal fluid is usually normal.

Other neuropathies have been described including acute weakness suggestive of GBS. Chronic motor neuropathy has been reported but a causal association with Lyme disease has not been convincingly established.

Electrophysiologic Findings

Nerve conduction and needle EMG findings in Lyme peripheral nerve disease are consistent primarily with an axonal neuropathy. Sensory and motor amplitudes are low with normal or borderline normal segmental velocities. However, F waves are prolonged in 50% of cases. Some reports suggest a demyelinating component with prolonged distal motor latencies. Nerve conduction studies are abnormal in 70% of cases 2-3 years after onset. Approximately 30% of patients have neurophysiological evidence of carpal tunnel syndrome.

Diagnosis

Cerebral spinal fluid analysis reveals lymphocytic pleocytosis, elevated immunoglobulin levels, and raised protein content. Diagnosis is complicated by the fact that the general population has a Lyme antibody seropositivity rate of 3-10%. The US Centers for Disease Control and Prevention recommend a two-test protocol employing enzyme-linked immunosorbent assays (ELISA) and Western blot techniques on serum or CSF. If results
are inconclusive, serology can be repeated at 3-4 weeks or PCR tests can be utilized. False positive ELISA can result from a number of conditions. Some patients, especially those with early disease, may be seronegative.

Treatment

Therapy for Lyme disease is summarized in Table 4. Prevention of Lyme disease is a more practical and effective approach than a cure. Preventative techniques include suitable clothing, the use of insect repellents, tick collars for pets, and routine checking of skin for ticks. Prophylaxis can be employed after a tick bite in an endemic area. Ticks are best removed after suffocating them with petroleum jelly. Borrelia eradication is achieved with appropriate antimicrobials: usually a 3-week course of oral doxycycline or amoxicillin for those with early disease, without evidence of CSF infection; for late or clinically severe disease, intravenous penicillin or ceftriaxone or cefotaxime for 2-4 weeks.

After appropriate therapy, the prognosis for early and late neurological manifestations is generally good. Cranial neuropathies typically recover in weeks to months; symptoms of radiculopathy usually recede within 2-16 weeks. Facial weakness or hemifacial spasm may persist in 5-10%. The use of corticosteroids for pain management is controversial.

**REFERENCES**


Peripheral Nerve II: HIV

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INTRODUCTION

The diverse neurologic complications of human immunodeficiency virus (HIV) infection were recognized early in the 1980s.33 Effective anti-retroviral therapy over the past decade has markedly lengthened survival and reduced central nervous system (CNS) opportunistic infections, but for the most part has not altered the prevalence of peripheral neuropathies in HIV patients. Neuropathy has emerged as the most common neurological complication of HIV infection.

A wide array of peripheral nervous system diseases have been linked to HIV infection (Table 1). They may occasionally be the first presentation of HIV infection.7,9,18,20,26 The etiologies of these disorders are not well understood. Some reported associations are probably fortuitous rather than causal. Different neuropathies occur preferentially at various stages of systemic HIV disease. For instance, an inflammatory and presumably autoimmune neuropathy preferentially occurs early in HIV infection, when the CD4 cell count is relatively high and immune deficiency is minimal. Patients with longstanding HIV disease are more likely to develop a distal symmetric polyneuropathy. A progressive lumbosacral polyradiculopathy, thought to be due to opportunistic cytomegalovirus (CMV) infection, occurs almost exclusively in immunocompromised patients with CD4 count of less than 100 cells/mm.

DISTAL SYMMETRIC POLYNEUROPATHY

Distal symmetric polyneuropathy (DSP) is the first recognized and by far the most common neuropathy in acquired immunodeficiency syndrome (AIDS) comprising over 90% of the neuropathies seen. The incidence increases greatly as the systemic disease progresses and the peripheral CD4 count falls below 200 cells/mm.1 About one-third of a cohort of hospitalized patients with AIDS had both clinical and electrophysiologic signs of polyneuropathy.34 Depending on the criteria of diagnosis and the study population, higher incidences have been reported.19

Tingling, numbness, or pain appears in the toes or plantar surfaces of both feet over the course of several weeks or a few months. Burning or shooting pain, or other descriptions of neuropathic pain, are almost universally present in patients referred for neuropathy.6 By contrast, prospective studies of HIV cohort often identify asymptomatic patients with neuropathy.21,34 Neurologic examination confirms a distal, predominantly
sensory neuropathy. Ankle jerks are either absent or diminished. Sensory threshold to vibration is elevated in the toes. Cutaneous sensations to light touch, temperature, or pinprick are diminished in a length-dependent distribution. Weakness, if present, is minimal and is restricted to the intrinsic foot muscles.

