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.
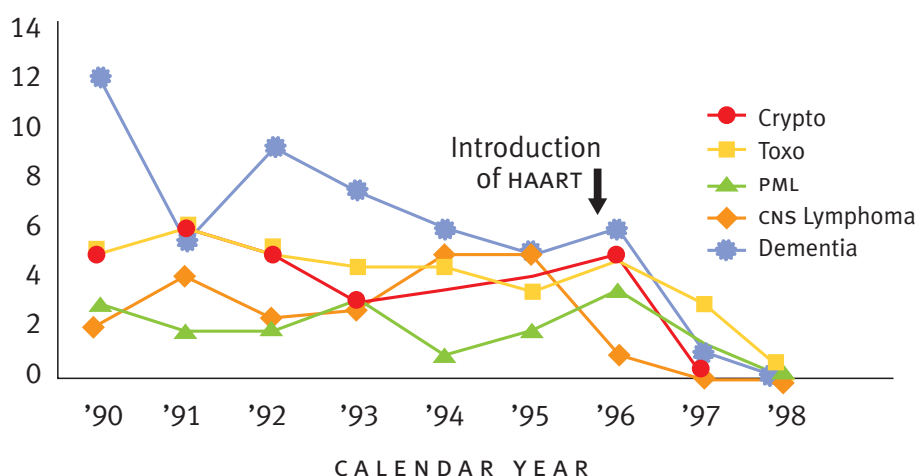
I. HIV-Associated Dementia

A REVIEW OF HIV-ASSOCIATED DEMENTIA (HAD) was provided by Dr. Morgello, the director of the Manhattan HIV Brain Bank (MHBB). The MHBB project is dedicated to elucidating the pathogenesis of HIV-related neurologic disorders; it recruits HIV-infected patients who agree to be followed in a longitudinal, noninterventional study and who, upon demise, will donate brain 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.

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

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

Legend: Crypto, Toxo, PML, CNS Lymphoma, Dementia

CALENDAR YEAR

Source: Justin McArthur, MD

design and differing populations.

With the introduction of HAART, a cohort in Frankfurt demonstrated a decrease in the incidence of HAD 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 HAD 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 HAD actually increased over this period: 4%, 6% and 6.5% for each consecutive year. So although the raw number of HAD cases was declining, the percentages were climbing. Interestingly, the mean CD4+ cell count at which HAD was being diagnosed rose over these three years, from 70 cells/mm³ from 1992 to 1995 to 120 cells/mm³ in 1996 and 170 cells/mm³ in 1997.

Dr. Morgello discussed the incidence of neurologic manifestations of HIV in 71 of the first 100 patients enrolled in the MHBB. Only 11 patients (15%) had no evidence of neurologic dysfunction. More than 80% had some degree of cognitive impairment; approximately 25% had minimal cognitive motor dysfunction and approximately 60% had frank dementia.

It is difficult to reconcile these figures with the remarkable clinical successes that have been reported in the literature since the advent of HAART. Two potentially confounding factors in the MHBB study population are: 1) many of the patients are at advanced stages of disease; and 2) there is a preponderance of patients with a history of substance abuse. Baseline cognitive functioning in patients with substance abuse may be slightly different from what might be anticipated. In one very interesting cohort being studied in Edinburgh, Scotland, by Dr. Jeanne Bell and her colleagues, it is clear that individuals with a history of substance abuse have an unexplained increase in HIV encephalitis and cognitive dysfunction compared to those with sexual exposure as a risk factor (Bell, 1996).

To summarize, the incidence of dementia decreased between 1982 and 1988 as corroborated by pathologic studies showing less evidence of inflammatory changes in the brain. This phenomenon is coincident with the advent of AZT. The incidence of dementia was constant between 1988 and 1992, when considering only an advanced cohort. Again, this observation is corroborated by pathology studies. HAART, which became widely available in 1996, coincided with a further decline in the incidence of dementia. Patients presenting with dementia today have a higher mean CD4+ cell count. However, dementia now accounts for a higher proportion of AIDS-defining illnesses.

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 tight endothelial junctions. There are reduced numbers of pinocytotic vesicles at the level of the endothelium. The feet of the astrocytes around the endothelium play a major role in regulating the BBB. A large variety of molecules at the endothelial surface are involved in passage of drugs and other molecules as they enter and leave the CNS (Figure 2).

