HIVRELATED SENSORY NEUROPATHY

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Original Article

Highly active antiretroviral therapy, or HAART, is one of modern medicine's most impressive success stories. For most patients taking it, HAART has converted HIV infection from a death sentence into a chronic and only mildly disabling condition. However, as opportunistic infections recede as the main source of HIV-related morbidity, neurologic complications have emerged to take their place.

“Sensory neuropathies in HIV-AIDS have become far and away the commonest complication of the disease,” said Justin McArthur, MD, Professor of Neurology at Johns Hopkins School of Medicine in Baltimore, MD. Risk factors for HIV-related sensory neuropathy, including the effects of antiretroviral therapy, were the focus of two studies by Dr. McArthur and colleagues, presented here in October at the Annual Meeting of the American Neurological Association.

“If you go back 15 years,” said Dr. McArthur, before the introduction of HAART, “neurologists were frequently dealing with opportunistic infections such as toxoplasmosis, cryptococcal meningitis, and other bizarre infections in the brain. We were also dealing with HIV dementia, a chronic slow encephalitis. With the introduction of HAART in 1996, we've seen about a 50 percent drop in the incidence of HIV dementia, and the types of dementia that are occurring are much milder. Opportunistic infections have dropped probably by as much as 85 percent. So what's left are sensory neuropathies.”

FORMS OF HIV SENSORY NEUROPATHY

Figure. Dr. Justin M...

There are two forms of HIV-related sensory neuropathy, explained Dr. McArthur. The first is thought to be provoked by HIV, not from direct infection, but from damage caused by activated macrophages. “This occurs within the dorsal root ganglia particularly, but also in a multifocal pattern,” he said. The second is antiretroviral

toxic neuropathy, caused by the drugs used to treat infection. “What we think in fact happens is that many patients with HIV infection have a mild, perhaps silent distal sensory polyneuropathy, which is unmasked by exposure to toxic antiretrovirals.”

Not all HIV drugs are equally suspect. Different antiretrovirals have different toxicities. One of the earliest drugs, AZT, causes myotoxicity and bone marrow suppression. In contrast, didanosine, stavudine, and zalcitabine, called “D drugs” because of their dideoxynucleotide structure, cause neurotoxicity.

“These are the only antiretrovirals that we know cause neurotoxicity,” said Dr. McArthur. The mechanism of this effect is thought to be through their inhibition of a mitochondrial DNA polymerase. Even though the neuron itself is post-mitotic, its mitochondria continue to divide and reproduce. “These three drugs are the most effective inhibitors of this polymerase,” he said.

While many HIV patients never develop neuropathy, and some remain asymptomatic despite the presence of electrophysiologic signs, about 30 percent of patients will get symptomatic sensory neuropathy, said Dr. McArthur. With 40 million infected individuals worldwide, including approximately one million in the United States, “that is a pretty substantial peripheral neuropathy burden.” In its most severe form, the patient may find that walking exerts too much pressure on the soles of the feet, and a wheelchair is required for mobility.

STUDYING RISK FACTORS

Figure. Dr. Igor Kor...

To understand more about modifiable risk factors associated with these neuropathies, Dr. McArthur collaborated with Catherine Cherry, MD, of Alfred Hospital in Melbourne, Australia. Their two groups of patients “are completely different in terms of ethnic makeup and risk factors for HIV,” Dr. McArthur said. The patients in the Hopkins cohort have a very high rate of coinfection with hepatitis C, while the Melbourne cohort has “essentially none.”

They were interested in two different questions – is exposure to particular drugs correlated with risk for neuropathy, and is there a correlation between epidermal fiber density and the degree of neuropathy? Testing protocols in both sites were identical, consisting of punch skin biopsies of the distal leg and proximal thigh, as well as computerized sensory testing. Thresholds for vibration, cooling, heat, and pain were determined. Patients were classified as neuropathy free, asymptomatic but with electrophysiologic signs, or symptomatic.