The diagnosis of DSP is straightforward in the hands of a neuromuscular specialist. Needle electromyography (EMG) and nerve conduction studies (NCSs) confirm the diagnosis and provide a measure of severity. Unrecordable or low-amplitude sural nerve action potential is the most frequent finding.34,37 Nerve conduction velocities are usually in the low range of normal or only mildly reduced. Reduction in amplitude of the peroneal or tibial compound muscle action potentials (CMAPs) of nerves is sometimes encountered. These electrophysiologic features are characteristic of an axonopathy. The severity of neuropathy correlates poorly with the neuropathic pain.

### Causes of Distal Symmetric Polyneuropathy

The syndrome of DSP is nonspecific. Its symptoms and signs are largely indistinguishable from those of many common neuropathies, such as in diabetes mellitus, alcoholism, drug toxicity, nutritional deficiency, and uremia, to name just a few. Even among HIV patients, a number of different causes are possible.

#### Idiopathic Distal Symmetric Polyneuropathy

Over half of the DSPs seen in AIDS patients do not have an identifiable cause despite thorough evaluation. Proposed mechanisms include direct infection by HIV, opportunistic infection by CMV, neuropathic effect of cytokines such as tumor necrosis factor and interleukins (TNF-alpha, IL-1, etc.), and autoimmune mechanisms. Current data are unfortunately inconclusive.

A high HIV viral load (>10,000 copies/mL) correlates with the risk of developing neuropathy.5 However, the HIV virus does not appear to infect the peripheral nerve directly. In contrast to HIV, there are extensive pathological documentations of CMV lesions in peripheral nerves at autopsy.10,19 A small retrospective case-control study suggested that patients with DSP had more frequent concurrent systemic CMV infections than control subjects.11 Interpretation of these data, however, is hindered by the high prevalence of asymptomatic CMV infection in terminal AIDS patients and the nearly ubiquitous presence of the virus in the nervous system of patients who died of AIDS. There is also no good data on the effect of anti-CMV on this neuropathy.

#### Toxic Neuropathy

The antiretroviral nucleoside analogues are important causes of neuropathy. The first nucleoside analogue, zidovudine, probably does not cause neuropathy.4 Others—didanosine, zalcitabine, and stavudine—have well-known toxicity. The protease inhibitors and the non-nucleoside reverse transcriptase inhibitors appear to be free of neuropathic side effect. Other drugs used in HIV treatment may also be neurotoxic. They include hydroxyurea (particularly when used in combination with didanosine and stavudine), thalidomide, antibiotics such as dapsone, isoniazid, and metronidazole, and antineoplastic agents like cisplatin and vincristine.

Toxic neuropathy due to nucleoside analogues is dose dependent, although the daily and cumulative doses provide only a rough estimate of risk. Patients with a lower CD4 cell count, of older age, or with poorer nutrition may develop neuropathy at a
lower cumulative dose. Neuropathic pain is a common dose-limiting factor in treatment. Moreover, when the toxic drug is withdrawn, patients may experience symptom progression or “coasting” for the first 2-3 weeks before stabilization of symptoms. The neuropathy in most patients is reversible after discontinuation of the responsible drug, and a re-challenge at a lower dose may be possible.

**Vitamin B12 Deficiency**

Vitamin B12 deficiency in the general population causes both a spinal cord disorder and a DSP, with limb paresthesias being a nearly universal symptom. Several studies in AIDS patients have noted that nearly one-fifth of AIDS patients have abnormally low serum level of vitamin B12. However, this author’s experience as well as others indicates that most patients with neuropathy do not have demonstrable vitamin B12 deficiency and do not respond to parenteral B12 supplementation.

Patients should be screened for other causes of neuropathy. This includes a history on alcohol and drug use, and other potentially toxic exposure (e.g., pyridoxine excess, dapsone), as well as serum testing for diabetes mellitus, B12 deficiency, and hypothyroidism. Lower than normal vitamin B12 level (200-300 pg/mL) should be followed with assay of homocysteine and methylmalonic acid.

**Management**

After excluding reversible causes, treatment is directed to neuropathic pain. The use of pain modulating agents is largely based on the experience in painful diabetic neuropathy. A beginning bedtime dose of 25 mg of amitriptyline, increasing by 25 mg weekly to a maximum of 100-150 mg, provides partial relief in some patients. Other tricyclic antidepressants such as desipramine and nortriptyline, may be substituted for those intolerant of the anticholinergic and sedating side effects of amitriptyline. Anticonvulsants such as carbamazepine and gabapentin, topical capsaicin (0.075%), and mexiletine may be effective. Lamotrigine is the only drug shown to be effective by randomized controlled trials specifically in HIV patients. It should be started at a low dose, 25 mg every other day, and titrated upwards over 6-7 weeks to a target dose of 200 mg twice a day. Patients on enzyme-inducing drugs may take up to 300 mg twice a day. Most patients require regular use of analgesics that may include opioids.

