Review Article

Recent advances in the neurology of HIV infection

Richard K.H. Petty

Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF, UK

Introduction

This article describes recent advances in our understanding of the pathogenesis and treatment of the neurological disorders associated with human immunodeficiency virus-1 (HIV-1) infection. Readers in search of a general overview of 'AIDS neurology' are referred to two recent reviews.1,2

Neurological disease in primary HIV-1 infection

Primary infection with HIV-1 may pass unnoticed or be passed off as an unremarkable viral illness. A glandular fever-like illness occurs in 30–60% of patients.3,4 Neurological symptoms have included headache in 30%, with nausea and vomiting in 20%, an encephalopathy in 8% and neuropathies in a further 8%, often including a peripheral seventh nerve palsy. Rarer manifestations have included an aseptic meningitis,5 encephalitis,6 a myelopathy7 and acute rhabdomyolysis.8 The Guillain–Barré syndrome is no longer regarded as being associated with HIV-1 more often than any other acute viral infection. HIV-1 can be isolated in high titre from blood and cerebrospinal fluid (CSF) of these patients9 and this should be borne in mind when performing lumbar punctures.

The route of entry of the virus into the CSF is not certain. The virus is tropic for cells bearing the CD4 receptor (although other receptors include galactocerebrosides10). Current dogma, extrapolating from knowledge of retroviral behaviour in other hosts, is that the virus gains entry to the central nervous system (CNS) early in the course of disease by infecting trafficking macrophages and/or CD4-positive lymphocytes.11,12 An alternative, and not mutually exclusive hypothesis is that virus may bind to endothelial cells in the cerebral circulation expressing CD4 or Fc receptors13 and gain entry to the CNS.

It is not yet clear whether neurological symptoms at this stage predispose to later CNS disease. There is some evidence from a retrospective study that symptomatic acute infection is associated with a 68% risk of developing AIDS in the subsequent 5 years, compared to 20% in asymptomatic seroconverters,14 although other factors such as mode of transmission and reporting characteristics may have influenced these data. Late clinical presentation with neurological features is associated with a worse prognosis.15

Neurological disease associated with established HIV-1 infection

The manifestations of established HIV-1 infection have traditionally, and for largely epidemiological purposes, been divided into those occurring during the 'asymptomatic' period and those associated with immunosuppression. The neurological features have been divided into infections, tumours, primary HIV-1-mediated diseases and vascular disease, although these divisions are of limited practical clinical value. Certain disorders are associated with particular levels of immunosuppression and these will therefore be discussed by presenting features, and the stages at which individual complications develop will be indicated.

1. Meningitis

A low-grade lymphocytic meningitis has been described in postmortems performed on asymptomatic infected drug users who have died early in the course of their disease from factors not related to HIV-1 infection.16,17 The CSF is abnormal with 50% or more of all patients showing a raised protein, oligoclonal bands and a lymphocytic pleocytosis. HIV-1 is present in 20%.18-20 Patients may experience recurrent episodes of an aseptic meningitis but the pathological changes would appear to be entirely asymptomatic in the majority. There is no evidence as yet that these changes predict the later development of any of the neurological complications of HIV infection.

Meningitis may also be due to organisms other than HIV-1 (Table I). There are no specific clinical
features to distinguish these various causes, and malaise or intellectual blunting may be the only presenting symptom. The relative frequencies of these infections varies worldwide and local epidemiological patterns should be established by those caring for patients.

Cryptococcal meningitis is the most frequent in the UK, is the AIDS-defining illness in about 50% of cases, and is associated with advanced immunosuppression (100 or less CD4 lymphocytes/mm$^3$ in the peripheral blood). Fever and headache are present in about 75% of cases$^{11}$ but clinical meningism in only 22%. Focal signs (11–15%), seizures (5%) and hydrocephalus related to cryptococcomia or endarteritis is less common.$^{22}$ No meningeal features were present in 65% of patients in one review.$^1$ Diagnosis depends on CSF examination for cryptococcal antigen and culture; protein, sugar and pressure are normal in up to 50%. This should only be performed after computed tomographic (CT) cranial scanning to exclude additional mass lesions or hydrocephalus. The diagnosis clearly requires a high index of suspicion and CSF must be examined in any patient with a compatible story or an undiagnosed fever. The detection of cryptococcal antigen in the blood has been reported as a sensitive marker for cryptococcal meningitis.$^1$

