

THE NEUROLOGY OF HIV INFECTION

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Since the onset of the AIDS pandemic in 1981, infection with the human immunodeficiency virus (HIV) has spread exponentially throughout the world with currently an estimated 40 million adults and children affected. Worldwide there are approximately 16 000 new infections per day. Every day 8000 HIV infected patients die. In the UK, there are currently about 50 000 individuals living with HIV/AIDS.

Since the introduction of highly active anti-retroviral therapy (HAART), in communities where this is available, HIV/AIDS has become a chronic disorder with dramatic reductions in mortality and morbidity both from the effects of HIV itself as well as from opportunistic infections and tumours.

In the UK, the clinician will encounter two broad groups of patients. The first group comprises individuals who have been infected with HIV for a number of years and are receiving HAART. This group is composed largely of homosexual men and those who acquired their infection in the UK. The second group consists of patients who present with opportunistic infections and tumours and who have late stage HIV infection. This is a situation that was previously encountered in the late 1980s and early 1990s. This cohort largely consists of men and women infected by heterosexual intercourse outside Europe.

CLINICAL AND PRACTICAL ASPECTS

HIV is neuro-invasive (with invasion occurring early in the course of the infection), neuro-virulent (causing a neuropathy, myopathy, myelopathy, and dementia), but it is not especially neurotrophic. The virus is rarely isolated from neurones either in the peripheral or central nervous system. Productive infection is usually found within the associated inflammatory infiltrate, predominantly macrophages.

Since all areas of the neuro-axis in an HIV infected individual may be affected by different aetiological agents, the clinical assessment of this group of patients may be more complex than assessment of the immune competent patient—the principle of “Ocam’s Razor” may not be applicable (table 1). Furthermore, dual infections frequently co-exist in the immunosuppressed population and this must be borne in mind when following up patients and in assessing a treatment response. For example, one study from Kenya showed that additional infection occurred in 18% of cases of tuberculous meningitis.

A symptomatic glandular fever-like syndrome occurs in up to 70% of cases at HIV seroconversion. In 10% this may be associated with neurological symptoms and signs—for example, an aseptic meningitis, encephalitis, acute disseminated encephalomyelitis, transverse myelitis, polymyositis, brachial neuritis or a cauda equina syndrome. Guillain Barré syndrome has been described at seroconversion and also during the asymptomatic immunocompetent phase of HIV infection; however, whereas usually CSF examination shows evidence of cytoalbuminaemic dissociation, in HIV infected individuals, there is a pleocytosis.

During the asymptomatic phase of HIV infection, when there is no clinically apparent immunosuppression, there is no evidence of neurological compromise either in the central (CNS) or peripheral nervous systems. This has been determined by a number of large cohort studies using clinical, neurophysiological, neuropsychological, and magnetic resonance imaging (MRI) methods of assessment. However, before the introduction of HAART, in up to 5% of cases HIV dementia was the AIDS defining illness; thus HIV infection should be considered in any patient, especially below the age of 50 years, presenting with cognitive dysfunction. HIV infection should also enter in the differential diagnosis of “young stroke” since it may be associated with a vasculitis or a thrombophilic state with detectable anticardiolipin antibodies and lupus anticoagulant.

There may be clues to underlying HIV infection that will be found on careful general history and examination— pyrexia of unknown origin (PUO), unexplained weight loss or diarrhoea, generalised lymphadenopathy, oral hairy leucoplakia, oral candidiasis, seborrhoeic dermatitis, molluscum contagiosum, Kaposi’s sarcoma (which may only be present on the hard palate), or

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Table 1 Common neurological complications of HIV-1 infection

