Human immunodeficiency virus associated central nervous system infections

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Practical Neurology, 2005, 5, 334–349

INTRODUCTION
Neurological disease is common in human immunodeficiency virus (HIV) infected individuals, affecting 39–70% of symptomatic patients (Janssen 1997; Simpson & Tagliati 1994). In advanced disease, involvement of the central nervous system (CNS) is a frequent problem and may be due to HIV infection itself, or may be caused by opportunistic pathogens or malignancies. The presentations of these disorders are overlapping and non-specific. The prompt diagnosis of potentially treatable CNS opportunistic infections is crucial, but is often limited by the lack of diagnostic tests of sufficient sensitivity and specificity, particularly in the developing world. Furthermore, treatment may be complicated by the need to treat the HIV infection in addition to the opportunistic infection. The optimal time to initiate antiretroviral therapy in CNS opportunistic infections remains unknown (Torok et al. 2005). In the developed world, the introduction of highly active antiretroviral therapy (HAART) has altered the epidemiology of these diseases (Maschke et al. 2000; Sacktor et al. 2001; Sacktor 2002). However, in developing countries, where the vast majority of HIV infections occur, CNS opportunistic infections are often the presenting feature of HIV infection and are a major burden to the health care sector. This review focuses on the epidemiology, pathology, clinical features, diagnosis and management of six common HIV-associated CNS infections.

CEREBRAL TOXOPLASMOSIS
Toxoplasmosis is a zoonotic disease caused by Toxoplasma gondii, an obligate intracellular protozoan. The definitive host is the cat, which excretes T. gondii oocysts in its faeces. Humans or other animals may ingest these, resulting in the release of tachyzoites in the intestine. Tachyzoites enter the blood stream, disseminate and encyst within various tissues, with a predilection for the eye, brain, myocardium, lung and skeletal muscle. Primary infection in humans is acquired by ingesting oocysts in cat litter or soil, or by ingesting tissue cysts in undercooked red meat. It is usually asymptomatic and the organism remains quiescent, with clinical infection only emerging when the host becomes immunocompromised.

Epidemiology
The seroprevalence of antibodies to T. gondii varies depending on geographical region and...
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Socio-economic group, and is 10–50% in HIV-infected individuals (Luft & Remington 1992; Cohen 1999). The frequency of symptomatic toxoplasma encephalitis varies from 25% to 50% of latently infected HIV patients, in the absence of antimicrobial prophylaxis (Cohen 1999). Cerebral toxoplasmosis was originally the most common CNS opportunistic infection in acquired immune deficiency syndrome (AIDS) patients (Simpson & Tagliati 1994). However, the incidence and associated mortality in the West have decreased with the introduction of HAART and antimicrobial prophylaxis (Abgrall et al. 2001). Disease is rare among patients with a CD4+ T-lymphocyte count > 200 cells/µL; the greatest risk is in patients with CD4 counts of < 50 cells/µL (Luft et al. 1984; Wong et al. 1984).

Pathology
The predominate neuropathological feature of cerebral toxoplasmosis is a necrotizing encephalitis. Lesions may be uni- or multifocal, and variable in size, and are most commonly located in the frontal and parietal regions of the brain, particularly in the cortico-medullary regions, and in the basal ganglia. However, they may occur throughout the brain, including the grey and white matter.

Clinical features
Patients present subacutely with headache, fever, psychomotor or behavioural changes, confusion, lethargy, hemiparesis, ataxia and cranial nerve palsies (Porter & Sande 1992; Renold et al. 1992). Seizures may occur, and about half the patients have focal neurological symptoms and signs (Murray 1999). 10% of patients may present with a diffuse encephalitis without any visible focal lesions on brain imaging (Luft & Remington 1992). Choroidoretinitis, pneumonia and evidence of multiorgan involvement may occur with disseminated infection, but are rare in the HIV-infected population.

Diagnosis
The definitive diagnosis of cerebral toxoplasmosis requires direct demonstration of the tachyzoite form in a biopsy specimen of the brain. However, in practice, a presumptive diagnosis can be made on the basis of a combination of clinical and radiological features, supported by serological tests and a response to empirical anti-toxoplasma therapy (Fig. 1) (Murray 1999). Cerebrospinal fluid (CSF) examination is unhelpful as it may be normal, or demonstrate pleocytosis, an elevated protein level or decreased glucose level (Renold et al. 1992). Serum anti-toxoplasma antibodies are usually detectable in patients with cerebral toxoplasmosis, but may be absent in advanced HIV infection (Grant et al. 1990; Hellerbrand et al. 1996; Raffi et al. 1997). Changes in antibody titre are unreliable in distinguishing acute infection from reactivation, or for following the course of the disease (Sadler et al. 1998). However, detection
of anti-toxoplasma antibodies in the CSF may be a useful adjunct in the diagnosis, but the sensitivity is only 69% (Potasman et al. 1988). Molecular methods, such as the use of polymerase chain reaction (PCR) amplification of T. gondii DNA in the CSF, have been disappointing.