Treatment remains difficult with high failure rates (up to 30%), relapse rates (30–50%) and toxicities, and there is no proven best regime. Standard therapy has been a combination of amphotericin B (0.3–0.8 mg/kg/day for up to 6 weeks) and fluconosine (150 mg/kg/day), although azoles such as fluconazole (200 mg/day) may be as effective with lower toxicities.$^{23}$ Alternative azoles such as itraconazole which do not penetrate CSF would appear to be less effective.$^{24}$ The recent introduction of liposomal preparations of amphotericin B (AmBisome) has been reported as reducing renal, hepatic and bone marrow toxicity at equivalent or higher dosages and may be a useful advance.$^{25}$ If a clinical and mycological response is achieved, it is essential to continue treatment and here again the best regime is in doubt. Current data would suggest the use of fluconazole at a dose of 200 mg/day indefinitely to prevent relapse.$^{26,27}$

Tuberculous meningitis due to Mycobacterium tuberculosis or atypical mycobacteria such as M. avium intracellulare is increasingly important in both Africa and the USA, and is likely to become so in the UK. It is also associated with severe immunosuppression (<200 CD4 cells/mm$^3$). Central nervous system involvement is usually due to M. tuberculosis presenting as a chronic meningitis and is similar to the disease occurring in the HIV-negative population, although the course may be more rapid.$^{28}$ Tuberculomas are more frequent, and may lead to focal features and seizures. The CSF contains fewer organisms than in the HIV-negative population and the constituents may be normal in 10% or more of cases. The polymerase chain reaction may improve diagnostic accuracy and speed.$^{29}$ At present in the UK organisms are sensitive to conventional agents but, despite this, overall mortality remains at 20%. Atypical mycobacterial disease is increasingly common with more advanced disease and is virtually always widely disseminated at the time of diagnosis and, it is usually overshadowed by the systemic infection.

Syphilis is present in about 1.5% of in-patients.$^{30,31}$ Progression to tertiary symptoms is said to be unusually rapid, and may not respond to conventional courses of penicillin.$^{32}$ The serological diagnosis can be difficult in advanced disease with up to 25% showing false-negative serology.$^2$ False-positive VDRL reactions also occur at a high frequency.$^{32}$ It has been suggested that the FTA and TPHA tests should be performed on CSF in any patients suspected of the diagnosis. Syphilitic gumma may present as an isolated mass lesion$^{33}$ and syphilis may produce easily misdiagnosed features, such as optic atrophy, Bell's palsy or stroke. It has been suggested that patients be treated with penicillin G, 2.0–4.0 megaunits, 4 hourly for 14 days.$^{32}$

Meningitis due to Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) is relatively uncommon in HIV-1-infected patients, and does not follow an atypical course. There has been concern that patients may be at increased risk of HSV-1 encephalitis, but case reports are rare or have occurred in association with other infections.$^{34,35}$ HSV-2 may give rise to troublesome perirectal and genital ulcers, has been described in association with meningitis and a myelitis, as seen in the HIV-1-seronegative population.$^{36}$ Therapy is with conventional doses of acyclovir.

Other fungal infections described in patients include histoplasmosis$^{37}$ and coccidiomycosis,$^{38}$ although these are extremely rare in the UK.

2. Encephalopathic symptoms

These can be divided into those associated with focal signs or symptoms and those associated with
diffuse cerebral dysfunction. It will become clear that there is considerable overlap between these two groups but the presence of focal features will influence investigation and management.

Diffuse encephalopathies The AIDS dementia complex (ADC) or HIV-associated cognitive-motor complex (among other aliases) is perhaps the most feared of the neurological diseases in AIDS. It is a diagnosis of exclusion during life with a very broad differential diagnosis (Table II). Early estimates were of an incidence up to 60% but more recent figures are lower at around 10%. The clinical presentation is as a subacutely evolving 'subcortical' dementia; characterized by slowness of thought, loss of initiative and poor memory often in association with neurological signs such as dysostias, ataxia and tetraparesis leading to death in 3–4 months from onset. Focal cortical symptoms such as aphasia, agnosias and apraxias are uncommon. Staging systems and diagnostic criteria have been proposed, but these are essentially descriptive and thorough investigation of all patients is essential. The aetiology of this dementing illness is not known. The neuropathological changes are listed in Table III. These changes may occur independently of one another implying distinct mechanisms. Atrophy is the most common change seen in over 90%. There are increased numbers of macrophages and microglia, and these cells form the nodules and multinucleate giant cells characteristic of the HIV encephalitis, a change seen in about 25% of postmortem. These cells contain HIV-1 and support viral replication within the central nervous system (CNS). In addition there is both diffuse pallor of white matter in 30–40%, with microscopic myelin loss, astrogliosis and infiltration of multinucleate giant cells. Finally, there is recent evidence for neuronal loss in cortex, basal ganglia and brainstem in up to 40% of cases with additional dendritic damage.