- ▶ Due to HIV
 - Distal sensory peripheral neuropathy (DSPN)
 - HIV dementia (HAD)
 - Vacuolar myelopathy (usually in association with HAD)
 - HIV polymyositis
- ▶ Opportunistic infections
 - Toxoplasmosis
 - Cryptococcal meningitis
 - Tuberculosis—meningitis, abscesses, tuberculoma
 - Cytomegalovirus (CMV) encephalitis, retinitis, lumbar polyradiculopathy, vasculitic peripheral neuropathy
 - Progressive multifocal leucoencephalopathy (PML)
- ▶ Tumours
 - Primary CNS lymphoma
 - Metastatic systemic lymphoma
- ▶ Drug related complications
 - Peripheral neuropathy caused by ddl, ddC and d4T; isoniazid
 - Myopathy (zidovudine)

cotton wool spots on fundoscopy. Investigations may show an unexplained thrombo- or lymphopaemia, or an elevated erythrocyte sedimentation rate due to the polyclonal hypergammaglobulinaemia associated with HIV infection. Brain imaging studies may reveal unexplained cerebral atrophy.

Cerebrospinal examination may be abnormal even in asymptomatic HIV infected patients. A mild cerebrospinal fluid (CSF) pleocytosis, an elevated CSF protein, and oligoclonal bands can all be found in such patients. On the other hand, as a result of HIV induced immunosuppression, the CSF cytochemical parameters may be entirely normal. The diagnosis of meningitic and encephalitic disorders therefore relies on specific tests on CSF such as the detection of cryptococcal antigen (by latex agglutination—CrAg) for cryptococcal

meningitis or CSF VDRL (venereal disease research laboratory) in suspected neurosyphilis (a negative test does not exclude the diagnosis, whereas a non-reactive CSF-FTA (fluorescent treponemal antibody) does exclude active infection).

Before HAART, the CD4 count was a useful guide in attempting to determine the specific aetiologies of the opportunistic infections and tumours. For example, toxoplasmosis and cryptococcal meningitis occur with CD4 counts below 200 cells/mm³; CMV retinitis, encephalitis, and polyradiculopathy occur with CD4 counts < 50 cells/mm³. Following institution of HAART, there is usually a rise in peripheral blood CD4 counts, although these cells may not all be fully functional (since some of the antigen specific clones are lost). HAART has led to a number of complications hitherto not encountered in HIV medicine. These include immune reconstitution inflammatory syndrome (IRIS) which has been defined as a paradoxical deterioration in clinical status attributable to recovery of the immune system. Clinically, within a few weeks of starting treatment there may be an exacerbation or an unusual manifestation of a specific infection. Neurological reconstitution syndromes described include progressive multifocal leucoencephalopathy (PML), cryptococcal meningitis, and cytomegalovirus (CMV) syndromes such as encephalitis and retinitis.

More recently, a rare, severe leucoencephalopathy has been described in patients who failed treatment with HAART.

