Current Views on Common Neurologic Manifestations of HIV

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While the advent of HAART has greatly reduced the incidence of various neurological manifestations over the last few years, some complications continue to have a serious impact on the lives of HIV-infected patients. However, neuropathogenesis in the setting of HIV disease is still not well understood by the majority of health-care providers, a fact that may be hindering the successful implementation of diagnostic and treatment strategies.

To provide its clinician members with an update on the pathogenesis, diagnosis, and treatment of three common neurological manifestations—HIV-associated dementia, myelopathy, and peripheral neuropathy—PRN dedicated its May 2000 meeting to this important topic. Featured by PRN were two clinical neurologists and a neuropathologist.

Dr. Susan Morgello, who addressed current concepts in HIV-associated dementia, also explored the issue of the central nervous system (CNS) as a “sanctuary” for HIV. Dr. David Simpson detailed advances in diagnosis and treatment of peripheral neuropathy in HIV-infected patients, and Dr. Alessandro Di Rocco discussed myelopathy in patients with HIV disease.

I. HIV-Associated Dementia

A review of HIV-associated dementia (HAD) was provided by Dr. Morgello, the director of the Manhattan HIV Brain Bank (MHB). The MHB has dedicated its May 2000 meeting to this important topic. Featured by PRN were two clinical neurologists and a neuropathologist.

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To shed light on this debate, a certain level of detail regarding the epidemiology and neurobiology of HAD is necessary.

Epidemiology of HAD

Discussed by Dr. Morgello were prevalence figures on HAD from four studies ranging from 1986 to 1997. These studies support the observation that, because of highly active antiretroviral therapy (HAART), the incidence of HAD has decreased.

In the pre-HAART era, the incidence of HAD at the University of Amsterdam declined dramatically after the introduction of AZT (Retrovir), which crosses the blood-brain barrier (BBB) efficiently (Portegies, 1993). In contrast, the Multicenter AIDS Cohort Study (MACS) demonstrated no change in HAD incidence over the period from 1985 to 1992 (Bacellar, 1994). Dr. Morgello noted, however, that discordance with the Amsterdam data may have resulted from study matter. To date, more than 100 individuals have joined the study. More than 200 specimens have been shipped to researchers in the U.S. and Europe.

Dr. Morgello framed her PRN discussion within the debate between those who believe that adequate systemic treatment of HIV is the appropriate way to address CNS disease and those who see the CNS as a “privileged” site requiring additional treatment strategies. In addition to the clinical issues, this debate has implications for allocation of research funds. Those on the former side of the debate believe that, as you control HIV in the periphery, neurologic sequelae will disappear. Those on the latter side of the debate consider that the CNS is a sanctuary for HIV, where the virus can remain protected from immunologic and pharmacologic assault.

To shed light on this debate, a certain level of detail regarding the epidemiology and the neurobiology of HAD is necessary.

FIGURE 1: MACS: Incidence Rates of Neurologic Complications of HIV Infections (per 1,000 person years)

Source: Justin McArthur, MD
design and differing populations.

With the introduction of HAART, a cohort in Frankfurt demonstrated a decrease in the incidence of HIV from 8.1% to 2.8% between 1994 and 1995 (Brodt, 1997). In 1994, only 2.4% of the participants were on combinations of antiretroviral therapy that included a protease inhibitor, whereas well over 60% were on HAART by 1995. Unfortunately, these data combined statistics for AIDS dementia and progressive multifocal leukoencephalopathy (PML).

Surveillance data from Australia showed similar trends (Dore, 1999). From 1992 to 1995, 167 patients in the cohort presented with HIV as their first AIDS-defining illness. In 1996, after the advent of HAART, the incidence had dropped to 43, and in 1997 to 24. Unfortunately, the percentage of first AIDS-defining illnesses that were accounted for by HIV actually increased over this period: 4%, 6% and 6.5% for each consecutive year. So although the raw number of HIV cases was declining, the percentages were actually increasing over this period.

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As people live longer, an increase in the percentage of dementia diagnoses may mean that we have achieved only suboptimal treatment of HIV in the CNS. We have already seen an example of this phenomenon; incidence of CNS lymphoma began to increase after AZT became available [and, consequently extended the lives of people infected with HIV]. As always, one must keep in mind that compliance clearly influences these trends. Drugs won't work if patients don't take them.

