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 galactocerebroside¹⁰). 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

Correspondence: R.K.H. Petty, M.D., M.R.C.P.(UK).
Accepted: 24 January 1994

Table 1 Causes of a meningitic illness in HIV-1 infection

HIV-1
Cryptococcosis
Tuberculosis
Atypical mycobacteria
Syphilis
<i>Herpes simplex</i> virus I and II
Other fungal infections

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/mm³ in the peripheral blood). Fever and headache are present in about 75% of cases²¹ but clinical meningism in only 22%. Focal signs (11–15%), seizures (5%) and hydrocephalus related to cryptococcoma or endarteritis are 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 flucytosine (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/mm³). 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 inpatients.^{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 lesion³³ 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 histoplasmosis³⁷ and coccidioidomycosis,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 aliases³⁹) 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%.⁴⁰ 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 dystonias, ataxia and tetraparesis leading to death in 3–4 months from onset.⁴¹ Focal cortical symptoms such as aphasia, agnosias and apraxias are uncommon. Staging systems and diagnostic criteria have been proposed,^{42,43} 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%.⁴⁴ There are increased numbers of macrophages and microglia,⁴⁵ and these cells form the nodules and multinucleate giant cells characteristic of the HIV encephalitis, a change seen in about 25% of postmortems.³⁹ These cells contain HIV-1 and support viral replication within the central nervous system (CNS).^{46–48} In addition there is both diffuse pallor of white matter in 30–40%,³⁹ with microscopic myelin loss, astrocytosis and infiltration of multinucleate giant cells.^{49,50} Finally, there is recent evidence for neuronal loss in cortex, basal ganglia and brainstem in up to 40% of cases with additional dendritic damage.^{51–55}

Table II Differential diagnosis of diffuse encephalopathy in AIDS patients

AIDS dementia complex
Toxoplasma encephalitis
Other viral encephalitides
Diffuse cerebral lymphoma
Chronic meningitis, for example, cryptococcosis
Syphilis
Intoxication
Drug toxicities
Metabolic encephalopathies, for example, pneumocystis pneumonia
Deficiency states, for example, vitamin B ₁₂
Severe depressive illness

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.^{56,57}) 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 gp120 and tat, thought to be directly toxic to both neurones and oligodendrocytes; and (2) the production of macrophage- and lymphocyte-derived factors, 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^{58–61} (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.^{55,62,63}

Table III Neuropathological changes in brain due to HIV infection

Non-specific
Atrophy
Micronodular encephalitis
Multinucleate giant cells (HIV containing)
Microglial nodules (HIV containing)
Leucoencephalopathy
Diffuse myelin pallor
Myelin loss and vacuolation
Astrocytosis
Multinucleate giant cells (HIV containing)
Poliodystrophy
Cortex, basal ganglia, brainstem

Table IV Suggested pathogenetic mechanisms in HIV-associated neuropathology

HIV-1-related
gp120 neurotoxic
gp120 oligodendrocyte toxic
gp41 mimics VIP
tat neuronotoxic
Macrophage activation related
TNF α
Quinolinic acid
Excitatory amino acids
Nitric oxide
Blood–brain barrier breakdown

Therapeutic options are limited. It has been suggested that zidovudine has led to a lowered incidence of the AIDS dementia complex (ADC),^{64,65} a reduction in the incidence of HIV encephalitis^{66,67} 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 dideoxyinosine and dideoxycytosine 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 perfusion⁸⁶ and functional magnetic resonance (MR) imaging⁸⁷ 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 CT⁸⁸ 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/mm³. The presentation is of a subacutely evolving mass lesion with headache (c.

Table V Causes of focal CNS disease in HIV-1 infection

Toxoplasma abscess
Primary cerebral lymphoma
Progressive multifocal leucoencephalopathy
Cryptococcoma
Tuberculoma
Abscesses due to atypical organisms and fungi
AIDS dementia complex
Secondary lymphomatous deposit
Cerebrovascular diseases including angiitis

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.⁹³ 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%.¹⁰³ CT or MR scans show single or multiple iso- or hyper-dense mass lesions, often with oedema and enhancement following contrast.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.^{105,106} High-dose steroids will produce 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.^{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.¹⁰⁹

Progressive multifocal leucoencephalopathy (PML) is a rapidly progressive central demyelinating disorder related to oligodendrocyte infection 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.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.¹¹¹ Cranial MR scans show areas of white matter abnormality, which rarely enhance,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.¹¹³ There may be an interaction between HIV-1 and the JC virus with tat stimulating JC virus replication *in vitro*.¹¹⁴ There is no proven treatment with only anecdotal reports of benefit with cytosine arabinoside or anti-retroviral agents.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.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'.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 haemophiliacs. There are recent reports of 'transient ischaemic attack' (TIA)-like episodes in patients.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^{60,61,119} as well as abnormalities in blood flow as assessed by single photon emission computerized tomography (SPECT)^{120,121} 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.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 B₁₂ deficiency, although abnormal B₁₂ metabolism has been described.¹²³ These changes may occur independently of the

Table VI Causes of a myelopathy in HIV-1 infection

Vacuolar myelopathy of AIDS
Gracile tract degeneration
Giant cell myelopathy
Extraneural compression from systemic lymphomatous deposit
Zoster myelitis
Compression due to abscess, for example, TB, other fungi
Chronic meningitis, for example, cryptococcosis
Incidental, for example, degenerative disc disease
Syphilis
Co-infection with human T-cell lymphotropic virus (HTLV-1)