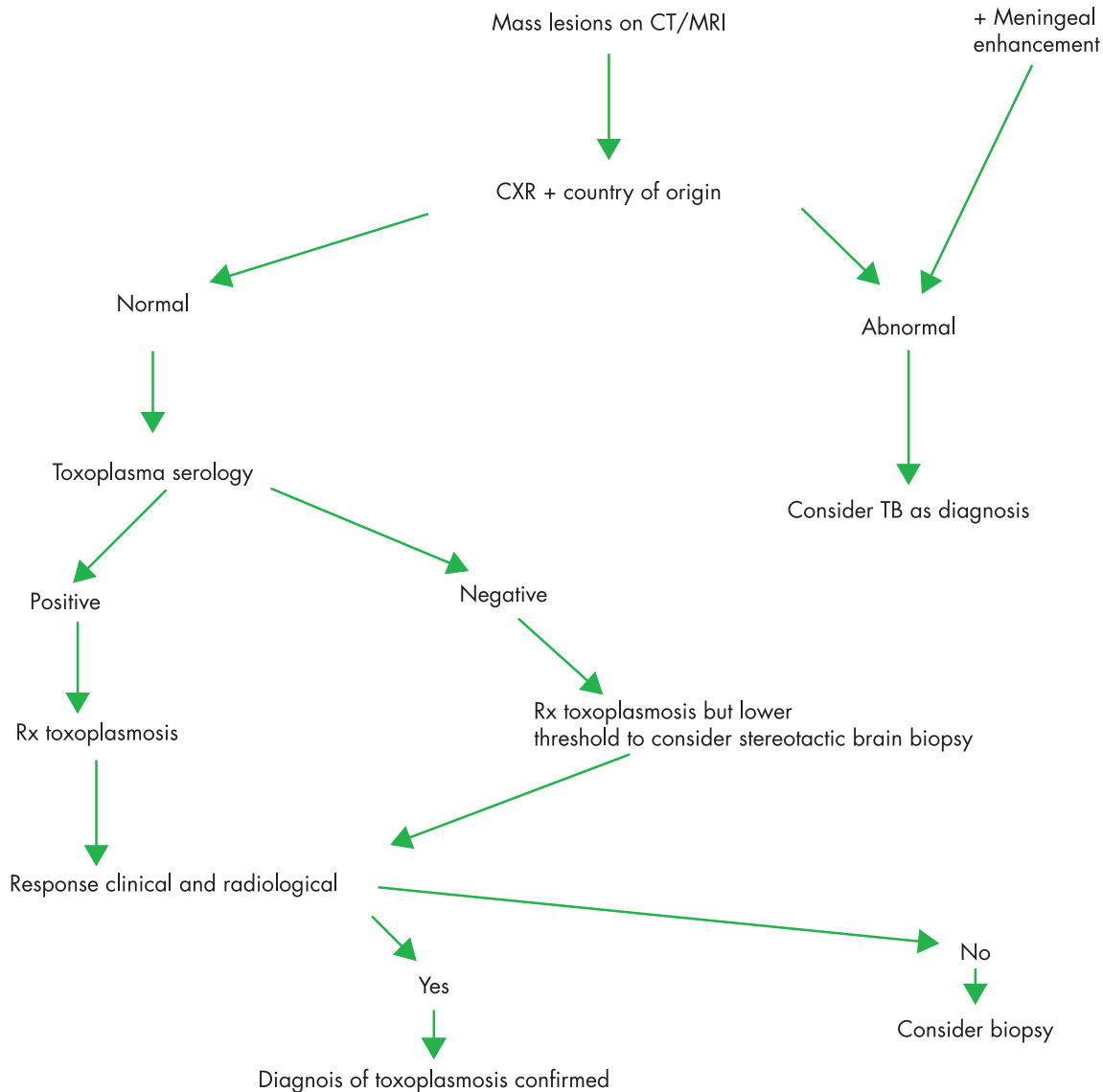
MANAGEMENT OF MASS LESIONS

In the context of significant immunosuppression (CD4 < 200/mm³), the most common causes of mass lesions are toxoplasmosis, primary CNS lymphoma (PCNSL), and tuberculous granulomata or tuberculous abscesses (fig 1). Although brain biopsy remains the gold standard, with increasing experience standard management protocols have been developed. An

Table 2 Drug treatment regimens for the common CNS infections

Infection	Side effects
Toxoplasmosis	
<i>Acute phase (for 6 weeks)</i>	
First line treatment:	
Pyrimethamine loading dose (100 mg orally for 3 days, then 75 mg/day)	Marrow suppression
+	
Sulfadiazine 6–8 g/day orally/iv	Rash, nephrotoxicity, marrow suppression
+	
Folinic acid 15 mg/day	
Second line treatment:	
Clindamycin 600–900 mg/day by mouth/iv instead of sulfadiazine	Rash, diarrhoea
<i>Maintenance treatment</i>	
Pyrimethamine 25–50 mg/day	
+	
Sulfadiazine 2–4 g/day	
+	
Folinic acid 10 mg/day	
Clindamycin 600 mg/day instead of sulfadiazine	
Cryptococcal meningitis	
<i>Acute phase treatment for 4–6 weeks or until CSF culture negative</i>	
Amphotericin B 0.7–1.0 mg/kg/day (via central line)	Nephrotoxicity, anaemia, hepatitis, marrow suppression
±	
Flucytosine 100–150 mg/kg/day orally	
<i>In milder cases</i>	
Fluconazole 400 mg iv/orally	Rash, hepatitis
<i>Maintenance treatment</i>	
Fluconazole 200–400 mg/day orally	

Stopping maintenance may be considered if after HAART is started the CD4 count remains above 200/mm³ for over four months.



