

Editorial

Neuropathies and HIV infection

It is now a decade since the first reports of an unusual collection of infections among previously healthy male homosexuals.^{1,2} As management of the life threatening opportunistic infections became better the frequency and morbidity of peripheral neuromuscular complications became recognised. Peripheral neuropathies were the most common and will be featured in this review but myopathy secondary to Zidovudine^{3,4} and polymyositis⁵ are important causes of morbidity. In addition to neuropathies accompanying the disease itself treatment with antiviral agents dideoxyinosine (ddI) and dideoxycytidine (ddC) are a cause of neuropathy.

In the first major report of peripheral nerve disease,⁶ 352 patients with AIDS were reviewed retrospectively, and 51 considered to have a peripheral neuropathy. The most common abnormality was a symmetrical distal predominantly sensory neuropathy which occurred in 13 patients. A further 12 patients had a chronic demyelinating picture. Since this early paper a number of series have better characterised the clinical electrophysiological and pathological features of these neuropathies, and recognised a minority of other neuropathies associated with HIV infection (see table). It is now recognised that about 30% of patients with AIDS have neuropathic symptoms and electrophysiological studies in asymptomatic patients, reveal reductions in the sensory and motor action potentials particularly in the lower limb.⁷ Pathological changes in the peripheral nerves of patients with AIDS are very frequent with up to 95% of patients having histological abnormalities.⁸ Fuller *et al*⁹ in the April issue of the journal provide an overview of neuropathies involved and describe the clinical features of the distal symmetrical polyneuropathy in detail (DSPN).

Distal symmetrical axonal neuropathy

This is a predominantly sensory neuropathy which is frequently painful and occurs in the later stages of HIV infection, usually in patients with AIDS or Aids Related Complex (ARC).¹⁰⁻¹⁴ Reflexes are reduced or lost distally and electrophysiology reveals small sensory action potentials, reduced sensory conduction velocities and absent F waves.¹⁵ The CSF is typically acellular with a moderately elevated protein content.¹⁶ The clinical and electrophysiological features are consistent with a distal axonal degeneration of primary sensory neurons or "dying-back axonopathy" and pathological studies confirm that the main pathological feature is axonal damage with secondary demyelination.⁸ Fuller *et al* have described a subgroup of patients with prominent pain in their symptomatology who demonstrate axonal atrophy on detailed histological examination.¹⁷

The pathogenesis of the neuropathy remains uncertain. Initially it was thought that direct infection of sensory neurons with HIV was responsible but this now seems unlikely since neurons do not express the CD4 receptor that mediates infection of T lymphocytes and macrophages. HIV can be cultured from peripheral nerve¹⁸ but this almost certainly represents infection of macrophages and other antigen presenting cells. The frequency of infected cells appears low and attempts to detect HIV within nerves either by immunoperoxidase¹⁹ or polymerase chain reaction technique have been unsuccessful.²⁰ Furthermore treatment of neuropathic patients with Zidovudine does not produce any striking resolution of symptoms. DSPN does become more frequent with a greater duration of disease but this association could be explained by the consequences of advancing immunosuppression rather than a direct HIV effect. Fuller *et al* have previously published evidence that the particularly painful varieties of this neuropathy seem to be associated with cytomegalovirus infection outside the nervous system:²¹ a theme which they pursue in their paper in this journal. Cytomegalovirus infection is frequent in this group of patients and would be an attractive candidate for a causal agent if it could be shown that CMV infection of the peripheral sensory ganglion was common in patients with DSPN. There is good evidence to incriminate CMV in the aetiology of a small group of patients with a progressive cauda equina syndrome that frequently leads to death within a few months. Post mortem studies reveal cytomegalovirus inclusions and positive immunofluorescence for CMV in the cauda equina.²² Such cases often have CSF pleocytosis and may show some response to ganciclovir. More recently typical cytomegalovirus cytopathology has been described in patients with a more multifocal clinical and electrophysiological picture.²³ Despite the convincing neuropathology incriminating CMV in the aetiology of these rarer subgroups of HIV related neuropathy there is little pathological evidence that CMV infection of dorsal root ganglia is frequent in patients with DSPN and one small prospective study could not find an association of painful neuropathy and CMV infection.¹⁹ A number of other possible aetiologies have been considered including vitamin B12 and other nutritional insufficiency,^{15,24} and chronic illness of the "critical care" type.²⁵ It is also possible that cytokines liberated from infected macrophages may have a toxic effect on neurons or that unidentified infectious agents may be involved. As yet there is no convincing evidence to support any of these suggestions. The prognosis of this neuropathy appears variable and is better in the series of Fuller *et al* as one other recent study²⁰ than in previous reports that suggested that it invariably progressed until the patients died from their illness.

Table Neuropathies associated with HIV infection

1)	Distal symmetrical axonal neuropathy (DSPN)
2)	Inflammatory demyelinating neuropathies (GBS + CIDP)
3)	CMV radiculopathy
5)	Zoster radiculopathy
6)	Vasculitic neuropathy
6)	Lymphomatous neuropathy
7)	Autonomic neuropathy
8)	Neuropathy secondary to ddI and ddC.