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.¹²⁴ Secondly, degeneration restricted to the gracile tracts occurs and may be associated with dorsal root ganglion necrosis.^{125,126} 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.¹²⁷

4. Peripheral neuropathies

A wide range of peripheral neuropathies have been described¹²⁸ (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’.^{128–130} This neuropathy may improve spontaneously¹²⁹ and its relationship to the generalized neuropathy associated with AIDS^{131,132} is uncertain. Patients who have progressed to AIDS frequently develop a painful axonal sensory neuropathy with distal numbness, dysaesthesias and parasthesias. 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%,¹³³ 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.¹³⁴ 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.¹³⁵

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.¹³⁶

Table VII Peripheral nerve disease in HIV-1 infection

Axonal sensory neuropathy
Chronic inflammatory demyelinating neuropathy
CMV-related lumbar radiculopathy
CMV-related mononeuritis multiplex
Zoster radiculopathy
Autonomic neuropathy
Entrapment mononeuropathies
Motor axonopathy
Drug-induced neuropathies

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.^{137–139} 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.^{138,140} These cases may present as a confluent 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 can 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.¹²⁹

There are recent reports of a motor axonopathy in HIV-1 infection, which may mimic motor neurone disease, although these must be extremely rare.^{141,142}

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.^{143,144}

5. Muscle disease

An inflammatory necrotizing myopathy occurs, most frequently during the asymptomatic period, clinically indistinguishable from polymyositis.^{145,146} 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.¹⁴⁷ 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-

rotizing myopathy occurring in the context of HIV infection and pre-existing inflammatory change.¹⁴⁸ 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 elevated serum creatine kinase levels and muscle biopsy shows myofibre degeneration, cytoplasmic bodies, nemaline rods and myofibrillar loss.¹⁴⁹ 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

1. Rudge, P. (ed.). *Neurological Aspects of Human Retroviruses*. Baillière's Clinical Neurology Series, London, April 1992.
2. Evans, B.K., Donley, D.K. & Whitaker, J.N. Neurological manifestations of infection with the human immunodeficiency viruses. In: Scheld, W.M., Whitley, R.J. & Durack, D.T. (eds) *Infections of the Central Nervous System*. Raven Press Ltd, New York, 1991, pp. 201-232.
3. Gaines, H., von Sydow, M., Pehrson, P.O. & Lungbergh, P. Clinical picture of primary HIV infection presenting as a glandular fever like illness. *Br Med J* 1988, **297**: 1363-1368.
4. Feinberg, J. The acute HIV seroconversion syndrome. *Curr Opin Infectious Dis* 1992, **5**: 221-225.
5. Hollander, H. & Stringari, S. Human immunodeficiency virus associated meningitis. Clinical course and correlations. *Am J Med* 1987, **83**: 813-816.
6. Carne, C.A., Tedder, R.S., Smith, A. *et al.* Acute encephalopathy coincident with seroconversion for anti HTLV-III. *Lancet* 1985, **ii**: 1206-1208.
7. Denning, D.W., Anderson, J., Rudge, P. & Smith, H. Acute myelopathy associated with primary infection with human immunodeficiency virus. *Br Med J* 1987, **294**: 143-144.
8. Del Rio, C., Soffer, O., Widdell, J.L., Judd, R.L. & Slade, B.A. Acute human immunodeficiency virus infection temporally associated with rhabdomyolysis, acute renal failure and nephrosis. *Rev Infect Dis* 1990, **12**: 282-285.
9. Daar, E.S., Moudgil, T., Meyer, R.D. & Ho, D.D. Transient high levels of viraemia in patients with primary human immunodeficiency virus type 1 infection. *N Engl J Med* 1991, **324**: 961-964.
10. Levy, J.A. HIV pathogenesis and long term survival. *AIDS* 1993, **7**: 1401-1410.
11. Narayan, O. & Clements, J.E. Biology and pathogenesis of Lentiviruses. *J Gen Virol* 1989, **70**: 1617-1639.
12. Davis, L.E., Hjelle, B.L., Miller, V.E., Palmer, D.L. *et al.* Early viral brain invasion in iatrogenic human immunodeficiency virus infection. *Neurology* 1992, **42**: 1736-1739.
13. Achim, C.L., Schrier, R.D. & Wiley, C.A. Immunopathogenesis of HIV encephalitis. *Brain Pathol* 1991, **1**: 177-184.
14. Sinicco, A., Fora, R., Sciandra, M. *et al.* Risk of developing AIDS after primary acute HIV-1 infection. *J AIDS* 1993, **6**: 575-581.
15. Casabona, J., Sanchez, E., Graus, F., Abos, J. & Segura, A. Trends and survival for AIDS patients presenting with indicative neurological diseases. *Acta Neurol Scand* 1991, **84**: 51-55.
16. Gray, F., Lesco, M.-C., Keohane, C. *et al.* Early brain changes in HIV infection: neuropathological study of 11 seropositive non-AIDS cases. *J Neuropath Exp Neurol* 1992, **51**: 177-185.
17. Gray, F., Hurtrel, M. & Hurtrel, B. Early central nervous system changes in human immunodeficiency virus (HIV) - infection. *Neuropath Appl Neurobiol* 1993, **19**: 3-9.
18. Marshall, D.W., Brey, R.L., Cahill, W.T. *et al.* Spectrum of cerebrospinal fluid findings in various stages of human immunodeficiency virus infection. *Arch Neurol* 1988, **45**: 954-958.
19. Hollander, H. & Levy, J.A. Neurologic abnormalities and recovery of human immunodeficiency virus from cerebrospinal fluid. *Ann Intern Med* 1987, **106**: 692-695.