Notes

1. MRI preferred as more sensitive.
2. If there are signs and symptoms of raised intracranial pressure, treat with dexamethasone 4 mg four times daily initially. Once the patient is stable, gradually tail off. Improvement on steroids may be due to the reduction of cerebral oedema or the partial response of lymphoma to corticosteroids.
3. At least two weeks maybe necessary to assess for a response to anti-toxoplasmosis therapy. In some cases, providing there is no urgency, one may need to wait one month.

Figure 1 Management of mass lesions (CD4 count < 200/mm³).

overall assessment using data from serological and radiological investigations may help in differentiating between the possible aetiologies. The country of origin may also be helpful, particularly with respect to the likelihood of tuberculosis and to a lesser extent toxoplasmosis. However, even in areas where tuberculosis is endemic, the most common cause of a mass lesion(s) is toxoplasmosis. See table 2 for the drug treatment regimens for toxoplasmosis.

Toxoplasma serology

In HIV, toxoplasmosis is almost always a reactivation and serology is positive in 85% of cases. Seronegative cases occur as a result of loss of antibody with increasing immunosuppression or rarely a primary infection. The prevalence of

previous exposure in a population varies worldwide and reflects dietary habits with respect to eating undercooked meat—in France > 90% compared to 35% in the UK.

Radiological studies

Toxoplasmosis usually causes multiple lesions located at the grey/white interface or involves the basal ganglia. A single lesion on MRI is more likely to be due to PCNSL as is a lesion adjacent to the ventricles (fig 2). Tuberculous abscesses have similar imaging appearances to toxoplasmosis, whereas tuberculomata tend to be smaller lesions with less mass effect (fig 3) The chest x ray is abnormal in up to 60% of cases with CNS tuberculosis. PML does not produce mass effect.

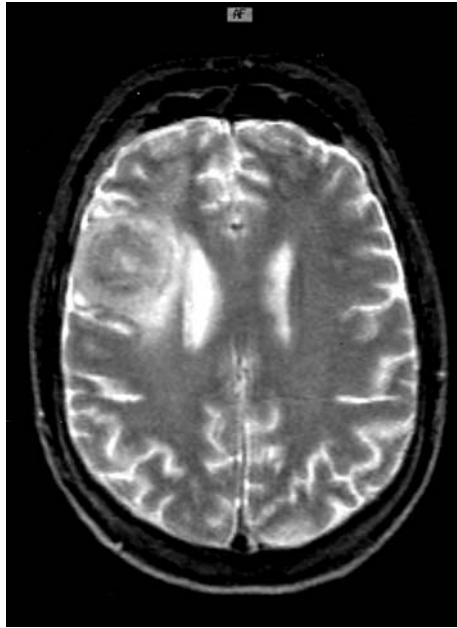


Figure 2 Primary CNS lymphoma (PCNSL): single lesion adjacent to the lateral ventricle.

Thallium SPECT scans

Thallium SPECT (single photon emission computed tomography) scans may help differentiate between abscesses and lymphoma—there is increased uptake in the latter but false negatives and positives occur.

CSF examination

Lumbar puncture is usually contraindicated in most patients with lesions causing mass effect. However, if there are no contraindications, CSF studies are useful in the diagnosis of PCNSL. The detection of Epstein-Barr virus (EBV) by polymerase chain reaction (PCR) is diagnostic as this tumour