They found a significantly lower density of epidermal fibers in patients who were symptomatic or had electrophysiologic signs, compared to those with no neuropathy. Curiously, those with signs only had lower densities than those with both symptoms and signs. “We're not sure quite what this means,” said Dr. McArthur, although low patient numbers in the former group may have skewed the data. There was no relationship between fiber density and hepatitis C status, vitamin B12 levels, or plasma lactate, all previously suggested as potential risk factors for neuropathy.

EFFECT OF DIFFERENT DRUG EXPOSURES

To determine the relative risk of different drug exposures, the two groups took treatment histories from 76 patients at Johns Hopkins, and 86 at Alfred Hospital, who were not chosen for presence of neuropathy but who had been exposed to at least one of the D drugs. Stavudine exposure was most common in both cohorts, followed by didanosine and zalcitabine. Only one third of patients were entirely neuropathy free. Symptomatic sensory neuropathy was significantly more common among patients with exposure to stavudine, with an odds ratio of 2.6, or to didanosine, with an odds ratio of 5.1. No effect was seen with zalcitabine, although the number of patients who had taken this drug was quite a bit lower than the others.

Dr. McArthur and colleagues were interested not only in the D drugs, but also whether there was an added effect from protease inhibitors. These drugs produce a host of metabolic changes, including insulin resistance, frank diabetes, and hypercholesterolemia, said Dr. McArthur. “With the insulin resistance, we're concerned about sensory neuropathy,” but the data did not reveal any increased risk from exposure to protease inhibitors.

Through logistical regression, they did find that the duration of exposure to didanosine had a significant effect on risk for sensory neuropathy. “If you are on didanosine for longer than a year, there is a strong association,” said Dr. McArthur, “but not if you've been on it for a shorter time.” There was not any association between how long a patient had been off the drug and the presence of neuropathy. This may mean that “it's a very long-term effect,” he said.

IMPLICATIONS OF RESEARCH

There are three implications to this study, according to Dr. McArthur. “First, it's still being debated from epidemiological studies whether there is or is not an association between these three drugs and symptomatic neuropathy. I think it's pretty clear from these data that there is.” Second, he said, so far only five percent of patients worldwide are being treated with antiretrovirals, but that number is likely to grow in the future. The drugs being used in resource-poor countries are generics, and most of the generic combinations contain stavudine. “So the concern is that we're going to see a very large number of individuals with antiretroviral toxic neuropathies in the years to come. Third, we really need to get a better handle on the interactions among these risk factors,” said Dr. McArthur.

According to Igor Koralnik, MD, Director of the HIV-Neurology Center at Harvard's Beth Israel Deaconess Medical Center in Boston, MA, the functional limitations of HIV-related sensory neuropathy can be major. “Even if patients are able to work, they will report their discomfort is often six to eight on a ten-point scale – it's very painful.” He said treatment with nonsteroidal anti-inflammatory drugs, gabapentin, or topical capsaicin can be effective. A tricyclic antidepressant can be added as well. “If this doesn't work, they may need long-term narcotics, and then it becomes a problem,” he said.

An additional problem, said Dr. McArthur, is that “many patients are so scared of developing neuropathy, they don't take their medications. The fear of neuropathy may have an impact, and that's important for epidemiological control” of HIV spread.

“Ten years ago, the survival was about six months. Now it's really a chronic management disease, like diabetes,” he said. “With the right drugs, you can keep patients largely controlled, and their systemic health improves dramatically. Now we as neurologists are really faced with helping to deal with the burden of neurologic disease. Many patients say to me, ‘the worst thing I have is my neuropathy.’”

ARTICLE IN BRIEF

In a study of risk factors for HIV-related sensory neuropathy, investigators reported that there appeared to a correlation between epidermal fiber density and the degree of neuropathy, as well as the duration of exposure to certain drugs such as didanosine.