**Neurobiology of HIV and Cognitive Dysfunction**

**The Blood-Brain Barrier (BBB) is Formed by a Series of Tightendothelial Junctions.** The feet of the astrocytes surrounding the capillary endothelium play a major role in regulating the blood-brain barrier, including the passage of drugs and perivascular macrophages and monocytes. In late-stage HIV disease, increased macrophage-colony stimulating factor (M-CSF) in the bone marrow leads to increased production of CD16+/CD69+ monocytes, cells primed for transependymal migration. In late-stage HIV infection, an increase in trafficking of monocytes to the brain has been suggested to be associated with the development of HIV neurological disease (Gartner, 2000). In this figure, a CD16+ monocyte is shown crossing the capillary endothelium in the CNS and entering the brain parenchyma.

*Source: Susan Morgello, MD*
proves a drug’s ability to cross the BBB. Drugs that are not highly bound to serum proteins have a greater chance of getting in. Lower pH favors proteins having a greater chance of getting out of the BBB.

Drugs that are not highly bound to serum proteins have a greater chance of getting in. Lower pH favors proteins having a greater chance of getting out of the BBB.

The calculation produces some counterintuitive results; AZT and d4T, which have similar structures with regard to size and lipophilicity, display ratios of 2.4 and 0.4. However, there is a probenecid-inhibitable pump that may actively transport d4T out of the CNS. Some protease inhibitors are also actively transported out of the CNS (Table 1).

"It is important to bear in mind that raw numbers may not tell you meaningful information," explained Dr. Morgello. For example, less than .5% of efavirenz actually penetrates the CNS. But the IC95 of efavirenz is so low that, even with the low concentration of the drug, enough is present to inhibit 95% of the virus present. Furthermore," she continued, "these CSF-to-plasma ratios are only a snapshot in time of a very dynamic process. It would be better to have multiple samples from an indwelling catheter that would allow you to calculate AUC, but very few drugs have been studied this way."

"The essential issue," posited Dr. Morgello, "is whether potent antiretrovirals improve neurocognitive function." According to at least three papers published over the last year, the answer is a definitive "Yes."

Combinations of potent antiretrovirals clearly improve psychomotor speed performance over time in impaired individuals. Data from the MACS have demonstrated this using a short battery of neuropsychological tests (Sacktor, 1999). These findings were true in patients who took antiretroviral combinations with or without protease inhibitors. An Italian cohort demonstrated neuropsychiatric improvement in patients treated with combinations, and it was sustained for 15 months (Tozzi, 1999). Most participants received indinavir as part of their regimen, yet indinavir has a poor CSF-to-IC50 ratio. The prevalence of cognitive impairment in this group dropped from 80% to 50%. The improvement was correlated with a drop in plasma viral load (-1.84 log), but no CSF analyses were performed.

Magnetic resonance spectroscopic (MRS) data have been published to document that indeed, potent therapies have an impact on brain chemistry. Dr. Linda Chang and her colleagues at the University of California, Los Angeles, have done a variety of interesting MRS studies. Last year, she published data on a cohort by which they were able to demonstrate amelioration of cognitive dysfunction (Chang, 1999). They correlated cognitive improvements with changes in brain myoinositol and choline peaks, reflecting changes in gliosis and cell membrane turnover. For a good percentage of individuals, changes in these indices occurred when treatment was started. These changes were evident in regions of interest, for example, frontal white matter and basal ganglia. However, in a substantial percentage of individuals, there was persistence of elevated choline, which indicated that at some level cell membrane turnover still increased despite clinical improvement. The significance of this has yet to be determined.