It is thought HIV-1 infects only the microglia, lymphocytes and possibly endothelial cells in the CNS and there is no convincing in vivo evidence that HIV-1 infects neurones, astrocytes or oligodendrocytes (although such infection has been produced in experimental models). A current hypothesis states that the neuronal death, the leucodystrophy and the dementia are secondary to the replication of HIV-1 in macrophages, and the products of the activation of macrophages and lymphocytes through two mechanisms: (1) the generation of virally encoded glycoproteins and regulatory proteins, such as tumour necrosis factor α, quinolinic acid, excitatory amino acids and nitric oxide which are also neuronotoxic, damage myelin and may play a part in the breakdown of the blood–brain barrier, another possible pathogenetic mechanism (see Table IV). It is important when considering mechanisms to recall that there is no correlation between these neuropathological and neurochemical changes, and the severity of the clinical dementia.

### Table III Neuropathological changes in brain due to HIV infection

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-specific</td>
<td></td>
</tr>
<tr>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>Micronodular encephalitis</td>
<td>Multinucleate giant cells (HIV containing)</td>
</tr>
<tr>
<td></td>
<td>Microglial nodules (HIV containing)</td>
</tr>
<tr>
<td>Leucoencephalopathy</td>
<td></td>
</tr>
<tr>
<td>Diffuse myelin pallor</td>
<td></td>
</tr>
<tr>
<td>Myelin loss and vacuolation</td>
<td></td>
</tr>
<tr>
<td>Astrocytosis</td>
<td></td>
</tr>
<tr>
<td>Multinucleate giant cells (HIV containing)</td>
<td></td>
</tr>
<tr>
<td>Poliodystrophy</td>
<td></td>
</tr>
<tr>
<td>Cortex, basal ganglia, brainstem</td>
<td></td>
</tr>
</tbody>
</table>

### Table IV Suggested pathogenetic mechanisms in HIV-associated neuropathology

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1-related</td>
<td></td>
</tr>
<tr>
<td>gp120 neurotoxic</td>
<td></td>
</tr>
<tr>
<td>gp120 oligodendrocyte toxic</td>
<td></td>
</tr>
<tr>
<td>gp41 mimics VIP</td>
<td></td>
</tr>
<tr>
<td>tat neuronotoxic</td>
<td></td>
</tr>
<tr>
<td>Macrophage activation related</td>
<td></td>
</tr>
<tr>
<td>TNF α</td>
<td></td>
</tr>
<tr>
<td>Quinolinic acid</td>
<td></td>
</tr>
<tr>
<td>Excitatory amino acids</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td></td>
</tr>
<tr>
<td>Blood–brain barrier breakdown</td>
<td></td>
</tr>
</tbody>
</table>
Therapeutic options are limited. It has been suggested that zidovudine has led to a lowered incidence of the AIDS dementia complex (ADC),\(^6,65\) a reduction in the incidence of HIV encephalitis,\(^6,67\) and neuroprotection,\(^68\) although others have not found this.\(^69\) Zidovudine is now established as being of benefit in AIDS and we are unlikely to be able to mount further trials. Those data that are available might imply that the dosage of zidovudine beneficial for the ADC may be in the range of 1,000–2,000 mg/day, considerably higher than that recommended at present.\(^65,66\) The value of other retroviral agents such as dideoxyninosine and dideoxyctytosine in treatment of the ADC is not established.