20. Appelman, M.E., Marshall, D.W., Brey, R.L. *et al.* Cerebrospinal fluid abnormalities in patients without AIDS who are seropositive for human immunodeficiency virus. *J Infectious Dis* 1988, **158**: 193–199.
21. Chuck, S.L. & Sande, M.A. Infections with cryptococcus neoformans in the acquired immunodeficiency syndrome. *N Engl J Med* 1989, **321**: 794–799.
22. Johnston, S.R.D., Corbett, E.L., Foster, O., Ash, S. & Cohen, J. Raised intracranial pressure and visual complications in AIDS patients with cryptococcal meningitis. *J Infection* 1992, **24**: 185–189.
23. Saag, M., Powderly, W.G., Cloud, G.A. *et al.* Comparison of amphoterecin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. *N Engl J Med* 1992, **326**: 83–89.
24. De Gans, J., Portegies, P., Tiessens, G. *et al.* Itraconazole compared with amphoterecin B plus flucytosine in AIDS patients with cryptococcal meningitis. *AIDS* 1992, **6**: 185–190.
25. Coker, R.J., Viviani, M., Gazzard, B.G. *et al.* Treatment of cryptococcosis with liposomal amphoterecin B (AmBisome) in 23 patients with AIDS. *AIDS* 1993, **7**: 829–835.
26. California Collaborative Treatment Group, Bozzette, S.A., Larsen, R.A., Chiu, J. *et al.* A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. *N Engl J Med* 1991, **324**: 580–584.
27. Powderly, W.G., Saag, M.S., Cloud, G.A. *et al.* A controlled trial of fluconazole or amphoterecin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1992, **326**: 793–798.
28. Berenguer, J., Moreno, S., Laguna, F. *et al.* Tuberculous meningitis in patients infected with the human immunodeficiency virus. *N Engl J Med* 1992, **326**: 668–672.
29. Kaneko, K., Onodera, O., Miyatake, T. & Tsuji, S. Rapid diagnosis of tuberculous meningitis by polymerase chain reaction (PCR). *Neurology* 1990, **40**: 1617–1618.
30. Katz, D.A. & Berger, J.R. Neurosyphilis in acquired immunodeficiency syndrome. *Arch Neurol* 1989, **46**: 895–898.
31. Berger, J.R. Neurosyphilis in human immunodeficiency virus type 1-seropositive individuals. *Arch Neurol* 1991, **48**: 700–702.
32. Hook, E.W., III & Marra, C.M. Acquired syphilis in adults. *N Engl J Med* 1992, **326**: 1060–1069.
33. Berger, J.R., Waskin, H., Pall, L. *et al.* Syphilitic cerebral gumma with HIV infection. *Neurology* 1992, **42**: 1282–1287.
34. Laskin, O.L., Stahl-Bayliss, C.M. & Morgello, S. Concomitant herpes simplex type 1 and cytomegalovirus ventriculoencephalitis in acquired immunodeficiency syndrome. *Arch Neurol* 1987, **44**: 843–847.
35. Tan, S.V., Guiloff, R.J., Scaravelli, F. *et al.* Herpes Simplex type 1 encephalitis in acquired immunodeficiency syndrome. *Ann Neurol* 1993, **34**: 619–622.
36. Britton, C.B., Mesa-Tejeda, R., Fenoglio, C.M., Hays, A.P. *et al.* A new complication of AIDS: thoracic myelitis caused by herpes simplex virus. *Neurology* 1985, **35**: 1071–1074.
37. Wheat, L.J., Batteiger, B.E. & Sathapatayavongs, B. Histoplasma capsulatum infection of the central nervous system. *Medicine* 1990, **69**: 244–260.
38. Bronnimann, D.A., Adams, R.D., Galgiani, J.N. *et al.* Coccidioidomycosis in acquired immunodeficiency syndrome. *Ann Intern Med* 1987, **106**: 372–379.
39. Budka, H., Wiley, C.A., Kleihues, P. *et al.* HIV associated disease of the nervous system: review of nomenclature and proposal for neuropathology-based terminology. *Brain Pathol* 1991, **1**: 143–152.
40. Janssen, R.S., Nwanyanwu, O.C., Selik, R.M. & Stehr-Green, J.K. Epidemiology of human immunodeficiency virus encephalopathy in the United States. *Neurology* 1992, **42**: 1472–1476.
41. Navia, B.A., Jordan, B.D. & Price, R.W. The AIDS dementia complex: 1: clinical features. *Ann Neurol* 1986, **19**: 517–524.
42. Price, R.W. & Brew, B.J. AIDS commentary: the AIDS dementia complex. *J Infectious Dis* 1988, **158**: 1079–1083.
43. World Health Organization. *Report of the Second Consultation on the Neuropsychiatric Aspects of HIV-1 Infection*, World Health Organization, Geneva, 1990, 11–13 January.
44. Lantos, P.L., McLaughlin, J.E., Scholtz, C.L. *et al.* Neuropathology of the brain in HIV infection. *Lancet* 1989, **ii**: 309–310.
45. Gelman, B.B. Diffuse microgliosis associated with cerebral atrophy in the acquired immunodeficiency syndrome. *Ann Neurol* 1993, **34**: 65–70.
46. Koenig, S., Gendelman, H.E., Orenstein, J.M. *et al.* Detection of AIDS virus in macrophages in brain tissue from AIDS patients with encephalopathy. *Science* 1986, **233**: 1089–1093.
47. Wiley, C.A., Schrier, R.D., Nelson, J.A. *et al.* Cellular localisation of human immunodeficiency virus infection within the brains of acquired immunodeficiency syndrome patients. *Proc Natl Acad Sci* 1986, **83**: 7089–7093.
48. Peudenier, S., Hery, C., Moutaignier, L. & Tardieu, M. Human microglial cells: characterisation in cerebral tissue and in primary culture, and study of their susceptibility to HIV-1 infection. *Ann Neurol* 1991, **29**: 152–161.
49. Budka, H. Neuropathology of human immunodeficiency virus infection. *Brain Pathol* 1991, **1**: 163–175.
50. Scaravelli, F. Neuropathology of HIV-1 and HTLV-1 infection. In: Rudge, P. (ed.). *Neurological Aspects of Human Retroviruses*. Baillière Tindall, London, 1992, pp. 211–238.
51. Masliah, E., Ge, N., Achim, C.L. *et al.* Selective neuronal vulnerability in HIV encephalitis. *J Neuropath Exp Neurol* 1992, **51**: 585–593.
52. Wiley, C.A., Masliah, E., Morey, M. *et al.* Neocortical damage during HIV infection. *Ann Neurol* 1991, **29**: 651–657.
53. Reyes, M.G., Faraldi, F., Senseng, C.S. *et al.* Nigral degeneration in acquired immune deficiency syndrome (AIDS). *Acta Neuropathol* 1991, **82**: 39–44.
54. Everall, I.P., Luthert, P.J. & Lantos, P.L. Neuronal loss in the frontal cortex in HIV infection. *Lancet* 1991, **337**: 1119–1121.
55. Everall, I., Luthery, P. & Lantos, P. A review of neuronal damage in human immunodeficiency virus infection: its assessment, possible mechanism and relationship to dementia. *J Neuropath Exp Neurol* 1993, **52**: 561–566.
56. Dubois-Dalcq, M.E., Jordan, C.A., Kelly, W.B. & Watkins, B.A. Understanding HIV-1 infection of the brain: a challenge for neurobiologists. *AIDS* 1990, **4** (Suppl 1): S67–S76.
57. Kunsch, C., Hartle, H.T. & Wigdahl, B. Infection of human fetal dorsal root ganglion glial cells with human immunodeficiency virus type 1 involves an entry mechanism independent of the CD4 epitope. *J Virol* 1989, **63**: 5054–5061.
58. Lipton, S.A. Models of neuronal injury in AIDS: another role for the NMDA receptor. *TINS* 1992, **15**: 75–79.
59. Epstein, L.G. & Gendelman, H.E. Human immunodeficiency virus type 1 infection of the nervous system: pathogenetic mechanisms. *Ann Neurol* 1993, **33**: 429–436.
60. Petito, C.K. & Cash, K.S. Blood–brain barrier abnormalities in the acquired immunodeficiency syndrome: immunohistological localisation of serum proteins in post mortem brains. *Ann Neurol* 1992, **32**: 658–666.
61. Power, C., Kong, P.-A., Crawford, T.O. *et al.* Cerebral white matter changes in acquired immunodeficiency syndrome dementia: alterations of the blood–brain barrier. *Ann Neurol* 1993, **34**: 339–350.