**PROGRESSIVE LUMBOSacRAL POLYRADICULOPATHY**

Progressive lumbosacral polyradiculopathy occurs typically in patients with advanced HIV infection with a history of opportunistic infections and very low CD4 cell counts. It is uncommon in the current era of protease inhibitors and other highly effective antiretroviral treatment, and is primarily encountered in those with inadequately controlled systemic disease.

The presenting complaint is progressive leg weakness that leads to difficulty in ambulation within days or a few weeks. Weakness may begin in one leg, but rapidly becomes diffuse with involvement of multiple myotomes in both legs. Mild asymmetry in strength is common. Along with the onset of weakness, deep tendon reflexes in the legs becomes unobtainable. Some patients have a fulminant course, with complete flaccid paraplegia developing within 1-2 weeks. Back pain is common, and a straight leg raising sign may be present. Urinary retention and constipation, as well as symptoms of cauda equina involvement, are prominent in many patients. Although some numbness or paresthesias are common, sensory loss is seldom severe. A characteristic, though infrequent, pattern of sensory loss is the involvement of the perineal and perianal areas, i.e., the lower sacral dermatomes.

Early in the disease, the leg weakness and areflexia mimic Guillain-Barré syndrome. Early sphincter disturbances and the sparing of the upper extremities until very late in the course of illness (several weeks after onset) help to diagnose a lumbosacral polyradiculopathy. Some authors call this disorder myeloradiculitis since some patients have Babinski sign or a thoracic sensory level. On the other hand, spasticity and hyperreflexia are absent. Hence, the dominant neurologic picture is that of a flaccid paraplegia.

Needle EMG shows evidence of acute denervation: decreased interference pattern with fast firing rate in clinically weak muscles. Fibrillation potentials appear only in muscles studied a week or more after onset of weakness. A concomitant polyneuropathy is common in this patient population. Thus, the preservation of sural sensory nerve action potential cannot be relied upon to distinguish a root lesion from a post-ganglionic lesion. The main finding on motor NCS is axonal loss, i.e., low-amplitude CMAP, without evidence of demyelination. Motor nerve conduction velocities are normal or mildly slow. Delayed or absent F waves are common.

Cytomegalovirus is the most important cause in this syndrome. This is true especially in those with advanced HIV disease (CD4 cell count < 50/mm³). Less common causes are leptomeningeal lymphoma and tuberculous myeloradiculitis. Other reported infectious causes include neurosyphilis, pneumocystis carinii, cryptococcus, and mycobacterium tuberculosis. There has even been one reported case of co-infection by two pathogens and also one reported case of toxoplasmosis abscess in the conus medullaris presenting with a lumbosacral polyradiculopathy syndrome. In theory, any process that affects the cauda equina or conus medullaris can lead to a similar clinical syndrome. The vulnerability of this patient population opens up the potential of...
a wide range of infectious, neoplastic, and inflammatory disorders.

Magnetic resonance imaging (MRI) is the preferred method to exclude mass lesions such as spinal cord toxoplasmosis and tuberculoma. In a typical case, MRI is either normal or shows gadolinium enhancement of the lumbosacral roots or conus medullaris. The finding is nonspecific and merely points to the leptomeningeal localization of the pathology. It can be seen in CMV infection, leptomeningeal lymphoma, and other infectious diseases.

Lumbar puncture is important for diagnosis. Many patients have a marked pleocytosis with a predominance of polymorphonuclear cells. It is not unusual to see pleocytosis in excess of 500 cells/mm³. Elevated protein and hypoglycorrhachia are common. This cerebrospinal fluid (CSF) finding is suggestive of an acute infection, of which CMV, neurosyphilis, pneumocystis carinii, cryptococcus, and mycobacterium tuberculosis are all possibilities. In a second group of patients, the dominant CSF finding is that of a mild, predominantly mononuclear pleocytosis. These patients usually have a less severe clinical course. Lymphomatous meningitis is an important diagnostic consideration in this group. Another possibility is an indolent host reaction to infections such as CMV and tuberculosis. Neither the severity nor the predominant cell type of the pleocytosis is specific enough to permit a confident etiologic diagnosis. Specific microbiological and cytological examination of the CSF is important. Polymerase chain reaction of the CSF is best for identifying CMV and mycobacterium tuberculosis in the spinal fluid.

Like lumbosacral polyradiculopathy, there are numerous potential causes of mononeuropathy multiplex in HIV infection. After excluding common causes, such as trauma, nerve entrapment, and compression, the possibilities fall into three categories: infiltrative, inflammatory, and infectious (Table 2).