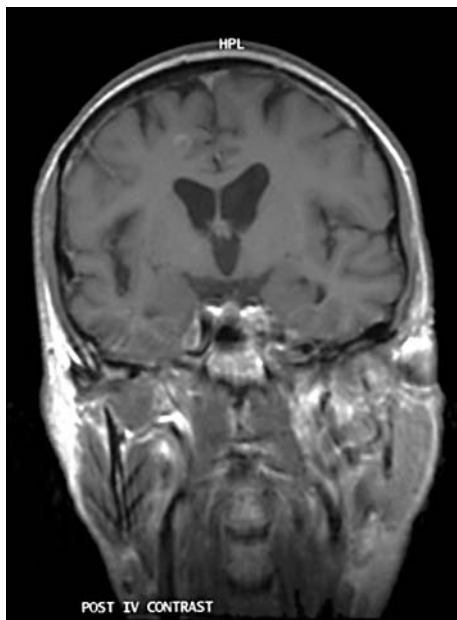


Figure 3 A small ring enhancing lesion is more suggestive of a tuberculoma, as seen on this contrast enhanced coronal MRI.

Table 3 Prognostic markers for cryptococcal meningitis

- ▶ Abnormal mental status
- ▶ CSF opening pressure >25 cm CSF
- ▶ CSF cryptococcal antigen titre >1:1024
- ▶ CSF white cell count <20 cells/ μ l
- ▶ Extra-neural culture of cryptococcus

is EBV “driven”; PCR for *Mycobacterium tuberculosis* is positive in 60% of tuberculous abscesses, and granulomata may occur in association with a tuberculous meningitis.

CRYPTOCOCCAL MENINGITIS

Before the introduction of HAART, meningitis caused by *Cryptococcus neoformans* was a common complication in patients with CD4 counts below 100/mm³. This ubiquitous organism is particularly found in the excreta of pigeons. Pulmonary infection, usually asymptomatic, occurs by inhalation followed by haematogenous spread to the meninges. Patients present with a short history of headache, fever, nausea, and vomiting. Only one third of patients will have the classic features of meningism—photophobia, neck stiffness, and a positive Kernig’s sign. The threshold for performing brain imaging studies followed by CSF examination should be low in HIV infected patients presenting with non-specific symptoms such as mild headache.

In 20% of cases there may be evidence of extraneurological involvement with diffuse pulmonary infiltrates, lobar consolidation or cavitating lesions on chest x ray, skin lesions (small papules which may resemble molluscum contagiosum), and infection of the urinary tract.

Brain imaging is usually normal but may reveal hydrocephalus, cryptococcomas or basal meningeal enhancement.

At lumbar puncture, CSF pressure is frequently elevated. In most cases there is a moderate mononuclear cell pleocytosis, an elevated protein, and a low glucose. In 25% of cases, the CSF may be normal. The diagnosis is established by the identification of India ink positive hyphae in 75% and the detection of cryptococcal antigen in 95% of cases.

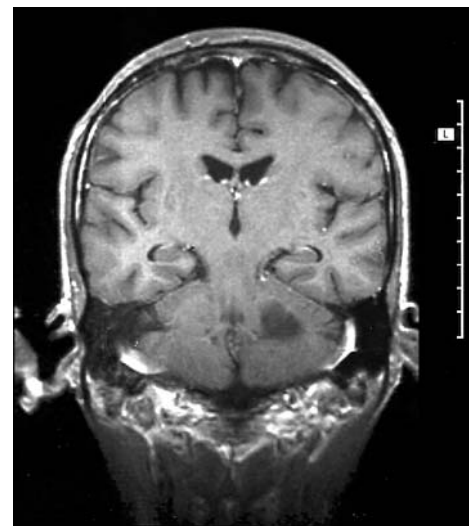


Figure 4 Progressive multifocal leucoencephalopathy: T1 weighted coronal MRI showing a low attenuation lesion in the white matter of the left cerebellar hemisphere.

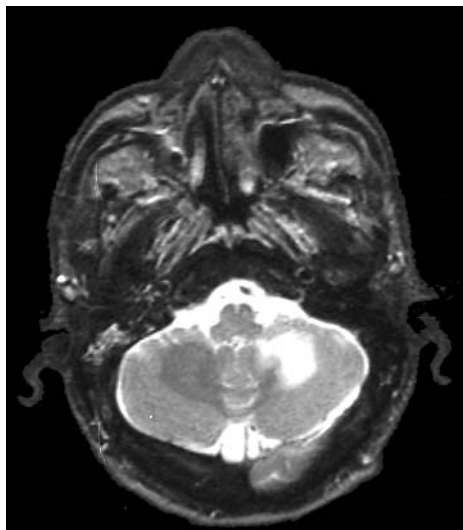


Figure 5 Progressive multifocal leucoencephalopathy: T2 weighted axial MRI showing a high signal lesion within the white matter of the left cerebellar hemisphere.