Finally, one central question remains: Where does HIV in the CSF come from, particularly with regard to the production of CSF from the choroid plexus? This year, Dr. Ellis published a study in Neurology in which he examined the effects of HAART on CSF and plasma viral load in individuals with and without cognitive impairment (Ellis, 2000). Patients were stratified to three groups: nondemented patients with early HIV disease (CD4+ count >400 cells/mm³) or CSF pleocytosis (CSF leukocytes >4/mL); nondemented patients with advanced HIV disease (CD4+ count <400 cells/mm³), and no pleocytosis; and pa-

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<tr>
<th>TABLE 1: CNS Penetration of Antiretrovirals†</th>
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<td>Source: Ronald Ellis, MD (unpublished data; courtesy of Susan Morgello, MD)</td>
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<th></th>
<th>Plasma</th>
<th>CSF</th>
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<tr>
<td>Nevirapine</td>
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<td>Nelfinavir</td>
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<td>Amprenavir</td>
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* Indeterminate because lower end of range was <LOD

† There are some caveats to keep in mind when reviewing these data. First, there are influx/efflux ratios to consider (i.e., the probenecid-inhibitable pump that actively transports d4T out of the CNS). There is also the ATP-dependent efflux transporter P-glycoprotein, for which protease inhibitors are substrates. Moreover, while <5% of efavirenz penetrates the CSF, the IC95 of the drug in vitro is so low that even small concentrations in the CSF are capable of inhibiting 95% of the virus present.
II. HIV-Related Myelopathy

AIDS-ASSOCIATED MYELOPATHY IS THE MOST common spinal cord disease in patients with HIV. Autopsy series conducted before the era of HAART revealed that 20% to 55% of patients examined had spinal cord changes consistent with vacuolar myelopathy (Petito, 1985; Dal Pan, 1994). It is unknown how many of these patients had actual clinical manifestations of myelopathy; the studies were conducted at a time when there was much less awareness of myelopathy in AIDS patients.

Clinical Features

"When people think of myelopathy," suggested Dr. Di Rocco, "they often envision a patient who is wheelchair bound, with spastic legs, and very debilitated. A lot of our patients with myelopathy are actually quite ambulatory, although they may have difficulty climbing stairs. Many clinicians probably see myelopathy in their practice, but may not recognize it."

At first, patients report nonspecific complaints such as weakness, spasticity, and urinary frequency and urgency. Patients may report having to urinate 15 or more times a day. Male patients may have difficulty achieving and maintaining an erection. Numbness and abnormal sensation to light touch may be present. Patients may also report constipation, leg cramps, and/or difficulty in walking.

Myelopathy is characterized by a spastic paraparesis, which is slowly progressive. This spastic paraparesis along with sensory abnormalities and loss of sphincter control lead to the diagnosis. Typical clinical findings include weakness, spasticity, hyperreflexia, clonus, and a positive Babinski sign. The symptoms and the findings can be hard to interpret because they are nonspecific and other pathologies may be present. Even for an experienced neurologist, distinguishing between what is myelopathy and what is neuropathy may be difficult. The same is true for sensory abnormalities: They can be caused by neuropathy, myelopathy, or a combination of the two.

Myelopathy is a slowly progressive entity. Data involving patients followed by Dr. Di Rocco and his colleagues chronicle an average time lapse of almost two years between onset of weakness or stiffness and the time the patients eventually became wheelchair-bound. Yet, some of these patients with a diagnosis of myelopathy have been followed for years, but are still ambulatory.

No confirmatory tests exist for vacuolar myelopathy; it is essentially a diagnosis of exclusion. There are very few data comparing myelopathy in the pre- and post-HAART eras, but one pattern that is emerging is that progression seems to be much slower. "The CSF is typically normal," explained Dr. Di Rocco. "A few white cells may be present and protein may be slightly elevated, but there usually isn’t anything truly remarkable. The MRI may be normal or there might be nonspecific findings such as swelling or atrophy or decreased signal on T2 images." In his clinical research and practice, Dr. Di Rocco uses electrophysiological tests to determine how fast an electrical impulse is propagated through the posterior columns of the spinal cord.

Pathogenesis of Myelopathy

THE PATHOGENESIS OF MYELOPATHY IN HIV-INFECTED patients remains something of a mystery. "We know it is associated with HIV," said Dr. Di Rocco, "but if you look for the virus in the spinal cord, you don’t find much."