An important but largely forgotten factor in this construct is the blood-cerebrospinal fluid (CSF) barrier, which is vastly different from the BBB. The barrier between blood and CSF is at the level of the choroid plexus and is formed by junctional complexes between choroid epithelial cells. Below these are fenestrated choroidal capillaries that have no barrier function whatsoever; they function as systemic vasculature. Here, transport is by active pumps, which occur in the epithelial layer as opposed to an endothelial layer. In the average adult, there are a total of 150 cc of CSF, and approximately 500 cc of CSF are synthesized daily, resulting in a high turnover. Only 20% to 30% of the CSF derives from brain interstitial fluid, and 70% to 80% is actively secreted by the choroid plexus. Thus, it is not clear how representative of brain may be the CSF commonly obtained at lumbar puncture, which will be an important factor in evaluating brain effects of HAART.

A number of characteristics facilitate or hinder a drug's penetrance of the BBB. Size matters, as smaller is better in order to penetrate the CNS. Lipophilicity also im-
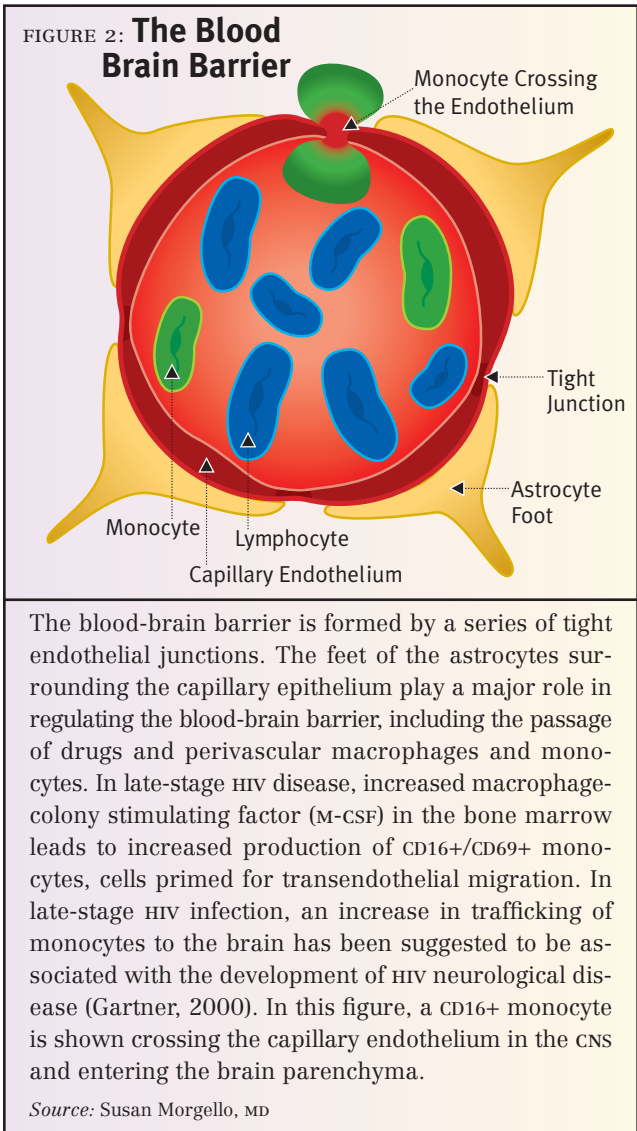

FIGURE 2: **The Blood Brain Barrier**

Monocyte Crossing the Endothelium

Tight Junction

Astrocyte Foot

Monocyte   Lymphocyte

Capillary Endothelium

The blood-brain barrier is formed by a series of tight endothelial junctions. The feet of the astrocytes surrounding the capillary epithelium 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 transendothelial 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

TABLE I: **CNS Penetration of Antiretrovirals†**			
Plasma	CSF	IC50	CSF:IC50 Ratio
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS			
AZT	4.49-5.62	0.12-0.20	0.01-0.05	2.40
ddI	3.39-4.24	0.13-0.20	1.0-2.5	0.05
ddC	0.03-0.08	0.003-0.03	0.03-0.5	0.01
d4T	3.35-6.43	0.20-0.36	0.05-0.5	0.40
3TC	6.55	0.17-0.55	0.003-0.09	1.89
Abacavir	0.10-10.89	0.5	0.26	1.92
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS			
Nevirapine	7.52-6.92	7.30	0.01-0.1	73.00
Delavirdine	15.0-35.0	0.06-0.14	0.066	0.91
Efavirenz	2.51-9.53	0.006-0.059	0.003	2.00
PROTEASE INHIBITORS			
Saquinavir	1.85- 3.23	<LOD-0.0085	0.002-0.007	Indeterminate*
Ritonavir	5.13-15.53	<LOD-0.079	0.045	Indeterminate*
Indinavir	0.25-12.61	0.05-0.66	0.025-0.1	0.50
Nelfinavir	1.76- 7.04	<LOD	0.022	Indeterminate*
Amprenavir	0.55-10.67	0.16	0.08	2.0

LOD = Level of detection

† 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 CNS are capable of inhibiting 95% of the virus present.