If the ADC is treatable, then the detection of the earliest signs of disease becomes of great importance. There are many reports of subtle neuropsychological abnormalities in both ‘asymptomatic’ patients and patients with AIDS, but none to date reliably predict the development of later dementia, and many are also present in appropriate control populations.\(^70\) Such abnormalities have included minor neuropsychological deficits\(^71-73\) but these have not been found by other workers.\(^74-76\) Most studies have not shown a decline in these parameters with time,\(^77,78\) although some do report this.\(^79,80\) Psychophysical assessments including reaction times\(^81-84\) have shown some abnormalities in asymptomatic as well as symptomatic patients and there are reports of improvements in these parameters with long-term zidovudine treatment of neurological asymptomatics.\(^85\) Abnormalities in cerebral perfusion\(^86\) and functional magnetic resonance (MR) imaging\(^87\) have also been described, but it has not proven possible as yet to correlate these changes with intellectual state or prognosis. Similar reservations apply to reports of atrophy on CT\(^88\) and MR scans.\(^89-91\) There is thus emerging evidence of subclinical cerebral pathology in patients infected with HIV-1, but the relevance of this to the ADC or clinical practice is not yet clear.

Cytomegalovirus (CMV) and Varicella zoster virus may produce a subacute encephalitis, and CMV may exacerbate HIV-1-related pathology by activating gene expression.\(^92\) CMV infections are associated with advanced disease and patients often have associated retinopathies, hypoadrenalism or evidence of neuropathy. The treatment of CMV infection is discussed below in the context of peripheral nerve disease.

There is also a wide range of possible causes of focal neurological dysfunction of which the most frequent are discussed below (and see Table V).

Toxoplasmosis develops in 6–12% of HIV-1-infected patients, usually as the CD4 cell count drops below 150/mm\(^3\). The presentation is of a subacutely evolving mass lesion with headache (c.

<table>
<thead>
<tr>
<th>Table V Causes of focal CNS disease in HIV-1 infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasma abscess</td>
</tr>
<tr>
<td>Primary cerebral lymphoma</td>
</tr>
<tr>
<td>Progressive multifocal leucoencephalopathy</td>
</tr>
<tr>
<td>Crytococcoma</td>
</tr>
<tr>
<td>Tuberculoma</td>
</tr>
<tr>
<td>Abscesses due to atypical organisms and fungi</td>
</tr>
<tr>
<td>AIDS dementia complex</td>
</tr>
<tr>
<td>Secondary lymphomatous deposit</td>
</tr>
<tr>
<td>Cerebrovascular diseases including angiitis</td>
</tr>
</tbody>
</table>

55%) and focal signs such as hemiparesis or ataxia (in 70%), with fever in 50%, and seizures in 20%.\(^93\) It may present as a diffuse illness without focal signs in 10% or more.\(^94\) The diagnosis relies on imaging which demonstrates multiple ring-enhancing mass lesions, often in deep white matter in basal ganglia, in over 70% of cases on CT scanning and over 80% of MR scans.\(^93,95\) Serological studies are not helpful, with many false negatives and, although polymerase chain reaction studies of CSF may detect toxoplasmosis sequences, lumbar puncture will be contraindicated in many patients because of mass effect.\(^96\) The diagnosis can only be made with certainty with brain biopsy and for this reason it is accepted practice to treat patients with a suggestive story and CT cranial scan. First-line therapy is a combination of sulphadiazine (4 g/day) and pyrimethamine (50–100 mg/day), with folinic acid (20 mg/day). A clinical response is apparent in some 80% of patients within 7–14 days.\(^97\) Steroids should be avoided as they will also lead to improvement in other mass lesions and thus potentially delay diagnosis. Patients with single, rather than multiple lesions, are usually treated as for toxoplasmosis, unless the radiological appearances are thought atypical. Brain biopsy is advised if patients do not show a clinical or radiological response, and have good quality of life.\(^97\) In these circumstances toxoplasmosis proves to be the diagnosis in about one third, lymphoma in a further third and progressive multifocal leuco-encephalopathy and other rarer pathologies in the remainder.\(^98,99\)