The pattern of cord changes in HIV-related myelopathy closely resembles that of subacute combined degeneration of the cord from vitamin B12 deficiency. In an article dating back to 1985 by Dr. Carol Petito and her colleagues, the most striking feature of the dramatic vacuolization of the spinal cord was its prominence in the posterior and lateral columns (Petito, 1985). This finding prompted Dr. Petito’s team to re-read the patients’ charts to look for abnormal vitamin B12 levels, which were not found. Moreover, supplementation with vitamin B12 does not affect the course of disease (Kieburz, 1991).

Vacuolization in the spinal cord is not specific for B12 deficiency; it is also associated with folate deficiency, nitrous oxide intoxication, congenital metabolic abnormalities, methylenetetrahydrofolate deficiency, and cobalamin G mutation. All of these disorders cause vacuolization and are directly related to impairment of methionine and transmethylation metabolism.

Methionine is an essential amino acid whose daily turnover is twice the dietary supply, derived from vitamin B12-dependent conversion of homocysteine to methionine and from diet. Methionine is metabolized to S-adenosylmethionine (SAM), an important methyl-group donor needed for various pathways, including stabilization of the myelin basic protein (MBP). This protein stabilizes the myelin sheath around nerves. In HIV-associated vacular myelopathy, the myelin sheath “falls apart.”

A few studies have suggested that, in HIV-infected patients with myelopathy, CSF levels of SAM and methionine are often decreased (Surtees, 1990; Kaoing, 1991). In Dr. Di Rocco’s research experience, several patients with myelopathy were found to have decreased levels of SAM. One patient in a control group followed by Dr. Di Rocco—the patient did not have a diagnosis of myelopathy—was found to have a relatively low level of SAM. Six months after this finding, she had developed symptoms of myelopathy.

“The pathogenesis of myelopathy in HIV-infected patients likely involves a complex chain of events,” suggested Dr. Di Rocco. “After HIV infection there is macrophage and cytokine production in the CNS. Any of these immune responses may be playing a role in the transmethylation impairment and myelin destruction that is associated with myelopathy.”
III. Peripheral Neuropathy

To complete the neuroAIDS trilogy, Dr. David Simpson took the podium to discuss peripheral neuropathy in the setting of HIV disease. “In the early years, I found it quite challenging to convince my infectious disease colleagues that neurologic disease was, in fact, important in the setting of HIV,” Dr. Simpson remarked. “At that time, patients were dying in a year or two and neurologic disease often did not capture people’s attention. People were dying too quickly for it to become a real factor.” Today, he noted, patients are remaining alive and free of AIDS-related diseases for considerably longer periods of time. Yet quality of life issues, which include peripheral neuropathy, are becoming even more prevalent.

Types and Epidemiology of Peripheral Neuropathy

Actually, several different forms of peripheral neuropathy can occur in the setting of HIV. For example, inflammatory demyelinating polyneuropathy (IDP) is often the first manifestation of HIV disease, when CD4+ cell counts are relatively high. With continual suppression of the immune system, the incidence of distal symmetric polyneuropathy (DSP) increases. And in advanced HIV disease, viral infections such as CMV can cause nerve-related diseases, including progressive polyradiculopathy or mononeuritis multiplex.

The most common form of peripheral neuropathy is a DSP. In the MACS database, rates of neuropathy, including DSP, increased substantially between 1988 and 1992 (Bacellar, 1994). This increase continues today.

Every clinician who treats a large number of HIV-infected patients likely sees DSP on a daily basis. Characteristically, patients experience hyperesthesia, pain and/or paresthesia, contact sensitivity, decreased ankle reflexes, and decreased responses to pinprick and temperature (Figure 3). Any departure from that pattern should raise a red flag that something else may be going on. For example, IDP differs from DSP in that it can cause facial nerve paresis, ascending weakness, generalized areflexia, and mild sensory involvement.

Dr. Simpson warned that some patients may have a combination of CNS and peripheral nerve manifestations. As an exam-

Treatment of Myelopathy

While not specifically discussed by Dr. Di Rocco, treatments for myelopathy—potentially or otherwise—are of central concern to HIV-treating clinicians. Unfortunately, data from myelopathy treatment studies are sparse and, as a result, there is no specific treatment.