Table 2 Causes of mononeuropathy multiplex in HIV infection

<table>
<thead>
<tr>
<th>Nerve infiltration</th>
<th>Inflammatory (autoimmune?)</th>
<th>Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma³⁹</td>
<td>Vasculitis²⁸</td>
<td>Cytomegalovirus²⁴,³⁰</td>
</tr>
<tr>
<td>Diffuse infiltrative lymphocytosis syndrome (DILS)²⁵</td>
<td>Cryoglobulinemia³⁶</td>
<td>Herpes zoster</td>
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<tr>
<td></td>
<td>Autoimmune plexitis</td>
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HIV = human immunodeficiency virus.

The typical setting for CMV infection is a patient with advanced HIV infection, often with symptoms or signs of systemic CMV infection especially CMV retinitis, presenting with rapidly deteriorating neurologic function. In these patients, empiric treatment with anti-CMV agents such as ganciclovir should be instituted without delaying to wait for laboratory results. The condition is potentially fatal and many patients deteriorated despite treatment. The less common causes of lumbosacral polyradiculopathy are not easy to diagnose and treat. Optimal outcome is only possible with thorough radiologic and CSF examination and prompt diagnosis of the underlying etiology.
A second syndrome occurs in patients with severe immunodeficiency, usually with CD4 cell counts of less than 100/mm³. These patients have more widespread weakness usually with involvement of two or more limbs. This may be confused with chronic inflammatory demyelinating polyneuropathy (IDP), but the weakness is asymmetric. Also, some patients have severe hoarseness and hypophonia from involvement of the recurrent laryngeal nerve, a distinctive feature that is not seen in other neuropathies. Cytomegalovirus inclusions were found at autopsy in four of five nerve biopsies of patients with mononeuropathy multiplex. Thus, there is reasonable evidence that CMV infection is the cause and should be presumptively treated in severely immunocompromised patients with mononeuropathy multiplex.

A third syndrome is the diffuse infiltrative lymphocytosis syndrome (DILS), characterized by high CD8 cell count (>1000/mm³), salivary glands, and other organ infiltration by CD8+CD29+ cells, and a sicca syndrome of xerophthalmia, xerostomia, uveitis, and keratoconjunctivitis. Sjögren’s antibodies (SSa and SSb) are negative. The neuropathy seen is due to an angiocentric infiltration of the epineurium and endoneurium. Clinically the neuropathy presents as an acute or subacute, frequently painful, axonal sensorimotor polyneuropathy. The neuropathy may be symmetric or multifocal in onset. The former probably reflects a confluence of multifocal lesions. The neuropathy responds to antiretroviral treatment with or without addition of steroids.

ACUTE OR CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHIES

Both acute and chronic IDP are recognized complications of HIV infection. In contrast to DSP and lumbosacral polyradiculopathy, most cases of IDP occur in patients with early HIV infection or CD4 counts greater than 300 mm³. In particular, acute IDP, or Guillain-Barré syndrome, may occur coincidentally with HIV seroconversion. The reported incidence depends on the referral population and the diagnostic criteria. Though earlier reports suggested an incidence as high as one-third, none was seen over a 15-month period in a cohort of 1500 patients.

In this author’s experience, the classic forms of IDP are uncommon. The clinical features are similar to those seen in the general population. Patients have progressive, symmetric weakness in the upper and lower limbs. Both proximal and distal muscles may be affected. Sensory symptoms are usually present, but sensory deficits on examination are mild in comparison to the degree of weakness. Most patients have diffuse areflexia or hyporeflexia. Focal weakness and sphincter disturbances are not features of these neuropathies. The most effective means of diagnosis is the EMG/NCS. There should be one or more electrophysiologic signs of demyelination: conduction block, moderate to severe slowing in motor nerve conduction velocity, temporal dispersion of the CMAPs, and prolonged F-wave minimum latencies. Additionally, there are signs of axonal loss, such as reduction in the amplitude of the sensory responses or the presence of fibrillation potentials and positive sharp waves during needle EMG examination of the weak muscles. Lumbar puncture typically shows elevation of CSF protein concentration. Unlike IDP in the general population, HIV-infected patients may have a mononuclear pleocytosis of up to 50 cells per cubic millimeter.

Little information is available on the treatment of HIV-related IDP. Most centers treat these disorders in a manner similar to those seen in the general population with prednisone, plasmapheresis, or intravenous immunoglobulin.

SUMMARY

The wide range of neuromuscular complications is largely a result of the varied systemic conditions at different stages of HIV infection. Recognition of the systemic condition, especially the degree of immunocompromise (for example, CD4 count), will facilitate the proper diagnosis and management of these conditions.

REFERENCES


INTRODUCTION

The issue of direct muscle involvement in systemic infections is relatively rare. However, muscle weakness, fatigue, and myalgias are more common. This manuscript attempts to outline the involvement of muscles in the following infections: West Nile virus, Lyme disease, human immunodeficiency virus (HIV) and other viral infections, as well as various parasites.