Adverse drug reactions occur in up to 62% of cases and alternative treatments are available including clindamycin (2–4 g/day) and atovaquone (750 mg, three times daily).\(^93,100\) Lifelong treatment after the initial illness is essential as relapse is common without secondary prophylaxis. Toxoplasmosis may be decreasing slightly in frequency in Europe and the USA as a consequence of the use of primary and secondary prophylaxis for Pneumocystis pneumonia.\(^101,102\)
Primary CNS lymphoma occurs in 5% of patients and is associated with very advanced immunosuppression, often less than 25 CD4 cells. Neurological involvement may occur in up to 30% of cases of systemic non-Hodgkin's lymphoma. Primary CNS lymphoma is very aggressive, usually widespread and multifocal in brain at presentation, and leads to headache and intellectual blunting in 60%, with seizures in 15% but focal signs in only 30–40%.\textsuperscript{103} CT or MR scans show single or multiple iso- or hyper-dense mass lesions, often with oedema and enhancement following contrast.\textsuperscript{104} These changes may mimic toxoplasmosis and, if in doubt, biopsy is essential. The prognosis is very poor with most patients dying within 2 months of diagnosis. Attempts at treatment with radiotherapy and chemotherapy have not as yet produced a useful improvement in survival.\textsuperscript{105,106} High-dose steroids will induce a temporary improvement only. Primary CNS lymphoma in AIDS is associated with Epstein–Barr virus (EBV) presence in all cases so far studied, and EBV sequences can be detected in CSF of patients possibly allowing non-invasive diagnosis.\textsuperscript{107,108} The CNS may be involved in systemic lymphoma, usually due to meningeal deposits which produce cranial neuropathies, compressive myelopathies and radiculopathies. Diagnosis is established by demonstration of lymphomatous cells in the CSF or biopsy, and here aggressive treatment with chemotherapy and radiotherapy does have more to offer.\textsuperscript{109}

Progressive multifocal leuкоencephalopathy (PML) is a rapidly progressing central demyelinating disorder related to oligodendrocyte infec-tion with a papavovirus (JC virus) and develops in 2–5% of cases, being the AIDS-defining illness of 50% of these. Cases are usually associated with advanced immunosuppression, although there are reports of cases occurring with over 500 CD4 cells.\textsuperscript{110} The virus is ubiquitous and most are infected by adult life. The clinical features resemble very aggressive multiple sclerosis and include hemiparesis and paraparesis, ataxia, visual defects and, in the late stages, dementia, with a 50% 3-month survival from diagnosis.\textsuperscript{111} Cranial MR scans show areas of white matter abnormality, which rarely enhance,\textsuperscript{112} but certain diagnosis is only possible with brain biopsy. Viral sequences can be detected using the polymerase chain technique in CSF in a minority of patients.\textsuperscript{113} There may be an interaction between HIV-1 and the JC virus with tat stimulating JC virus replication \textit{in vitro}.\textsuperscript{114} There is no proven treatment with only anecdotal reports of benefit with cytosine arabinoside or anti-retroviral agents.\textsuperscript{115} The relationship of PML to cases of a remitting and relapsing neurological disease clinically indistinguishable from multiple sclerosis (MS) remains conjectural, and indeed these cases may simply be the coincidence of two common disorders, MS and HIV-1 infection.\textsuperscript{116}

The incidence of cerebrovascular disease in HIV infection depends on the population studied. Pathological studies have reported frequencies of infarction and haematoma up to 20%, while clinical reports are of <1–10% incidence of 'stroke'.\textsuperscript{117} The majority of clinical events are due to embolization in intravenous drug abusers and other patients with infective or non-infective endocarditis, as well as haemorrhage in haemophilia. There are recent reports of 'transient ischaemic attack' (TIA)-like episodes in patients.\textsuperscript{118} These attacks are often longer lasting than true TIAs, occur up to 20 times per day, do not seem to presage ischaemic stroke, and may respond to zidovudine and may therefore be on a different basis. There are pathological reports of vasculopathies\textsuperscript{109,110,116} as well as abnormalities in blood flow as assessed by single photon emission computerized tomography (SPECT)\textsuperscript{109,112} and it is conceivable these are in some way related to these episodes. Stroke syndromes may also follow trigeminal zoster and be associated with the chronic meningitides and syphilis.

3. Myelopathies

There are three myelopathies associated with HIV-1, but their diagnosis is one of the exclusion and myelography or spinal MR imaging are essential to exclude compressive lesions, such as lymphomatous deposits or chronic meningitis (Table VI). A vacuolar myelopathy occurs in up to 20% of patients, with neuropathological features similar to subacute combined degeneration with posterior and lateral column vacuolation.\textsuperscript{122} The clinical features are of a subacutely progressive spastic ataxic paraparesis, often with a sensory level on the trunk and sparing of upper limbs in the early stages. The cause is not known, there is no convincing evidence of vitamin B\textsubscript{12} deficiency, although abnormal B\textsubscript{12} metabolism has been described.\textsuperscript{123} These changes may occur independently of the