Treatment of myelopathy is, in essence, intended to provide symptom management and to limit disability. To help control spasms and cramps, particularly when pain or discomfort is present, antispas-

Incidence and Symptoms

- Most common type of neuropathy in HIV infection
- Detectable in >33% of patients with AIDS
- More common in late HIV infection (low CD4+ count)
- Detectable pathologically in nearly all patients
- Chief complaint: numbness or burning pain in the feet
- Sensory complaints typically symmetrical
- Weakness unusual until DSP advanced
- Affects quality of life and adherence

Clinical Signs

- Depressed ankle reflexes relative to knees (caution: combined CNS and PNS)
- Abnormal vibration in feet
- Abnormal pinprick and cold (stocking-glove distribution)
- Muscle strength (objective) usually normal

Source: David Simpson, MD
ple, he illustrated that “some patients may have a combination of myelopathy and DSP. Such a patient might have increased reflexes characteristic of myelopathy, but may also have lower extremity numbness and paresthesias associated with DSP.”

In general, Dr. Simpson stated that approximately one-third of all patients with AIDS have signs and symptoms indicative of DSP. Turning to the realm of the pathologist, sural nerve biopsies and autopsies would ultimately reveal that most—if not all—patients with HIV disease have evidence of axonal degeneration. DSP is more common in late HIV infection, particularly in patients with suppressed CD4+ cell counts (Tagliati, 1999). As for viral load, rising HIV-RNA levels increase the risk of developing—and the severity of—DSP (Chiods, 1999).

Pathogenesis

As with HAD and myelopathy, the pathogenesis of peripheral neuropathy is not clearly understood.

A number of pathogenic mechanisms have been proposed for DSP. These include direct damage to nerves by HIV or its glycoprotein gp120; the neurotoxic effects of cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukins 1 and 6 (IL-1 and IL-6); malnutrition; vitamin B12 deficiency; and other possible infections, such as CMV.

As for neurotoxic drugs, vincristine for the treatment of KS and lymphomas, isoniazid for the prevention and treatment of Mycobacterium tuberculosis, and thalidomide have all been shown to cause DSP. Several nucleoside analogues used to treat HIV infection are widely known to cause DSP, particularly the “D” drugs: ddI (Videx), ddC (Hivid), and d4T (Zerit).

With respect to the potential of these drugs to impair mitochondrial function—and thus contribute to the pathogenesis of peripheral neuropathy—Dr. Simpson stated that it is still too early to blame mitochondrial dysfunction for manifestations such as DSP, lipodystrophy, and other complications that have been thrown into the mix (see “Mitochondrial Toxicities of NRTIs,” published in the June 2000 issue of The PRN Notebook). “What we do know,” confirmed Dr. Simpson, “is that nucleoside analogues do inhibit mitochondrial DNA polymerase-gamma. And there have been some animal data linking ddC to mitochondrial dysfunction in peripheral nerves. Whether or not this is the operative mechanism in HIV drug-related peripheral neuropathy in humans is still unproven.”

Diagnosis and Treatment of Peripheral Neuropathy

The diagnosis of DSP is reached more or less by a process of exclusion. Blood samples should be collected to screen for diabetes mellitus and vitamin B12 deficiency. Electrodagnostic procedures are also possible and, in the case of DSP, will yield evidence of decreased sural nerve conduction velocity or amplitude, as well as EMG evidence of active or chronic partial denervation in distal leg muscles. DSP analyses and sural nerve biopsies can also be conducted, but are widely considered to be unnecessary in the clinical diagnosis of DSP, other than for research purposes.

DSP is a difficult condition to manage, and the primary goal with the treatments currently available is to help alleviate symptoms of peripheral neuropathy. For starters, there is often a significant benefit in stopping or switching an offending HIV/AIDS drug. But, as Dr. Simpson warns, this must be balanced against the antiviral benefit that the drug is providing to the patient. It is important to note, however, that neuropathic symptoms may continue to escalate for up to six weeks after treatment is discontinued (called the “coasting period”).

Mild neuropathic pain can sometimes be treated using non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen; moderate to severe cases may respond to tricyclic antidepressants (e.g., amitriptyline or nortriptyline), anticonvulsants (e.g., phenytoin carbamazepine, and gabapentin), or narcotic analgesics (e.g., methadone or fentanyl transdermal patches). Yet, none of these treatments has proved to be effective in clinical trials.