INFECTIONS AND PARASITES

West Nile Virus Infection

West Nile virus is a member of the Flaviviridae family and is transmitted to humans via Culex species mosquitoes. Typically infections occur in the late summer and several outbreaks have recently been reported. The incubation period is 5-15 days. Neurological manifestations include encephalitis with symptoms that include a decreased level of consciousness, cerebellar ataxia, and neuromuscular weakness. In severe cases, there can be marked brainstem involvement. The neuromuscular involvement has been described as acute flaccid paralysis or a poliomyelitis-like syndrome. Electrophysiological studies show evidence of severe denervation in paralyzed limb muscles suggesting either motor neuron or multiple nerve root damage. Changes on muscle biopsy show only mild direct or indirect muscle damage. Cerebrospinal fluid analysis typically shows elevated protein and pleocytosis. Autopsy studies suggest that inflammation in the anterior horns of the spinal cord, with motor neuron dropout, is the cause of the motor neuronopathy and subsequent muscle weakness. Evidence does not support either an acute myopathy or Guillain-Barré syndrome as the most typical cause of the muscle weakness.

Lyme Disease

In the United States, Lyme disease is the most common arthropod-borne infection. The infection is caused by Borrelia burgdorferi (B. burgdorferi) and is most frequently transmitted by ixodid ticks. The systemic illness occurs days or weeks after the typical rash, erythema migrans. Skin rash, fever, malaise, myalgia, and arthralgia are predominant. Cardiac and muscle involvement occur in stage II of the disease. Myositis is a rare but proven manifestation of Lyme disease of unknown pathogenesis. Patients have been described with generalized myositis (although typically the myositis is localized to the area of the skin lesions), arthritis, or neuropathy. Myocarditis caused by B. burgdorferi has also been described. On biopsy, the inflammation was typically found in the region of small blood vessels. Although B. burgdorferi was not successfully cultured, antibiotic therapy has successfully treated the myositis in two-thirds of patients studied.

Human Immunodeficiency Virus Infection

Human immunodeficiency virus has been known to cause several different myopathies. Inflammatory myopathies are more common in the HIV-infected patient than in the general population. The best defined has been a polymyositis-like myopathy with typical clinical and electromyographic features, but varying features on biopsy. This has been seen as the initial manifestation of the disease. The symptoms are typical of polymyositis in that there is a progressive, symmetric, proximal limb girdle weakness affecting the lower extremities more often. The clinical and electrophysiologic picture is indistinguishable from HIV-negative polymyositis.

A myopathy attributed to the use of zidovudine has also been described. However, some features histologically supported
mitochondrial impairment. The key clinical features are myalgias with fatigue and without significant weakness.

**Human T Cell Lymphotrophic Virus Type TLV-1 Infection**

Human T cell lymphotrophic virus has been found to cause a myositis as well as a myelopathy, tropical spastic paraparesis. The clinical picture is of a proximal muscle weakness although distal weakness has also been described. The muscle biopsy may show evidence of a polymyositis like syndrome or noninflammatory myopathy. Diagnosis can only be made by identifying the virus.

**Coxsackie Virus**

Coxsackie virus can rarely cause an acute rhabdomyolysis and myoglobinuria. In one documented epidemic, the myopathy responded dramatically to corticosteroid therapy with a normalization of muscle strength.

**Influenza Virus**

Two types of myopathies have been described with influenza. Benign influenza myopathy presents with myalgias and swelling. Influenza-B has most often been the cause. However, it is not clear whether this is a direct infection or an immune-mediated reaction. There is also a more serious condition with a generalized myopathy with rhabdomyolysis. In this situation there is associated weakness and it can occur in the acute or convalescent stage. This is most often associated with influenza-A infection.

**Cysticerosis Infection**

Although cysticerosis infection is now restricted to tropical and developing countries it is seen in North America in immigrants and travelers. The muscle involvement in cysticerosis is largely asymptomatic. Calcification in dead and dying cysticeri in muscles has been found. Patients with suspected cysticerosis may report subcutaneous swellings. These swellings can be single or in crops and are oval. Myalgias can be reported in the initial stages and can be associated with fever, headache, and even seizures. The muscle involvement can also occur in the form of pseudohypertrophy in the setting of disseminated cysticercosis. The enlargement results from dissemination of thousands of living cysticeri throughout the musculature. The process takes weeks or months and can last 1-5 years. The calves and thighs usually enlarge first. Mild weakness can occur. The key is the association with seizures and dementia, and the clinical diagnosis rests on palpating subcutaneous nodules. Imaging can confirm diagnosis as can biopsy of a subcutaneous nodule or affected muscle. Treatment is with praziquantel and albendazole. However, this must be done carefully as inflammatory edema can be extraordinary.