A number of prognostic markers have been identified (table 3). For drug treatment regimens see table 2.

A complication that needs close vigilance is the development of raised intracranial pressure, unrelated to hydrocephalus, accompanied by loss of vision. This should be managed by repeated lumbar puncture with high volume CSF removal and, when indicated, the placement of a lumbar or ventricular drain. Acetazolamide, but not corticosteroids, has a significant adjunctive role.

PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

PML is caused by the reactivation of the Jamestown Canyon virus (JCV), a common polyoma virus, which infects 75% of the general population. It is usually a mild childhood respiratory tract infection. Cell mediated immunity is the chief predisposing factor for the development of PML, and before the AIDS epidemic was generally encountered in patients with lymphoproliferative disorders or those treated with immunosuppressive drugs—for example post-transplant surgery and sarcoidosis.

Abbreviations

CMV: cytomegalovirus
CNS: central nervous system
CT: computed tomography
EBV: Epstein-Barr virus
DSPN: distal sensory peripheral neuropathy
HAART: highly active anti-retroviral therapy
HAD: HIV dementia
HIV: human immunodeficiency virus
JCV: Jamestown Canyon virus
MRI: magnetic resonance imaging
NCT: nerve conduction tests
NRTI: nucleoside reverse transcriptase inhibitor
PCNSL: primary CNS lymphoma
PCR: polymerase chain reaction
PML: progressive multifocal leucoencephalopathy

Neurology of HIV infection: key points

- ▶ Neurological complications are seen at all stages of HIV infection
- ▶ Many of the neurological complications of HIV are treatable
- ▶ Ocam's Razor does not apply in assessment of HIV patients
- ▶ Highly active anti-retroviral therapy has substantially altered the patterns of neurological disease in patients with HIV

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HIV induced immunosuppression currently accounts for 85% of cases of PML. Before HAART, 5% of AIDS patients developed PML with CD4 counts usually below 100/mm³. After HAART, although the incidence of most neurological complications such as HIV dementia have declined, it is not clear whether there has been a similar reduction in PML. However, it does seem that PML is more prevalent in HIV infection than expected—underlying reasons may be related to increased activation of JCV by the HIV proteins. The pathological changes result from replication of the virus within the oligodendrocytes, causing lysis and demyelination. It is unclear whether PML within the CNS results from reactivation of the virus following immunosuppression or is caused by invasion of the CNS by infected lymphocytes from the peripheral circulation.

The clinical presentation is subacute with a progressive hemiparesis, hemianopia or ataxia. Cognitive dysfunction usually occurs with focal neurological signs. Cortical involvement may occasionally result in dysphasia and seizures. By contrast with other more common causes of focal intracranial lesions in HIV infected patients such as toxoplasmosis, there are usually no symptoms or signs of systemic infection or raised intracranial pressure.

Cranial computed tomography (CT) shows hypodense lesions. Typically, MRI shows large single or multiple lesions involving white matter, with scalloping at the grey/white interface. The parieto-occipital and frontal lobes are most commonly affected. The affected areas are low signal on T1 weighted images (fig 4) and hyperintense on T2 weighted sequences (fig 5). This may help distinguish PML from HIV dementia. There is no mass effect. Some contrast enhancement may be seen which has been identified as a good prognostic marker.

Until recently the diagnosis was only possible by brain biopsy with the histological demonstration of demyelination, enlarged oligodendrocyte nuclei with JCV inclusion particles and bizarre enlarged astrocytes. It is now possible to isolate JCV-DNA in the CSF by PCR with a sensitivity of 75% and almost complete specificity. It may be necessary to repeat the CSF examination in PCR negative cases (raising the yield to 85%) before considering stereotactic brain biopsy.