Inflammatory demyelinating neuropathies

The identification of inflammatory demyelinating neuropathies of both the acute (Guillain-Barré syndrome) and chronic types in patients with HIV infection caused considerable interest since this type of neuropathy is generally considered to be immune mediated and it was hoped that the immunological derangements in AIDS might shed some light on the aetiology of demyelinating neuropathy in general. So far this has not proved to be the case. The presence of an inflammatory neuropathy among patients with HIV was first recognised by Lipkin *et al* in 1985.²⁶ He and his colleagues described an acute inflammatory neuropathy in homosexual men accompanied by fever, night sweats, malaise and generalised lymphadenopathy. At the time that these patients were seen an HIV test was not available although four of twelve such patients subsequently developed AIDS. The clinical picture was rather heterogeneous with some patients having a symmetrical neuropathy while others had a multifocal process.

Subsequently Cornblath *et al*²⁷ described three patients with Guillain-Barré syndrome (GBS) and a further 6 with a more chronic demyelinating inflammatory neuropathy (CIDP) in association with HIV infection. The CSF contained a raised protein together with a mild pleocytosis and electrophysiology was typical of a demyelinating neuropathy. Nerve biopsy revealed macrophage mediated demyelination with lymphocyte infiltration with predominantly CD8 positive cells and increased class II MHC expression. The natural history of the disease seems similar to idiopathic CIDP or GBS and response to plasma exchange or steroids is recorded. The majority of such cases are reported in asymptomatic patients with HIV rather than those patients with greater degrees of immuno-suppression.

The frequency of GBS and CIDP associated with HIV is difficult to determine and seems much lower in England than in the USA even allowing for the disparity in numbers of individuals infected. The initial American reports suggested that GBS followed HIV infection very much more commonly than it followed other major recognised antecedent infections such as cytomegalovirus or *Campylobacter*. This impression may have arisen from a bias towards recognition of such cases in the USA where a large number of patients were HIV positive. Recent studies in the United Kingdom have identified few cases of GBS or CIDP secondary to HIV infection but data from large scale prospective studies are needed. It is possible that HIV triggers demyelinating neuropathy no more frequently than other infections that do not result in such severe dysregulation of immune responses.

Idiopathic GBS and CIDP are thought to be immune mediated although the relative roles of antibody and T cells is disputed. The evidence implicating a humoral factor in their aetiology is relatively strong with plasma exchange effective in limiting disability in both diseases. HIV infection is associated with considerable derangement of T cell function and frequently leads to B cell stimulation, lymphadenopathy and raised levels of certain immunoglobulins. It is therefore possible to speculate that demyelination could result from the production of

auto-immune antibodies reacting with a constituent of myelin. The fact that plasma exchange appears effective in CIDP associated with HIV infection gives some support for a common aetiology.

Other neuropathies

Isolated mononeuropathies are seen in a small percentage of HIV positive individuals and are most frequent in the lateral cutaneous nerve of the thigh. This may progress to a more generalised neuropathy which is unusual for meralgia paraesthetica in non HIV positive individuals. Overt vasculitis is rare as a cause of neuropathy in association with HIV but may be responsible for some cases.⁸ Most studies of neuropathy in association with HIV infection report a small percentage of patients with radiculopathies secondary to herpes zoster, cases of lymphomatous nerve infiltration and autonomic dysfunction thought to be neuropathic in origin.²⁸

Two antiretroviral drugs have been shown in phase 1 trials to cause neuropathy. Lambert²⁹ *et al* reported that 8 of 20 patients receiving ddI developed a tingling, burning discomfort in the legs especially at night. Vibration sense and ankle reflexes were both reduced but nerve conduction studies were initially normal. The symptoms appeared to correlate with both dose level and total dose received. Studies with a single dose regime³⁰ obtained similar results with a slightly reduced incidence of neuropathy. Patients receiving ddc³¹ develop similar symptoms and signs with nerve conduction studies showing evidence of a distal axonopathy if treatment is continued. Stopping such drugs leads to resolution of symptoms within two months in most cases.

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Neurological stamp

Benjamin Rush (1745–1813)

Benjamin Rush actively supported the American Declaration of Independence and in 1776 was one of the 56 signatories. Later he was Treasurer of the USA Mint from 1799 until his death in 1813.

A graduate of Princeton and Edinburgh he became Professor of Chemistry and later of Medicine in Philadelphia. Rush was a prolific writer and a tireless reformer. Lettsom called him the American Sydenham. Rush believed that there was only one disease process and that was “irregular, convulsive or wrong action of the system affected”. To correct this he advocated a regime of bleeding and purgatives. His most important work *Medical Enquiries upon Diseases of the Mind* (1812) was the first American book of psychiatry. However, at a time when Pinel (born in the same year as Rush) was removing chains from the mentally afflicted of Paris, Rush was

advocating a strait waistcoat or a chair named “the tranquilliser”.

In his book Rush describes several types of aphasia as disturbances of memory. He recognised that multilingual patients may revert to another language when the facility for one language was disturbed. He also recognised the role of heredity in malformations of the brain and was probably the first to advocate that general disease (for example, arthritis, epilepsy) could be relieved by the extraction of decaying teeth.

John Trumbull's famous painting of the signing of the Declaration of Independence was reproduced on a United States stamp in 1869. This was the start of medical philately and the mint value of that stamp is now around US\$2500. The painting was again reproduced in 1976 for the American Bicentenary (Stanley Gibbons 1668–1671, Scott 1691–1694).

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