62. Glass, J.D., Wesselingh, S.L., Selnes, O.A. & McArthur, J.C. Clinico-pathological correlation in HIV-associated dementia. *Neurology* 1993, **43**: 2230–2237.
63. Everall, I., Glass, J., McArthur, J.C., Spargo, E. & Lantos, P. Neuronal loss in the superior frontal gyrus correlates with HIV associated dementia. *Clin Neuropath* 1993, **12** (Suppl 1): S10.
64. Portegies, P., Enting, R.H., de Gans, J. *et al.* Presentation and course of AIDS dementia complex: 10 years of follow up in Amsterdam, The Netherlands. *AIDS* 1993, **7**: 669–675.
65. Sidtis, J.J., Gatsonis, C., Price, R.W. *et al.* Zidovudine treatment of the AIDS dementia complex: results of a placebo-controlled trial. *Ann Neurol* 1993, **33**: 343–349.
66. Gray, F., Geny, C., Dourmon, E. *et al.* Neuropathological evidence that zidovudine reduces incidence of HIV infection of brain. *Lancet* 1991, **337**: 852–853.
67. Vago, L., Castagna, A., Lazzarin, A. *et al.* Reduced frequency of HIV induced brain lesions in AIDS patients treated with zidovudine. *J AIDS* 1993, **6**: 42–45.
68. Spargo, E., Everall, I.P. & Lantos, P.L. Evidence that AZT is neuroprotective in the hippocampus in HIV infection. *Clin Neuropath* 1993, **12** (Suppl 1): S14.
69. McArthur, J.C., Hoover, D.R., Bacellar, H. *et al.* Dementia in AIDS patients: incidence and risk factors. *Neurology* 1993, **43**: 2245–2252.
70. Burgess, A. & Riccio, M. Cognitive impairment and dementias in HIV-1 infection. In: Rudge, P. (ed.) *Neurological Aspects of Human Retroviruses*. Ballière Tindall, London, 1992, pp. 155–174.
71. Grant, L., Hampton Atkinson, J., Hesselink, J.R. *et al.* Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. *Ann Intern Med* 1987, **107**: 828–836.
72. Poutiainen, E., Elovaara, I., Raininko, R. *et al.* Cognitive performance in HIV-1 infection: relationship to severity of disease and brain atrophy. *Acta Neurol Scand* 1993, **87**: 88–94.
73. Wilkie, F.L., Morgan, R., Fletcher, M.A. *et al.* Cognition and immune function in HIV-1 infection. *AIDS* 1992, **6**: 977–981.
74. Reinvang, I., Froland, S.S. & Skripeland, V. Prevalence of neuropsychological deficit in HIV infection. Incipient signs of AIDS dementia complex in patients with AIDS. *Acta Neurol Scand* 1991, **83**: 289–293.
75. Miller, E.N., Selnes, O.A. & McArthur, J.C. Neuropsychological performance in HIV-1 infected homosexual men: the multicenter AIDS cohort study (MACS). *Neurology* 1990, **40**: 197–203.
76. McAllister, R.H., Herns, M.V., Harrison, M.J.G. *et al.* Neurological and neuropsychological performance in HIV seropositive men without symptoms. *J Neurol Neurosurg Psychiatr* 1992, **55**: 143–148.
77. Selnes, O.A., McArthur, J.C., Royal, W., III *et al.* HIV-1 infection and intravenous drug use: longitudinal neuropsychological evaluation of asymptomatic subjects. *Neurology* 1992, **42**: 1924–1930.
78. Karlsen, N.R., Reinvang, I. & Froland, S.S. A follow up study of neuropsychological function in asymptomatic HIV-infected patients. *Acta Neurol Scand* 1993, **87**: 83–87.
79. Hall, C., Robertson, K., Messenheimer, J. *et al.* Progression of CNS dysfunction in the systemically asymptomatic stages of human immunodeficiency virus infection. *Clin Neuropath* 1993, **12** (Suppl 1): S17.
80. Bornstein, R.A., Nasrallah, H.A., Para, M.F. *et al.* Neuropsychological performance in symptomatic and asymptomatic HIV infection. *AIDS* 1993, **7**: 519–524.
81. Karlsen, N.R., Reinvang, I. & Froland, S.S. Slowed reaction time in asymptomatic HIV-positive patients. *Acta Neurol Scand* 1992, **86**: 242–246.
82. Raggazzoni, A., Grippo, A., Ghidini, P. *et al.* Electrophysiological study of neurologically asymptomatic HIV1 seropositive patients. *Neurol Scand* 1993, **87**: 47–51.