The treatment of PML in patients with HIV is two pronged: improving the underlying immunosuppression with HAART, and anti-JCV therapy. Institution of the former has resulted in fourfold prolongation of survival, with patients' neurological status stabilising or even improving.

A number of drugs have been shown to have anti-JCV activity and have been tried with variable success. Cytosine arabinoside (AraC) given intravenously or intrathecally confers no significant benefit. The use of α interferon was prompted by its antiviral and immune enhancing effect in a

Table 4 HAART related drug toxicities

Drug	Toxicity
<i>Nucleoside reverse transcriptase inhibitors (NRTIs)</i>	
Class associated	Lactic acidosis, hepatic steatosis, lipodystrophy
Drug specific	
Zidovudine	Myelosuppression, myopathy
Stavudine (d4T)	Peripheral neuropathy
Zalcitabine (ddC)	Peripheral neuropathy
Didanosine (ddl)	Peripheral neuropathy, pancreatitis
Lamivudine (3TC)	? Neuropathy
<i>Non-NRTIs</i>	
Efavirenz	Dysphoria, mood changes, vivid dreams, hypercholesterolaemia
Nevirapine	Hepatitis, Stevens-Johnson syndrome
<i>Protease inhibitors</i>	
Class associated	Lipodystrophy, hyperlipidaemia, diabetes
Drug specific	
Nefinavir	Diarrhoea
Indinavir	Nephrolithiasis
Ritonavir	Perioral dysaesthesia, flushing, diarrhoea, hyperuricaemia
Amprenavir	Diarrhoea
Lopinavir	Diarrhoea

pre-HAART retrospective open labelled observational study. About one third of patients showed some neurological benefit with some also showing radiological improvement.

The anti-CMV drug cidofovir used in conjunction with HAART has shown, in a number of small studies, increased neurological improvement or stability when compared to HAART alone. There was also faster clearance of the virus from the CSF. However, others have failed to confirm this finding. Cidofovir has a number of serious side effects: nephrotoxicity due to a dose dependent renal tubular acidosis, neutropenia, and ocular hypotonia. The results of larger, better controlled studies are awaited.

A number of other drugs that are also currently undergoing study include topotecan and chlorpromazine, both of which suppress replication of JCV in vitro.

HIV DEMENTIA

Prior to HAART, HIV developed in 20% of patients with AIDS. The risk factors identified included low CD4 count, high plasma viral load, older age group, intravenous drug use, female sex, and constitutional symptoms such as anaemia. Since HAART, the incidence of HAD has been reduced by 50% although the prevalence has increased as a result of improved survival.

The clinical features of HIV dementia (HAD) in the early stages may be mild with symptoms of poor concentration, mental slowing, and apathy which may mimic depression. Later on, as the syndrome progresses, more specific cognitive changes develop with memory loss and personality change associated with motor and sphincter difficulties as a result of an associated vacuolar myelopathy. Examination may show impaired saccadic eye movements, generalised hyperreflexia, and cerebellar and frontal release signs.

Investigations are indicated to exclude other causes—MRI typically shows evidence of atrophy and diffuse white matter signal changes. The CSF shows non-specific cytochemical abnormalities but must be examined for conditions such as neurosyphilis, CMV, and PML. The CSF viral load correlates with severity of the dementia. However, this test is not sensitive enough for diagnostic purposes.

Neuropsychological assessment typically shows abnormalities in the following cognitive domains: psychomotor speed,

attention, frontal lobe function, and verbal and non-verbal memory.

Pre-HAART, the mean survival rate for patients with HAD was one year. Since HAART, most patients stabilise or improve. Although there are concerns as to whether the various antiretroviral drugs actually cross the blood–brain barrier, no specific HAART regimen has been shown to be superior in the management of HAD. Adjuvant treatments such as selegine and memantine are under trial.

PERIPHERAL NERVE COMPLICATIONS

Whereas there has been a decline in other neurological complications, the incidence and prevalence of peripheral neuropathy has increased as a result of increased longevity and the use of neurotoxic antiretroviral therapies.

