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Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann. Neurol.* 14:403-18, 1983.

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This paper reports the neurological complications of acquired immune deficiency syndrome (AIDS). A variety of neurological illnesses previously seen in immunosuppressed patients were encountered. In addition, many AIDS patients suffered from a subacute demyelinating illness not previously described in the setting of immunosuppression. [The *SCI*® indicates that this paper has been cited in more than 680 publications.]

## AIDS and the Nervous System

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In 1980, as residents at the Cornell Neurology program in New York City, we began to encounter a variety of unusual neurological illnesses. Perhaps the most distinctive of these were cases of intracerebral toxoplasmosis, previously considered quite uncommon, and an unusual demyelinating illness resulting in a profound dementia requiring total care. Both of these illnesses appeared in young homosexual men and in intravenous drug users. The dementia was particularly striking because it is unusual for progressive dementia in younger patients.

As we encountered these patients, the initial cases of the acquired immune deficiency syndrome (AIDS) were being described in young homosexual men in New York, San Francisco, and Los Angeles.<sup>1,2</sup> It became apparent that there was substantial overlap between our unusual neurological patients and patients who were being diagnosed as having AIDS.

What began as a trickle of cases in 1980 became a steady stream in 1981 and 1982. The initial neurological syndromes expanded to include a number of other serious conditions. It

was clear that most of these illnesses fit into broad categories that one might expect in patients who were immunosuppressed, such as organ transplant recipients. However, the demyelinating illness afflicting AIDS patients was new and did not fit the course of any known infectious, autoimmune, or toxic process that had been described in neurology.

As some of the patients came to autopsy, examiners found two very distinct types of pathology in the brain. In some, examiners found microglial nodules previously reported in certain viral infections, most notably cytomegalovirus. Other brains showed areas of demyelination, sometimes populated by giant astrocytes of bizarre form. Often, these two pathologies coexisted in the same individual. As the glial nodules seemed to be a marker of infection, we coined the term "subacute encephalitis."

By 1982, we had encountered 50 patients with unusual neurological manifestations associated with AIDS, including 13 with subacute encephalitis. Our description remains a fair analysis of the spectrum of the neurological complications of AIDS. The frequency of nervous system involvement in AIDS has been confirmed in many studies. The virus causing AIDS, human immunodeficiency virus (HIV), was identified shortly after our paper appeared. Subsequently, evidence for the viral genome was found in the brain,<sup>3</sup> and virus was isolated from brains and spinal cords of affected patients.<sup>4</sup>

The mechanism by which HIV infection causes dementia is still not known. In the absence of strong evidence of a direct role of HIV in causing neuronal damage, several other mechanisms have been proposed, including effects of cytokines and calcium-mediated neurotoxicity.<sup>5</sup> Unfortunately, treatment of the encephalopathy associated with AIDS remains unsatisfactory, although the antiviral agent Zidovudine (AZT) appears to slow its progression. Several experimental trials are currently underway in search of a more effective therapy for this disorder.

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