83. Pagano, M.A., Cahn, P.E., Garau, M.L. *et al.* Brain-stem auditory evoked potentials in human immunodeficiency virus-seropositive patients with and without acquired immunodeficiency syndrome. *Arch Neurol* 1992, **49**: 166–169.
84. Dumlop, O., Bjorkland, R.A., Abdelnoor, M. & Myrvang, B. Five different tests of reaction time evaluated in HIV seropositive men. *Acta Neurol Scand* 1992, **86**: 260–266.
85. Arendt, G., v. Geisen, H.-J., Heftner, H. & St Maus. Effects of long-term AZT, DDI and AZT/DDC combination treatment on electrophysiologically detectable CNS deficits in clinically asymptomatic HIV-1 positive patients. *Clin Neuropath* 1993, **12** (Suppl 1): S15.
86. Rosci, M.A., Pigorini, F., Bernabei, A. *et al.* Methods of detecting early signs of AIDS dementia complex in asymptomatic HIV-1-infected subjects. *AIDS* 1992, **5**: 1309–1316.
87. Chong, W.K., Sweeney, B., Wilkinson, I.D. *et al.* Abnormalities of cerebral proton MR spectra in HIV infection with clinical, immunological and MRI correlation. *Clin Neuropath* 1993, **12** (Suppl 1): S21.
88. Elovaara, I., Poutiainen, E., Raininko, R. *et al.* Mild brain atrophy in early HIV infection: the lack of association with cognitive defects and HIV-specific intrathecal immune response. *J Neurol Sci* 1990, **99**: 121–136.
89. Menon, D.K., Baudouin, D., Tomlinson, D. & Hoyle, C. Proton magnetic resonance spectroscopy and imaging of the brain in AIDS: evidence of neuronal loss in regions that appear normal with imaging. *J Comp Assist Tomog* 1990, **14**: 882–885.
90. Dooneief, G., Bello, J., Todak, G. *et al.* A prospective controlled study of magnetic resonance imaging of the brain in gay men and parenteral drug users with human immunodeficiency virus infection. *Arch Neurol* 1992, **49**: 38–43.
91. Sweeney, B.J., Chong, W.K. & Wilkinson, I.D. Neuropsychological correlates of cerebral proton magnetic resonance spectroscopy in HIV infection. *Clin Neuropath* 1993, **12** (Suppl 1): S23.
92. Skolnik, P.R., Kosloff, B.R. & Hirsch, M.S. Bidirectional interactions between human immunodeficiency virus type 1 and cytomegalovirus. *J Infectious Dis* 1988, **157**: 508–514.
93. Porter, S.B. & Sande, M. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med* 1992, **327**: 1643–1648.
94. Wijds, E.F.M., Borleffs, J.C.C., Hoepelman, A.I.M. & Jansen, G.H. Fatal disseminated hemorrhagic toxoplasmic encephalitis as the initial manifestation of AIDS. *Acta Neurol* 1991, **29**: 683–686.
95. De la Paz, R. & Enzmann, D. Neuroradiology of the acquired immunodeficiency syndrome. In: Rosenblum, M.L., Levy, R.M. & Bresenden, D.E. (eds) *AIDS and the Nervous System*. Raven Press, New York, 1988, pp. 121–153.
96. Verhofstede, C., Reniers, S., Colebunders, R. *et al.* Polymerase chain reaction in the diagnosis of toxoplasma encephalitis. *AIDS* 1993, **7**: 1539–1541.
97. Anon. Brain biopsy for intracranial mass lesions in AIDS. *Lancet* 1992, **340**: 1135–1136.
98. Levy, R.M., Russel, E., Yungbluth, M. *et al.* The efficacy of image-guided stereotactic brain biopsy in neurologically symptomatic acquired immunodeficiency syndrome patients. *Neurology* 1992, **42**: 186–190.
99. Zimmer, C., Marzheuser, S., Patt, S. *et al.* Stereotactic brain biopsy in AIDS. *J Neurol* 1992, **239**: 394–400.
100. Kovacs, J.A. *et al.* Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. *Lancet* 1992, **340**: 637–638.
101. Girard, P.-M., Landman, R., Gaubert, G. *et al.* Dapsone-pyrimethamine compared with aerosolised pentamidine as primary prophylactic agents against pneumocystis pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993, **328**: 1514–1520.