**Hydatidosis**

The larvae in the cystic form of hydatidosis is the hydatid cyst and it can lodge in the muscles, the third most common site after the liver and lungs. It presents as a muscle mass and is slow growing, deep, lobular, and occurs most frequently in the paravertebral and quadriceps muscles. There is no weakness or tenderness unless it gets secondarily infected. Diagnosis is made by serology for echinococcosis. Surgical excision is the cure.

**Trichinosis**

Trichinella spiralis is a nematode and produces an inflammatory myopathy in humans. Infection is usually the result of eating raw or undercooked pork. There is a diarrhoeal illness initially lasting about 2 weeks. Leukocytosis and eosinophilia are seen acutely. Severe cases have multiorgan system involvement. There is both muscle weakness and pain with elevation of creatine kinase. Biopsy shows characteristic changes with endomyosial and perivascular inflammation and Trichinella larvae. Treatment is with steroids and often albendazole.

**Toxoplasmosis**

Involvement of the muscle has been described in toxoplasmosis and symptoms include myalgias and generalized weakness. Toxoplasma is rarely recovered from the muscle. Biopsies have shown evidence of a more generalized inflammatory myopathy. However, in suspected cases, treatment with pyrimethamine, sulfadiazine or clindamycin have shown rapid improvement.

**Chagas Disease**

Chagas disease is caused by trypanosoma cruzi and has three stages. In the acute stage, the patient has fever and general malaise with enlargement of the lymph nodes, liver, and spleen. Acute myocarditis can be seen, and fatigue and myalgias can also occur. Stage two is asymptomatic and may last years. The third or chronic stage most frequently presents with a dilated cardiomyopathy usually manifesting by arrhythmias or a cardioembolic events such as cerebral embolisms.

**Bibliography**


1. Based on the virus taxonomy, which of the following viruses likely has a cross-reaction with West Nile virus (WNV) antibodies?
   A. Japanese encephalitis virus.
   B. St. Louis encephalitis virus.
   C. Murray Valley virus.
   D. Tick-borne encephalitis virus.
   E. All of the above.

2. Most patients with WNV infection will present with which of the following clinical syndrome?
   A. Encephalitis.
   B. Meningitis.
   C. Asymptomatic or flu-like symptoms.
   D. Poliomyelitis.
   E. Acute motor axonal neuropathy.

3. Which of the following symptoms is inconsistent with WNV poliomyelitis?
   A. Conspicuous sensory loss in limbs.
   B. Muscle atrophy.
   C. Asymmetric flaccid paralysis.
   D. Reduced or exaggerated deep tendon reflexes.
   E. Mental status alteration.

4. Typical electrodiagnostic features in WNV poliomyelitis include all of the following EXCEPT:
   A. Abnormal spontaneous activities (positive waves and fibrillations) in weak limbs.
   B. Severely reduced sensory nerve action potentials (SNAPs) in symptomatic limbs.
   C. Positive waves or fibrillations in the paraspinal muscles.
   D. Normal or reduced amplitudes of compound muscle action potentials.
   E. Reduced recruitment during needle electromyography examination

5. Which of the following statements is true in patients with WNV poliomyelitis?
   A. These patients are always immunologically compromised or have some chronic illnesses.
   B. Nerve conduction studies demonstrate significantly slowed conduction velocities in most of these patients.
   C. The onset of paralysis in these patients can be quite rapid and reaches the maximum within hours.
   D. Absence of flu-like viral prodrome excludes the diagnosis of WNV poliomyelitis.
   E. Mental status alteration or meningismus signs are non-avoidable features.

6. Primary pathological lesion in most patients with WNV paralysis is:
   A. Massive muscle necrosis.
   B. Selective motor neuron damage in the spinal cord anterior horn.
   C. Demyelination in peripheral nerves.
   D. Diffuse white matter lesions.
   E. Destruction of dorsal root ganglion.

7. A definitive diagnosis of WNV poliomyelitis requires:
   A. Electrodiagnostic evidence of diffuse denervation in the paralytic limbs and corresponding paraspinal muscles.
   B. Abnormal magnetic resonance imaging signal intensity in the anterior horn of the spinal cord.
   C. Characteristic paralysis and presence of IgM antibodies against WNV in the cerebrospinal fluid (CSF).
   D. Inflammatory infiltration in the muscle biopsy.
   E. Elevation of protein and lymphocytic cells in CSF.

8. Patients who have rabies typically live:
   A. Normal lives with no side effects from the virus.
   B. Normal lives but have many side effects as a result of the virus.
   C. Only weeks.
   D. 10-15 years.
   E. None of the above.
9. Which of the following stages is NOT part of the clinical features of rabies?
   A. Coma.
   B. Symptomatic.
   C. Incubation.
   D. Acute neurological.
   E. Prodrome.