<table>
<thead>
<tr>
<th>Table VI Causes of a myelopathy in HIV-1 infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacuolar myelopathy of AIDS</td>
</tr>
<tr>
<td>Gracile tract degeneration</td>
</tr>
<tr>
<td>Giant cell myelopathy</td>
</tr>
<tr>
<td>Extraneural compression from systemic lymphomatous deposit</td>
</tr>
<tr>
<td>Zoster myelitis</td>
</tr>
<tr>
<td>Compression due to abscess, for example, TB, other fungi</td>
</tr>
<tr>
<td>Chronic meningitis, for example, cryptococcosis</td>
</tr>
<tr>
<td>Incidental, for example, degenerative disc disease</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Co-infection with human T-cell lymphotrophic virus (HTLV-1)</td>
</tr>
</tbody>
</table>
brain pathology described above, and have also been described in rare immunosuppressed patients who are not infected with HIV-1, suggesting a possible opportunistic viral aetiology. Secondly, degeneration restricted to the gracile tracts occurs and may be associated with dorsal root ganglion necrosis. Finally the HIV-1-associated multinucleate giant cell encephalitic changes may extend down into the spinal cord. This develops in up to 50% of children while being rare in adults.

4. Peripheral neuropathies

A wide range of peripheral neuropathies have been described in HIV-1 infection (Table VII). A sensory neuropathy can be detected using thermal and vibration threshold testing in 5–10% of asymptomatic patients, rising to over 30% at CDC stage 3 or with ‘ARC’. This neuropathy may improve spontaneously and its relationship to the generalized neuropathy associated with AIDS is uncertain. Patients who have progressed to AIDS frequently develop a painful axonal sensory neuropathy with distal numbness, dysaesthesias and paraesthesias. Initially only distal reflexes are lost and weakness is mild but with progression patients become weak and areflexic. Autonomic symptoms may occur in up to 50%, but are rarely troublesome, and must be distinguished from the adrenal failure that may occur in disseminated cytomegaloviral disease. It may lead to pain but only rarely causes functional disability. The cause is not known and as in AIDS dementia complex investigation centres on the exclusion of treatable neuropathies. There is an unconfirmed report of gp 120 binding to sensory ganglion neurones and it has been suggested that this is in some way related to these neuropathies.

Chronic inflammatory demyelinating neuropathies, though rare, occur with increased frequency in seropositive patients, most often during the asymptomatic period. The clinical presentation, nerve conduction studies and nerve biopsy are similar to those in the HIV-negative population, and the only hint of HIV seropositivity may be a CSF lymphocytosis, atypical for inflammatory demyelinating polyneuropathy.

Cytomegalovirus has been implicated in a variety of neuropathies, usually in association with advanced disease. It is associated with a painful lumbosacral polyradiculopathy presenting with foot parasthesiae, weakness and, over a few days, paraparesis, or paraplegia and urinary retention. The upper limbs are usually spared unless the infection is untreated. CSF shows a marked polymorphocytosis up to 1,000/mm³, with a raised protein and slightly lowered sugar. Cytomegalovirus can be isolated from CSF and electromyography studies of affected muscles show evidence of acute denervation. Early treatment with ganciclovir (5 mg/kg i.v. twice daily for 10–14 days) may preserve lower limb function and maintenance therapy is essential to avoid relapse. Both CMV and Varicella zoster virus have been implicated in a mononeuritis multiplex and diffuse polyradiculopathies. These cases may present as a con fluent neuropathy, so mimicking the axonal neuropathy of HIV, and full assessment with nerve conduction studies is essential to make the diagnosis. There are anecdotal reports of a response to zidovudine but, more often, therapy is directed toward symptomatic measures, such as carbamazepine, phenytoin, tricyclic drugs and transcutaneous nerve stimulation. Entrapment neuropathies may become a problem as patients lose weight. The most commonly involved is the lateral cutaneous nerve of thigh, and its involvement may herald a more diffuse neuropathy.

There are recent reports of a motor axonopathy in HIV-1 infection, which may mimic motor neurone disease, although these must be extremely rare.

Finally, it is important to recognize that many of the drugs used in the treatment of HIV-1-infected patients may cause neuropathies and, of the retroviral agents, both dideoxycytidine and dideoxyinosine may cause a painful sensory neuropathy.