102. Hardy, W.D., Feinberg, J., Finkelstein, D.M. *et al.* A controlled trial of trimethoprim-sulphamethoxazole or aerosolised pentamidine for secondary prophylaxis of pneumocystis carinii pneumonia in patients with acquired immunodeficiency syndrome. *N Engl J Med* 1992, **327**: 1842–1848.
103. So, Y.T., Bechstead, J.H. & Davis, R.L. Primary central nervous system lymphoma in acquired immunodeficiency syndrome: a clinical and pathological study. *Ann Neurol* 1986, **20**: 566–572.
104. Post, M.J.D., Kursunoglu, S.J., Hensley, G.T. *et al.* Cranial CT in acquired immunodeficiency syndrome: spectrum of diseases and optimal contrast enhancement techniques. *Am J Radiol* 1985, **145**: 929–940.
105. Baumgartner, J.E., Rachlin, J.R., Beckstead, J.H. *et al.* Primary central nervous system lymphomas: natural history and response to radiation therapy in 55 patients with acquired immunodeficiency syndrome. *J Neurosurg* 1990, **73**: 206–211.
106. Remick, S.C., Diamond, C., Migliozi, J.A. *et al.* Primary central nervous system lymphomas in patients with and without the acquired immunodeficiency syndrome. A retrospective analysis and review of the literature. *Medicine* 1990, **69**: 345–360.
107. MacMahon, E.M.E., Glass, J.D., Hayward, S.D. *et al.* Epstein–Barr virus in AIDS related primary central nervous system lymphoma. *Lancet* 1991, **338**: 969–973.
108. Cinque, P., Brytting, M., Vago, L. *et al.* Epstein–Barr virus DNA in cerebrospinal fluid from patients with AIDS related primary lymphoma of the central nervous system. *Lancet* 1993, **342**: 398–401.
109. Levine, A.M., Wernz, J.C., Kaplan, L. *et al.* Low dose chemotherapy with central nervous system prophylaxis and zidovudine maintenance in AIDS-related lymphoma: a prospective multi-institutional trial. *JAMA* 1991, **266**: 84–88.
110. Britton, C.B., Romagnoli, M., Sisti, M. & Powers, J.M. Progressive multifocal leucoencephalopathy: analysis of outcome and response to intrathecal ara-C in 26 patients. *Neuroscience of HIV Infection. Basic and Clinical Frontiers*, Amsterdam, 14–17 July 1992, p. 40 (abstract).
111. Gillespie, S.M., Chang, Y., Lemp, G. *et al.* Progressive multifocal leucoencephalopathy in persons infected with human immunodeficiency virus, San Francisco, 1981–1989. *Ann Neurol* 1991, **30**: 597–604.
112. Marks, A.S. & Atlas, S.W. Progressive multifocal leucoencephalopathy in patients with AIDS: appearance of MR images. *Radiology* 1989, **173**: 517–520.
113. Henson, J., Rosenblum, M., Armstrong, D. & Furneaux, H. Amplification of JC virus DNA from brain and cerebrospinal fluid of patients with progressive multifocal leucoencephalopathy. *Neurology* 1991, **41**: 1967–1971.
114. Tada, H., Rappaport, J., Lastigani, M. *et al.* Transactivation of the JC virus late promoter by the tat protein of type 1 human immunodeficiency virus in glial cells. *Proc Natl Acad Sci* 1990, **87**: 3479–3483.
115. Lidman, C., Lindqvist, L., Mathiesen, T. & Grane, P. Progressive multifocal leucoencephalopathy in AIDS. *AIDS* 1991, **5**: 1039–1041.
116. Berger, J.R., Tornatore, C. & Major, E.O. Relapsing and remitting human immunodeficiency virus-associated leucoencephalomyelopathy. *Ann Neurol* 1992, **31**: 34–38.
117. Snider, W.D., Simpson, D.M., Nielsen, S. *et al.* Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann Neurol* 1983, **14**: 403–418.
118. Brew, B.J. & Miller, J. Transient ischaemic attacks (TIAs) in HIV-1 infection. *Clin Neuropath* 1993, **12** (Suppl 1): S15.
119. Mintz, M., Epstein, L.G., Koenigsberger, M.R. *et al.* Neurological manifestations of acquired immunodeficiency syndrome in children. *Int Pediatrics* 1989, **4**: 161–171.