* Indeterminate because lower end of range was <LOD

Source: Ronald Ellis, MD (unpublished data; courtesy of 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 CNS penetration. Finally, an underlying disruption of the BBB facilitates passage of a drug into the CNS.

However, there are exceptions to every rule. Dr. Ron Ellis of the University of California, San Diego and his colleagues have prepared calculations to assess how well individual antiretrovirals penetrate the CSF: The numerator includes the CSF concentration of the drug, and its IC50—the concentration at which HIV is 50% inhibited—goes in the denominator. A ratio greater than 1.0 means that the drug penetrates the CSF well; less than 1.0 reflects poor penetration.

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 trans- port 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 CSF. 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-

tients with HAD. These individuals were then placed on new HAART regimens.

In patients with higher CD4+ cell counts, the rate of decline of viral load in CSF and plasma was similar. For individuals with advanced disease and lower CD4+ cell counts, the CSF decline lagged behind plasma viral load decline. In patients with HAD, there was a more marked dissociation between systemic and CSF response. The conclusion here was that the source of CSF viral load may be dependent on disease stage. "This," Dr. Morgello remarked, "is a very important conclusion. When you look at patients with dementia, CSF viral load is consistently high in the face of lower plasma viral load. It may very well be that brain parenchyma is the source of virus, and that CNS-targeted therapy is necessary. We must consider that there may be different sources of CSF virus depending on patient's disease stage and cognitive function."

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 (Kieburtz, 1991).
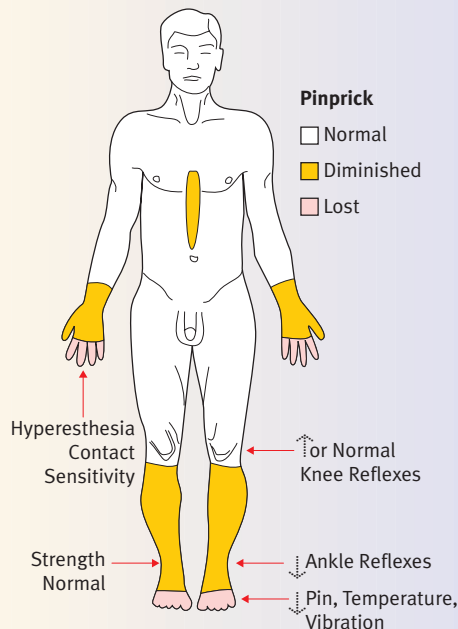
Vacuolization in the spinal cord is not specific for B12 deficiency; it is also associated with folate deficiency, nitrous oxide intoxication, congenital metabolic abnormalities, methylenetetrahydrofolate deficiency, and cobalamine G mutation. All of these disorders cause vacuolization and are directly 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 vacuolar 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; Keating, 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."

FIGURE 3: Distal Symmetrical Polyneuropathy

Pinprick
- ☐ Normal
- 🟧 Diminished
- 🟥 Lost

Hyperesthesia
Contact
Sensitivity

↑or Normal
Knee Reflexes

Strength
Normal

Ankle Reflexes

Pin, Temperature,
Vibration

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

Treatment of Myelopathy

WHILE NOT SPECIFICALLY DISCUSSED BY DR. DI Rocco, treatments for myelopathy—potential 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-ticity medications—including baclofen, dantrolene, or injections of botulinum toxin—may offer some relief. Physical therapy may help improve lower extremity function. As for urinary function, bladder training and anticholinergic medications may be helpful.

In an effort to reverse abnormal transmethylation metabolism, Dr. Di Rocco and his colleagues conducted an open-label pilot study of oral methionine in 12 HIV-infected patients with myelopathy (Di Rocco, 1998). All patients had been receiving antiretroviral therapy for at least six weeks prior to study entry and were treated using Carlson Laboratories' L-methionine at an oral dose of 3 grams twice a day for six months.