5. Muscle disease

An inflammatory necrotizing myopathy occurs, most frequently during the asymptomatic period, clinically indistinguishable from polymyositis. Patients present with a subacute painful proximal myopathy, associated with elevated levels of serum creatine kinase and a myopathic electromyogram. Muscle biopsy, essential to distinguish this process from the myopathies associated with advanced HIV disease and zidovudine treatment described below, shows necrosis with a macrophage and CD8+ lymphocytic infiltrate. Perifascicular atrophy is infrequently seen, nemaline rods may be prominent, and the inflammatory infiltrate may be minor. These features have led some to question whether this is true polymyositis or a novel nec-

<table>
<thead>
<tr>
<th>Table VII</th>
<th>Peripheral nerve disease in HIV-1 infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axonal sensory neuropathy</td>
<td>Chronic inflammatory demyelinating neuropathy</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating neuropathy</td>
<td>CMV-related lumbar radiculopathy</td>
</tr>
<tr>
<td>CMV-related mononeuritis multiplex</td>
<td>Zoster radiculopathy</td>
</tr>
<tr>
<td>Zoster radiculopathy</td>
<td>Autonomic neuropathy</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>Entrapment mononeuropathies</td>
</tr>
<tr>
<td>Entrapment mononeuropathies</td>
<td>Motor axonopathy</td>
</tr>
<tr>
<td>Motor axonopathy</td>
<td>Drug-induced neuropathies</td>
</tr>
</tbody>
</table>
rotizing myopathy occurring in the context of HIV infection and pre-existing inflammatory change.\(^{48}\) The pathogenesis is unclear and HIV is only present within infiltrating macrophages. There are no trials to support any mode of therapy but most workers recommend prednisolone in the doses used for conventional polymyositis with anecdotal reports of response. There is evidence for a HIV-specific myopathy distinct from the inflammatory myopathy referred to above and the zidovudine myopathy referred to later. This is usually associated with advanced disease. Patients develop weakness, myalgia and muscle biopsy shows myofibre degeneration, cytoplasmic bodies, nemaline rods and myofibrillar loss.\(^{49}\) The cause is unclear and there is no proven treatment.

There is considerable debate concerning whether or not zidovudine may give rise to a mitochondrial myopathy.\(^{148,150}\) It has an inhibiting action on the mitochondrial γ-DNA polymerase and has been shown in animal models to produce morphological and biochemical changes consistent with a mitochondrial myopathy.\(^{151-153}\) In six out of eight patients studied phosphorus magnetic resonance spectroscopy studies demonstrated abnormalities consistent with an impairment in mitochondrial biochemistry.\(^{154}\) The proposed clinical syndrome is a painful proximal myopathy, with moderate elevations of the serum creatine kinase and myopathic changes on electromyography. Muscle biopsy shows myofilament loss, microvacuolation, cytochrome oxidase negative fibres and mitochondrial accumulations producing a histological picture reminiscent of the mitochondrial myopathies.\(^{155,156}\) The risk of developing this myopathy is related to the total dose of zidovudine used and is associated with haematological toxicity.\(^{157}\) The serum creatine kinase often rises prior to symptoms developing and may be used as a marker of myotoxicity. The muscle symptoms resolve over a few weeks after stopping the drug and may not reappear if the drug is restarted at a lower dosage.\(^{158,159}\) The peripheral nerve and muscle disorders associated with HIV-1 infection are well reviewed in a recent article.\(^{160}\)

**Note added in proof**

Two recent studies of subclinical neurological disease in asymptomatic HIV-1 seropositive subjects found no evidence of either abnormal long latency event related brain potentials or abnormalities on cranial MRI scans.\(^{161,162}\)

**Acknowledgement**

Dr R.K.H. Petty is supported by the Greater Glasgow Health Board HIV Allocation.

---

**References**


---

Note added in proof

Two recent studies of subclinical neurological disease in asymptomatic HIV-1 seropositive subjects found no evidence of either abnormal long latency event related brain potentials or abnormalities on cranial MRI scans.

## Acknowledgement

Dr R.K.H. Petty is supported by the Greater Glasgow Health Board HIV Allocation.

## References


Recent advances in the neurology of HIV infection.

R. K. Petty

Postgrad Med J 1994 70: 393-403
doi: 10.1136/pgmj.70.824.393

Updated information and services can be found at:
http://pmj.bmj.com/content/70/824/393.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/