120. Renshaw, P., Johnson, K. & Worth, J. Proton MR spectroscopy and HMPAO single photon emission computerised tomography (SPECT) in patients with mild AIDS dementia complex (ADC). *Clin Neuropath* 1993, **12** (Suppl 1): S23.
121. Geier, S.A., Schielke, E., Tatsch, K. *et al.* Brain HMPAO-SPECT and ocular microangiopathic syndrome in HIV-1 infected patients. *AIDS* 1993, **7**: 1589–1594.
122. Petit, C.K., Navia, B.A., Cho, E.-S. *et al.* Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1985, **312**: 874–879.
123. Kiebert, K.D., Giang, D.W., Schiffer, R.B. & Vakil, N. Abnormal vitamin B12 metabolism in human immunodeficiency virus infection. Association with neurological dysfunction. *Arch Neurol* 1991, **48**: 312–314.
124. Kamin, S.S. & Petit, C.K. Idiopathic myelopathies with white matter vacuolation in non-acquired immunodeficiency syndrome patients. *Hum Pathol* 1991, **22**: 816–824.
125. Rance, N.E., McArthur, J.C., Cornblath, D.R. *et al.* Gracile tract degeneration in patients with sensory neuropathy and AIDS. *Neurology* 1988, **38**: 265–271.
126. Scaravelli, F., Sinclair, E., Arango, J.-C. *et al.* The pathology of the posterior root ganglia in AIDS and its relationship to the pallor of the gracile tract. *Acta Neuropathol* 1992, **84**: 163–170.
127. Sharer, L.R., Dowling, P.C., Michaels, J. *et al.* Spinal cord disease in children with HIV-1 infection: a combined molecular biological and neuropathological study. *Neuropathol Appl Neurobiol* 1990, **16**: 317–331.
128. Fuller, G.N., Jacobs, J.M. & Guilloff, R.J. Nature and incidence of peripheral nerve syndrome in HIV infection. *J Neurol Neurosurg Psychiatr* 1993, **56**: 372–381.
129. Winer, J.B., Bang, B., Clarke, J.R. *et al.* A study of neuropathy in HIV infection. *Q J Med* 1992, **83**: 473–488.
130. Gulevich, S.J., Kalmijn, J.A., Thal, L.J. *et al.* Sensory testing in human immunodeficiency virus type 1-infected men. *Arch Neurol* 1992, **49**: 1281–1284.
131. De la Monte, S.M., Gabuzda, D.H., Ho, D.D. *et al.* Peripheral neuropathy in the acquired immunodeficiency syndrome. *Ann Neurol* 1988, **23**: 485–492.
132. Freeman, R., Roberts, M.S., Friedman, L.S. & Broadbridge, C. Autonomic function and human immunodeficiency virus infections. *Neurology* 1990, **40**: 575–580.
133. So, Y.T., Holtzman, D.M., Abrams, D.I. & Olney, R.K. Peripheral neuropathy associated with acquired immunodeficiency syndrome. *Arch Neurol* 1988, **45**: 945–948.
134. Petty, R.K.H. & Kennedy, P.G.E. The neurological features of HIV-positive patients in Glasgow – a retrospective study of 90 cases. *Q J Med* 1992, **82**: 223–234.
135. Apostolski, S., McArthur, T., Quattrini, A. *et al.* The gp120 glycoprotein of human immunodeficiency virus type 1 binds to sensory ganglion neurones. *Ann Neurol* 1993, **34**: 855–863.
136. Cornblath, D.R., McArthur, J.C., Kennedy, P.G.E., Witte, A.S. & Griffin, J.W. Inflammatory demyelinating peripheral neuropathies associated with human T-cell lymphotropic virus type III infection. *Ann Neurol* 1987, **21**: 32–40.
137. Fuller, G.N., Jacobs, J.N. & Guilloff, R.J. Association of painful peripheral neuropathy in AIDS with cytomegalovirus infection. *Lancet* 1989, **2**: 937–941.
138. Said, G., Lacroix, C., Chemouilli, P. *et al.* Cytomegalovirus neuropathy in acquired immunodeficiency syndrome: a clinical and pathological study. *Ann Neurol* 1991, **29**: 139–146.
139. Miller, R.G., Storey, J.R. & Greco, C.M. Ganciclovir in the treatment of progressive AIDS-related polyradiculopathy. *Neurology* 1990, **40**: 569–574.