10. Which of the following features suggest paralytic rabies and differentiate it from Guillain-Barré syndrome:
    A. Persistent fever from the onset of limb weakness.
    B. Percussion myoedema.
    C. Bladder dysfunction.
    D. Intact sensory function of all modalities except at the bitten region.
    E. All of the above.

11. The following statement is true regarding both herpes simplex and varicella zoster EXCEPT:
    A. They lay dormant in sensory ganglia.
    B. The have been associated with Bell’s Palsy.
    C. They cause skin eruptions.
    D. They cause post-herpetic neuralgia.
    E. They can be treated with acyclovir.

12. The tuberculoid form of leprosy:
    A. Occurs in patients who are anergic to the bacilli.
    B. Is less aggressive and more self-contained than the lepromatous form.
    C. Involves only motor nerves.
    D. Is treated with dapsone as monotherapy.
    E. Is easily diagnosed by skin biopsy due to the large numbers of bacilli in the lesion.

13. Lyme disease:
    A. Occurs throughout the United States but is not present in Europe.
    B. Causes Bell’s Palsy in the first stage of the disease.
    C. Is easily confirmed by enzyme-linked immunosorbent assays.
    D. Causes a painful symmetric predominantly sensory neuropathy.
    E. Rarely causes a meningoradiculitis.

14. The recommended treatment of Lyme disease:
    A. Is independent of the stage of the disease.
    B. Is intravenous for localized infection.
    C. Is intravenous ceftriaxone or cefotaxime for neurologic disease.
    D. Should include corticosteroids for all patients.
    E. Does not affect the course of the disease in most patients.

15. Leprosy:
    A. Is no longer a world health problem.
    B. Occurs only in people who are immune deficient.
    C. Usually causes hyperpigmented skin lesions.
    D. Does not cause an immune or inflammatory response.
    E. Causes marked nerve swelling.

16. Which of the following symptom or sign is NOT typically seen in distal symmetrical polyneuropathy?
   A. Burning pain in feet.
   B. Hypersensitivity over soles.
   C. Foot drop.
   D. Numbness.
   E. Diminished or unobtainable ankle jerk.

17. The following may cause a toxic neuropathy EXCEPT:
    A. Hydroxyurea.
    B. Zidovudine.
    C. Didanosine.
    D. Neviripine.
    E. Dapsone.

18. A 45-year-old man has newly diagnosed human immunodeficiency virus (HIV) infection but his CD4 count is 50/mm³. He presents with back pain, progressive leg weakness, and urinary retention over 1 week. The most likely diagnosis is:
    A. Guillain-Barré syndrome.
    B. Cytomegalovirus (CMV) infection.
    C. HIV encephalopathy.
    D. Lumbar stenosis.
    E. Polymyositis.

19. The most common electrodiagnostic finding in HIV-associated distal symmetric polyneuropathy is:
    A. Unobtainable or low-amplitude sural sensory nerve action potential.
    B. Sural sensory nerve conduction velocity below 30 m/s.
    C. Peroneal nerve conduction velocity below 30 m/s.
    D. Unobtainable or low-amplitude peroneal compound muscle action potential.
    E. Fibrillation potentials in one of the quadriceps muscles.

20. Neuropathies seen in HIV infection may be due to:
    A. CMV infection.
    B. Vasculitis.
    C. Antiretroviral drugs.
    D. Vitamin B₁₂ deficiency.
    E. All of the above.
Neuromuscular Complications of Infectious Disease

EVALUATION

Select ANY of the answers that indicate your opinions.

Your input is needed to critique our courses and to ensure that we use the best faculty instructors and provide the best course options in future years. Please use the computer form to answer the following questions. For the purpose of tabulating evaluations, please enter the last 4 digits of your telephone number in the ID NUMBER box beginning with the left column and fill in the appropriate ovals below each number. Make additional comments or list suggested topics or faculty for future courses on the comment form provided at the end.

21. How would you rate the quality of instruction received during Dr. Li's presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

22. Select any item(s), that, if changed, would have appreciably improved Dr. Li's presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.

23. How would you rate the quality of instruction received during Dr. Mitrabhakdi's presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

24. Select any item(s), that, if changed, would have appreciably improved Dr. Mitrabhakdi's presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.

25. How would you rate the quality of instruction received during Dr. Lewis' presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

26. Select any item(s), that, if changed, would have appreciably improved Dr. Lewis' presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.

27. How would you rate the quality of instruction received during Dr. So's presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

28. Select any item(s), that, if changed, would have appreciably improved Dr. So's presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.
29. How would you rate the quality of instruction received during Dr. Genge's presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

30. Select any item(s), that, if changed, would have appreciably improved Dr. Genge's presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.