In one particular study conducted by the ACTG (ACTG 242), researchers compared amitriptyline and mezipatine, either as single agents or in combination with placebo (Kieburtz, 1998). In an interim analysis conducted after 170/240 patients were accrued, no significant difference was seen between the treatment and placebo arms. The study was terminated early as a result of the researchers’ prediction that no difference would be seen at study completion.

Lamotrigine, a novel anticonvulsant, has shown to be effective in a small placebo-controlled trial involving HIV-infected patients with DSP (Simpson, 2000). A larger study is in progress.

With respect to “alternative” or “complementary” approaches to managing neuropathic symptoms, Dr. Simpson pointed out that many patients avail themselves of these modalities in the face of limited recognized options. “We have patients who have tried peptide T, acupuncture, meditation, L-carnitine, alpha-lipoic acid, and a slew of other complementary approaches,” he pointed out. “Unfortunately, there’s not much data to prove their worth and, in fact, some might be dangerous.”

A study of Peptide T for treatment of neuropathy showed no benefit from the drug (Simpson, 1996). Nor was there any benefit associated with acupuncture therapy in a study conducted by the Community Program for Clinical Research on AIDS (CP-CCRA) (Shlay, 1998). As for vitamin B6, high-dose pyridoxine therapy has been associated with ataxia and severe sensory deficits.
dysfunction in some patients (Schaumburg, 1983). Explained Dr. Simpson: “the only role for pyridoxine supplementation is with isoniazid treatment for tuberculosis.”

Topical agents, including capsaicin and lidocaine, may offer some relief to patients with NGF. Encouraging results were reported by a team that included Dr. Simpson in an open-label study of 5% lidocaine gel (Lidoderm) in 30 patients with painful NGF (Dorffman, 1999). “The results of this study were very encouraging,” Dr. Simpson said. “Approximately three-quarters of the participants showed significant relief upon applying the gel to their feet. The same group recently completed a placebo-controlled trial of the gel and these data are now under analysis.” Lidoderm is now commercially available in the United States, is relatively nontoxic, and easy to use.

As for recombinant human nerve growth factor (NGF), results from clinical trials have been mixed and difficult to interpret. Results of a clinical trial involving HIV-infected patients were published this year. The results of another study enrolling patients with diabetic NGF were reported in April 1999.

The HIV-related neuropathy study of NGF (ACTG 291) was conducted by Dr. Justin McArthur and his colleagues (McArthur, 2000). In the trial, 270 patients with NGF were randomized to receive either a placebo or one of two doses of NGF. The study lasted for 18 weeks and required that all study volunteers self-inject NGF twice daily. While volunteers who received either dose of NGF saw their pain decrease during the study, the drug did not appear to improve their neurological function and failed to show evidence of nerve repair. Dr. McArthur’s team commented that it can take at least 18 weeks to repair damaged nerves and that the study might not have been long enough to test the true benefit of the drug.

For people with diabetes, two large studies have been conducted. While the results of the manufacturer’s first study involving diabetics seemed to paint an optimistic picture, results of a larger trial completed last year were sobering. The second trial, conducted in more than 1,000 diabetics who were sobering. The second trial, conducted in more than 1,000 diabetics in the U.S., was published this year. The results of a clinical trial involving diabetics seemed to paint an optimistic picture. While the results of the study might not have been long enough to repair damaged nerves and that Dr. McArthur’s evidence of nerve repair. Dr. McArthur’s team commented that it can take at least 18 weeks to repair damaged nerves and that the study might not have been long enough to test the true benefit of the drug.

Based on the lackluster trial and diabetes study results, Genentech has decided to cease development of the drug. “We simply don’t know if we’ll be able to continue studying this agent,” Dr. Simpson said.

### Conclusion

In his concluding remarks, Dr. Simpson provided a subtle yet crucial reminder: “Educating ourselves, as clinicians, and our patients about neurologic disease is a primary goal we must continue to strive towards. At the same time, clinicians must attempt to identify risk factors for any of the neurologic complications discussed here. As for treatment, symptom management will always be important. But we must continue to focus on pathogenesis-based therapies, including those currently under development.”

### References