140. Gray, F., Chretien, F., Lescs, M.C., Scaravelli, F. & Vintners, H.V. Varicella-zoster virus infection in the central nervous system in AIDS. *Clin Neuropath* 1993, **12** (Suppl 1): S11.
141. Goldstein, J.M., Azizi, S.A., Booss, J. & Vollmer, T.L. Human immunodeficiency virus-associated motor axonal polyradiculopathy. *Arch Neurol* 1993, **50**: 1316–1319.
142. Huang, P.P., Chin, R., Song, S. & Lasoff, S. Lower motor neurone dysfunction associated with human immunodeficiency virus infection. *Arch Neurol* 1993, **50**: 1328–1330.
143. Moyle, G.J., Nelson, M.R., Hawkins, D. & Gazzard, B.G. The use and toxicity of didanosine (ddI) in HIV antibody-positive individuals intolerant to zidovudine (AZT). *Q J Med* 1993, **86**: 155–163.
144. Dubinsky, R.M., Yarchoan, R., Dalakas, M. & Broder, S. Reversible axonal neuropathy from the treatment of AIDS and related disorders with 2,3-dideoxycytidine (ddC). *Muscle Nerve* 1989, **12**: 856–860.
145. Simpson, D.M. & Bender, A.N. Human immunodeficiency virus-associated myopathy: analysis of 11 patients. *Ann Neurol* 1988, **24**: 79–84.
146. Dalakas, M.C. & Pezeshkpour, G.H. Neuromuscular diseases associated with human immunodeficiency infection. *Ann Neurol* 1988, **23** (Suppl): S38–S48.
147. Illa, I., Nath, A. & Dalakas, M. Immunocytochemical and virological characteristics of HIV-associated inflammatory myopathies: similarities with seronegative polymyositis. *Ann Neurol* 1991, **29**: 474–481.
148. Lane, R.J.M., McLean, K.A., Moss, J. & Woodrow, D.F. Myopathy in HIV infection: the role of zidovudine and the significance of tubuloreticular inclusions. *Neuropathol Appl Neurobiol* 1993, **19**: 406–413.
149. Pezeshkpour, G., Illa, I. & Dalakas, M.C. Ultrastructural characteristics and DNA immunocytochemistry in human immunodeficiency virus and Zidovudine associated myopathies. *Hum Pathol* 1991, **22**: 1281–1288.
150. Till, M. & MacDonell, K.B. Myopathy with human immunodeficiency virus type 1 (HIV-1) infection: HIV-1 or Zidovudine. *Ann Intern Med* 1990, **113**: 492–494.
151. Lamperth, L., Dalakas, M.C., Dagani, F. *et al.* Abnormal skeletal and cardiac mitochondria induced by Zidovudine (AZT) in human muscle in vitro and in an animal model. *Lab Invest* 1991, **65**: 742–751.
152. Herzberg, N.H., Zorn, I., Zwart, R. *et al.* Major growth reduction and minor decrease in mitochondrial enzyme activity in cultured human muscle cells after exposure to Zidovudine. *Muscle Nerve* 1992, **15**: 706–710.
153. Lewis, W., Gonzalez, B., Chomyn, A. & Papoian, T. Zidovudine induces molecular, biochemical and ultrastructural changes in rat skeletal muscle mitochondria. *J Clin Invest* 1992, **89**: 1354–1360.
154. Weissman, J.D., Constantinitis, I., Hudgins, P. & Wallace, D.C. ³¹P magnetic resonance spectroscopy suggests impaired mitochondrial function in AZT-treated patients. *Neurology* 1992, **42**: 519–523.
155. Dalakas, M.C., Illa, I., Pezeshkpour, G.H. *et al.* Mitochondrial myopathy caused by long term Zidovudine therapy. *N Engl J Med* 1990, **322**: 1098–1105.
156. Peters, B.S., Winer, J., Landon, D.N., Stotter, A. & Pinching, A.J. Mitochondrial myopathy associated with chronic zidovudine therapy in AIDS. *Q J Med* 1993, **86**: 5–15.
157. Grau, J.M., Masanes, F., Pedrol, E. *et al.* Human immunodeficiency virus type 1 infection and myopathy: clinical relevance of Zidovudine therapy. *Ann Neurol* 1993, **34**: 206–211.
158. Chalmers, A.C., Greco, C.M. & Miller, R.G. Prognosis in AZT myopathy. *Neurology* 1991, **41**: 1181–1184.
159. Mhiri, C., Baudrimont, M., Bonne, G. *et al.* Zidovudine myopathy: a distinctive disorder associated with mitochondrial dysfunction. *Ann Neurol* 1991, **29**: 606–614.
160. Lange, D.J. Neuromuscular diseases associated with HIV-1 infection. *Muscle Nerve* 1994, **17**: 16–30.
161. Connolly, S., Manji, H., McAllister, R.H. *et al.* Long latency event-related potentials in asymptomatic Human Immunodeficiency virus type 1 infection. *Ann Neurol* 1994, **35**: 189–196.
162. Manji, H., Connolly, S., McAllister, R.H. *et al.* Serial MRI of the brain in asymptomatic patients infected with HIV: results from the UCMSM/Medical Research Council neurology cohort. *J Neurol Neurosurg Psychiatr* 1994, **57**: 144–149.