Nine of the 12 (75%) patients completed the six-month study. L-methionine was well tolerated, with only minor complaints of abdominal discomfort in one patient (one patient withdrew because of a history of dyspepsia and gastrointestinal symptoms while receiving L-methionine, one withdrew after two months for reasons not related to the study, and one patient died of congestive heart failure and pneumonia after three months). Six patients had improvement in strength, and five patients had mild to moderate improvements in spasticity. Two experienced resolution of urinary symptoms; and two male patients regained erectile function.

All patients who entered the study had prolonged central conduction time (CCT) at somatosensory evoked potentials (SEPs), determined using electro-physiologic testing. Five patients experienced a marked improvement in CCT, findings that were directly associated with clinical improvement seen in these patients. In one patient, CCT worsened. Upon conducting a global myelopathy evaluation (GME), 7/9 (78%) had improvements in GME scoring, including one patient who experienced clinical remission of myelopathy and normalization of CCT.

Not only may L-methionine lead to an effective strategy of prevention and treatment of myelopathy, but it may also help in understanding the complex relationship between HIV and metabolic abnormalities in the neuropathogenesis of AIDS.

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 PE-ripheral 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 increases 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-

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 (Childs, 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. Electrodiagnostic 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 with reinnervation in distal leg muscles. CSF analyses and seral 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 carbamezipine, 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 mex-
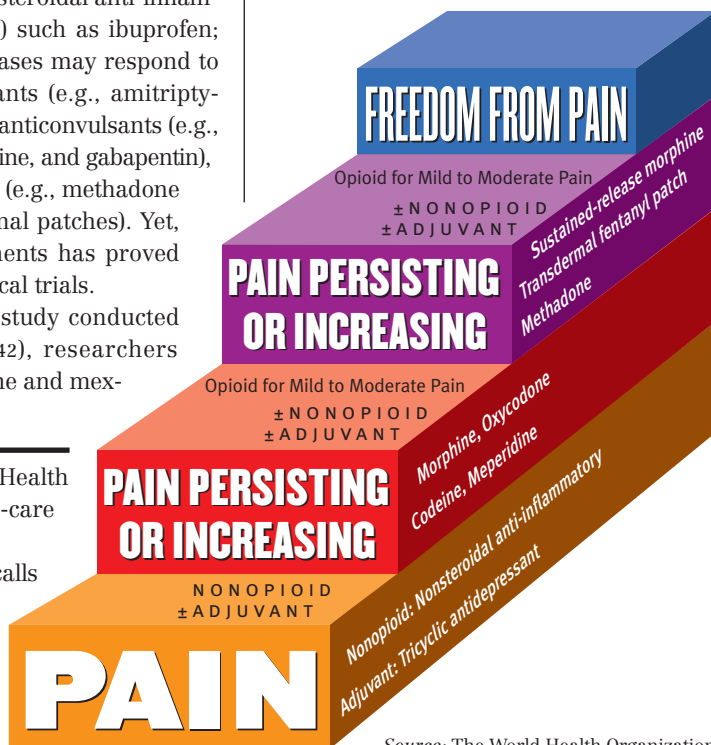
FIGURE 4: The World Health Organization stepped-care strategy for pain management which calls for the addition of increasingly potent analgesics, can be applied to CNS-related pain.

ilitine, 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.

Lamotragine, 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 (CPCRA) (Shlay, 1998). As for vitamin B6, high-dose pyridoxine therapy has been associated with ataxia and severe sensory

FREEDOM FROM PAIN

Opioid for Mild to Moderate Pain
± NONOPIOID
± ADJUVANT

Sustained-release morphine
Transdermal fentanyl patch
Methadone

PAIN PERSISTING OR INCREASING

Opioid for Mild to Moderate Pain
± NONOPIOID
± ADJUVANT

Morphine, Oxycodone
Codeine, Meperidine

PAIN PERSISTING OR INCREASING

NONOPIOID
± ADJUVANT

Nonopioid: Nonsteroidal anti-inflammatory
Adjuvant: Tricyclic antidepressant

PAIN

Source: The World Health Organization

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 DSP. 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 DSP (Dorfman, 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 DSP 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 DSP 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 received either NGF or placebo, lasted for 48 weeks. Even though the drug was continued for seven months longer than the HIV study, NGF still failed to show evidence of nerve regeneration or improved function.

Based on the lackluster HIV 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." prn

References

Bacellar H, Munoz A, Miller A, et al. **Temporal trends in the incidence of HIV-1 related neurologic diseases: Multicenter AIDS Cohort Study, 1985-1992.** *Neurology* 44:1892-1900, 1994.