31. As a result of your attendance at this course, did you learn anything that will improve the care of your patients?
   A. Yes, substantially.
   B. Yes, somewhat.
   C. Not sure.
   D. Probably not.
   E. This course was not applicable to my patients.

32. Select ALL items where improvement was needed.
   A. The accuracy of advance descriptions of this course.
   B. The specific topics selected for presentation.
   C. The number of speakers in this course.
   D. The amount of time allotted for discussion in this course.
   E. Other: please add other areas and outline specific recommendations for areas needing improvement on the comment form at the back of this handout.

33. Should this topic be presented in the future by a different method of presentation.
   A. No, the topic of presentation should remain as a course.
   B. Yes, the topic should be presented as a dinner seminar.
   C. Yes, the topic should be incorporated into the plenary session.
   D. Yes, the topic should be discussed during a breakfast session.
   E. Yes, the topic should be organized as a special interest group.
FUTURE MEETING RECOMMENDATIONS

Select ANY of the answers that indicate your opinions.

The following questions are included with all dinner seminar, course, and plenary session evaluations. **It is only necessary to answer these questions once during the course of the entire meeting.**

34. Please indicate below your specialty:
   A. Neurologist.
   B. Physiatrist.
   C. PhD.
   D. Other.

35. How often do you attend AAEM meetings?
   A. Annually.
   B. Every 2-3 years.
   C. Every 4 or more years.
   D. This is the first AAEM meeting I have attended.

36. With regard to this year’s meeting, which of the smaller group sessions did you attend? (mark all that apply)
   A. Experts’ roundtables.
   B. Workshops.
   C. Dinner seminars.
   D. None of the above.

37. If you answered none of the above to the previous question, please answer the following. The reason I did not attend the small group sessions was due to:
   A. The timing of the event.
   B. The cost of the event.
   C. My lack of interest in the topics offered.
   D. The session was full.

38. Did this meeting provide information that will enhance care of your patients?
   A. Extremely.
   B. Somewhat.
   C. Very little.
   D. Not at all.

39. With regard to the social event:
   A. I am signed up to attend the social event.
   B. I did not sign up because of the cost of the event.
   C. I did not sign up because of the day the event was offered.
   D. I did not sign up because I am not interested in attending this type of function.

40. How would you rate this meeting?
   A. Poor.
   B. Fair.
   C. Good.
   D. Very good.
   E. Excellent.

41. Did this meeting meet your expectations?
   A. Not at all.
   B. Somewhat.
   C. As expected.
   D. Exceeded expectations.
   E. Best ever.

42. Was the printed program clear and easy to follow?
   A. Yes.
   B. No.

43. With regard to the meeting hotels:
   A. I stayed at one of the meeting hotels.
   B. I did not stay at one of the meeting hotels.

44. If you answered B to the question above, please explain why you did not stay at one of the meeting hotels (please make your comments under Comments, page 39).

45. How did you first learn about the meeting? (choose the method where you first learned about the meeting)
   A. Preliminary brochure mailing.
   B. Registration brochure mailing.
   C. The internet.
   D. Email message.
   E. From a friend.

46. Did you perceive any commercial bias in any of the educational sessions offered by the AAEM at this meeting?
   A. Yes.
   B. No.

47. Did you attend any of the industry forums provided this year?
   A. Yes.
   B. No.
48. If you answered yes to question 47 and you attended the Pfizer Industry Forum, how would you rate the quality of the session?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.
   On Page 39 under comments, please provide any other comments you have about your attendance at the Pfizer Industry Forum.

49. If you answered yes to question 47 and you attended the Allergan Industry Forum, how would you rate the quality of the session?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.
   On Page 39 under comments, please provide any other comments you have about your attendance at the Allergan Industry Forum.

50. How do you prefer to learn new information?
   A. Lecture only.
   B. Lecture in conjunction with questions and answers.
   C. Small group hands-on.
   D. Small group discussion.

51. I plan to attend the 2005 AAEM meeting in Monterey, California, September 21-24.
   A. Yes, definitely.
   B. No, definitely.
   C. Will wait to see the program content.
   D. Will wait to see if budget allows my attendance.

52. I would be more likely to attend the 2005 AAEM meeting if (please make your comments under Comments, page 39):
COMMENTS

Given time and budget constraints, is there something we could do in terms of altering the format of the meeting that would significantly increase the likelihood of your attendance at future AAEM meetings? Explain:

Write out any additional comments about specific courses or the plenary session (please indicate which), and list suggestions for topics and speakers for future meetings. Leave at the AAEM Registration and Information Center or mail to the AAEM Executive Office at 421 First Avenue SW, Suite 300 East, Rochester, MN 55902.