The most common peripheral nerve disorder encountered due to HIV is a distal sensory peripheral neuropathy (DSPN). The prevalence rate pre-HAART was estimated to be around 35% and at necropsy, 95% of patients had sural nerve pathological abnormalities.

Risk factors for the development of DSPN include higher HIV viral load and lower CD4 counts. Patients with other neuropathic risk factors such as diabetes, excess alcohol intake, and genetic neuropathies may be more liable to develop the complication.

The presentation is with ‘painful, numb feet’. A significant proportion of patients complain of hyperpathia. There is little or no weakness and the upper limbs are usually not involved. Abnormal neurological signs include depressed or absent reflexes and impaired sensation to pain and temperature characteristic of a small fibre neuropathy. Nerve conduction tests (NCT) may be normal or show mild axonal abnormalities. Thermal thresholds are abnormal.

Since clinically DSPN is reasonably well defined further investigations are usually not necessary. It seems prudent to check a random blood glucose and a vitamin B12 value. In cases where on examination there are signs of significant weakness—such as a foot drop or presence of prominent upper limb involvement—NCT and nerve biopsy should be considered to exclude vasculitis, demyelinating neuropathies, and lymphomatous infiltration.

The nucleoside reverse transcriptase inhibitors (NRTIs) didanosine (ddI), zalcitabine (ddC), and stavudine (d4T) have all been shown to cause a dose dependent peripheral neuropathy (table 4). The association with lamivudine (3TC) is less well documented. Zidovudine causes a myopathy when used in high doses but does not cause a neuropathy. Mitochondrial toxicity from inhibition of DNA polymerase may be the underlying mechanism for NRTI related side effects. The same mechanism could also account for the other side effects with this class of drug—pancreatitis, fulminant hepatic failure, and lactic acidosis. Abnormal fat distribution (lipodystrophy), in which there is fat wasting around the buttocks, face, and limbs, and internal viscera disposition with distension, is associated with both NRTIs and protease inhibitors.

The clinical presentation of these antiretroviral drug related neuropathies is similar to that seen with DSPN. However, the drug related neuropathies are more likely to be painful, have an abrupt onset, and rapidly progress. After stopping the culprit antiretroviral drug, there may be a paradoxical worsening of neuropathic symptoms over a period of 4–8 weeks (“coasting”). An improvement of symptoms can be expected in some but not all as some may be left with the underlying DSPN that has been unmasked by the drug treatment.

The risk of neuropathy is increased when combinations of drugs are used—for example, when hydroxyurea is used to potentiate the antiretroviral effects of ddI and d4T. The risk of isoniazid induced neuropathy is higher when used in combination with the antiretroviral drugs.

As with the treatment of painful sensory neuropathy in general, the management of this group of patients can be difficult. The development of a painful sensory neuropathy is a significant cause of morbidity and poor drug compliance. If the patient is on one of the three neurotoxic drugs (ddI, ddC or d4T), the issue of stopping the drug needs to be discussed with the patient and their HIV physician. In practice, this may be a difficult decision, especially if there has been a good virological response and CD4 has significantly risen. Also lowering the dose of an offending drug raises the possibilities of HIV viral resistance.

The drugs used in the symptomatic treatment of DSPN and the antiretroviral related neuropathies are those used in all painful neuropathies. Gabapentin, which has been shown to be effective in diabetic neuropathy, is first line treatment although there are no published data to date in HIV related neuropathies. A starting dose of 300 mg at night can be gradually increased to 300 mg three times daily. A maximum dose of up to 2.4 g per day should be tried if tolerated. There is no interaction with the antiretroviral drugs which is an important consideration when introducing any new drug in this group of patients. Lamotrigine has been shown to reduce pain scores in a small placebo controlled trial. The starting dose was 25 mg/day for two weeks gradually titrating the dose to 150 mg daily. Other drugs that merit consideration include amitriptyline, starting at 10 mg at night, even though one trial failed to show any group benefit.

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