Bell JE, Donaldson YK, Lowrie S, et al. **Influence of risk group and zidovudine therapy on the development of HIV encephalitis and cognitive impairment in AIDS patients.** *AIDS* 10:493-499, 1996.

Brodt HR, Kamps BS, Gute P, et al. **Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy.** *AIDS* 11:1731-1738, 1997.

Chang L, Ernst T, Leonido-Yee M, et al. **Highly active antiretroviral therapy reverses brain metabolite abnormalities in mild HIV dementia.** *Neurology* 53(4):782-9, 1999.

Childs E, Lyles R, Selnes O, et al. **Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy.** *Neurology* 52(3):607-13, 1999.

Dal Pan C, Glass J, McArthur J, et al. **Clinicopathologic correlation of HIV-1 associated vaculoar myelopathy: an autopsy based case-control study.** *Neurology* 44:2159-64, 1994.

Di Rocco A, Tagliati M, Danisi F, et al. **A pilot study of L-methionine for the treatment of AIDS-associated myelopathy.** *Neurology* 51:266-268, 1998.

Dore G, Correll P, Li Y, et al. **Changes to AIDS dementia complex in the era of highly active antiretroviral therapy.** *AIDS* 13(10):1249-53, 1999.

Dorfman D, Dalton A, Markarian Y, et al. **Treatment of painful peripheral neuropathy in HIV infection with a topical agent: results of an open label study using 5% lidocaine.** *AIDS* 13:1589-90, 1999.

Gartner S. **HIV infection and dementia.** *Science* 287:602-4, 2000.

Keating J, Trible K, Mulcahy F, et al. **Evidence of brain methyltransferase inhibition and early brain involvement in HIV-positive patients.** *Lancet* 337:935-9, 1991.

Kieburtz K, Simpson DM, and the ACTG 242 Study Team. **A randomized trial of amitriptiline and mexiletine for painful neuropathy in HIV infection.** *Neurology* 51:1682-8, 1998.

Kieburtz K, Giang D, Schiffer R, et al. **Abnormal vitamin B12 metabolism in human immunodeficiency virus infection.** *Arch Neurol* 48:312-4, 1991.

McArthur J, Yiannoutsos C, Simpson D, et al. **A phase II trial of recombinant human nerve growth factor for sensory neuropathy associated with HIV infection.** *Neurology* 54:1080-8, 2000.

McArthur J, Yiannouotsos C, Simpson D, et al. **Trial of recombinant human nerve growth factor for HIV-associated sensory neuropathy.** *J Neurovirol* 4:359, 1998.

Petito C, Navia B, Jordan B, et al. **Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome.** *N Engl J Med* 312:874-9, 1985.

Portegies P, Enting R, de Gans J, et al. **Presentation and course of AIDS dementia complex: 10 years of follow-up in Amsterdam, The Netherlands.** *AIDS* 7(5):669-75, 1993.

Sacktor N, Lyles R, Skolasky R, et al. **Combination antiretroviral therapy improves psychomotor speed performance in HIV-seropositive homosexual men. Multicenter AIDS Cohort Study (MACS).** *Neurology* 52(8):1640-7, 1999.

Schaumburg H, Kaplan J, Windebank A, et al. **Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome.** *N Engl J Med* 309(8):445-8, 1983.

Shlay J, Chaloner K, Max M, et al. **Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS.** *J Amer Med Assoc* 280(18):1590-5, 1998.

Simpson D, Olney R, McArthur J, et al. **A placebo-controlled study of lamotrigine in the treatment of painful HIV-associated neuropathy.** *Neurology* 54:2115-9, 2000.

Simpson D, Dorfman D, Olney R, et al. **Peptide T in the treatment of painful distal neuropathy associated with AIDS: results of a placebo-controlled trial. The Peptide T Neuropathy Study Group.** *Neurology* 47(5):1254-9, 1996.

Surtees R, Hyland K, Smith I. **Central nervous system methyl group metabolism in children with neurological complications of HIV infection.** *Lancet* 335:619-21, 1990.

Tagliati M, Grinnell J, Godbold J, et al. **Peripheral nerve function in HIV infection: Clinical, electrophysiological and laboratory findings.** *Arch Neurol* 56: 84-89, 1999.

Tozzi V, Balestra P, Galgani S, et al. **Positive and sustained effects of highly active antiretroviral therapy on HIV-1-associated neurocognitive impairment.** *AIDS* 13(14):1889-97, 1999.