Radiological features

Imaging of the brain typically shows multiple ring enhancing lesions, oedema and mass effect (Sadler et al. 1998). However, these appearances may vary, with about one-third of patients having only a single lesion (Fig. 2) (Porter & Sande 1992; Renold et al. 1992; Luft et al. 1993). MRI appears to be more sensitive than CT (Levy & Rothholtz 1997). The absence of increased uptake in mass lesions on single photon emission computed tomography (SPECT), and decreased activity on positron emission tomography (PET), are reported to be characteristic of toxoplasma encephalitis, but this technology is irrelevant in the developing world, and indeed in most advanced countries too (Pierce et al. 1995; Ruiz et al. 1997).

Acute treatment

Treatment of cerebral toxoplasmosis is usually initiated on presumptive diagnosis: clinical and radiological features, along with anti-toxoplasma IgG antibody in the serum in a patient with a CD4+ T-lymphocyte count of < 200 cells/µL. Brain biopsy is recommended for patients who do not fulfil the criteria for presumptive diagnosis, or who fail to respond to empirical therapy (Holloway & Mushlin 1996).

Cerebral toxoplasmosis is usually treated with combination chemotherapy. First line therapy is high-dose pyrimethamine and sulfadiazine for 6 weeks, followed by maintenance therapy (Table 1) (Benson et al. 2004). The most common adverse effect of pyrimethamine is dose-related bone marrow suppression, which can be prevented by folinic acid supplementation. Unfortunately, up to 40% of patients with AIDS-associated cerebral toxoplasmosis are unable to tolerate sulfonamides. In such patients, pyrimethamine and clindamycin may be used, although this is somewhat less effective. Three other regimens have been shown to be effective in non-randomized trials:

- atovaquone plus pyrimethamine;
- atovaquone plus sulfadiazine;
- azithromycin plus pyrimethamine.

In addition, the following regimens have been reported to have activity in small cohorts of patients or case reports:

- pyrimethamine plus clarithromycin;
- 5-fluorouracil plus clindamycin;
- dapsone plus pyrimethamine;
- doxycycline or minocycline plus pyrimethamine or sulfadiazine or clarithromycin.

Acute therapy should be continued for at least 6 weeks, or longer if clinical or radiological disease is extensive, or response is incomplete. Most patients respond promptly to appropriate therapy; 86% will show clinical improvement by day 7 and 95% will show radiographic improvement by day 14 of treatment (Porter & Sande 1992; Luft et al. 1993). Patients should have repeat brain imaging after 2 weeks to confirm response to treatment. In patients who fail to respond, alternative diagnoses should be considered, such as primary CNS lymphoma or progressive multifocal leucoencephalopathy, and brain biopsy performed.
<table>
<thead>
<tr>
<th>Opportunistic infection</th>
<th>Initial treatment</th>
<th>Continuation phase</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Cerebral toxoplasmosis</td>
<td>Pyrimethamine (75–100 mg, daily oral) + sulfadiazine (1–1.5 g oral qds) for 6 weeks.</td>
<td>Pyrimethamine (25–75 mg oral daily) + sulfadiazine (500–1000 mg oral qds), for life or until CD4 count remains &gt; 200 in patients on HAART.</td>
<td>Pyrimethamine causes bone marrow suppression; folinic acid, 10–15 mg/day is given to prevent this. For patients with sulfa allergy use alternative second drug, e.g. clindamycin.</td>
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<tr>
<td>Cryptococcal meningitis</td>
<td>Amphotericin B (0.7–1 mg/kg/day iv) + flucytosine (25 mg/kg oral qds) for 2 weeks followed by fluconazole 400 mg oral daily for 8 weeks.</td>
<td>Fluconazole 200 mg oral daily, for life, or until CD4 count remains &gt; 100 in patients on HAART.</td>
<td>Regular lumbar punctures are often required to relieve symptomatic raised intracranial pressure.</td>
</tr>
<tr>
<td>Tuberculous meningitis</td>
<td>Rifampicin 10 mg/kg/day (max 600 mg) oral + isoniazid 5 mg/kg/day (max 300 mg) oral, + pyrazinamide 15–30 mg/kg/day (max 2 g) oral and ethambutol 15–25 mg/kg/day (max 1.6 g) oral or streptomycin 15 mg/kg/day (max 1 g) im for 2 months.</td>
<td>Rifampicin 10 mg/kg/day (max 600 mg) oral and isoniazid 5 mg/kg/day (max 300 mg) oral for 10 months.</td>
<td>Optimum drug regimens and duration are unknown. Drug regimen may need to be modified according to mycobacterial drug resistance patterns or interactions with antiretrovirals. In particular, protease inhibitors should not be given with rifampicin (seek expert advice).</td>
</tr>
<tr>
<td>Primary central nervous system lymphoma</td>
<td>No specific treatment.</td>
<td></td>
<td>Radiotherapy improves symptoms, slightly improves survival. HAART prolongs survival.</td>
</tr>
<tr>
<td>Progressive multifocal leucoencephalopathy</td>
<td>No specific treatment.</td>
<td></td>
<td>Cytosine arabinoside and cidofovir have been investigated.</td>
</tr>
<tr>
<td>CMV encephalitis</td>
<td>No specific treatment.</td>
<td></td>
<td>Ganciclovir and foscarnet have been investigated.</td>
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Adjuvant corticosteroids may be administered when clinically indicated (e.g., focal lesions with mass effect or associated oedema), but should be discontinued as soon as is clinically feasible because of the risk of developing other opportunistic infections. Anti-epileptic drugs should be given to patients with a history of seizures, and continued at least through the period of acute therapy.

**Maintenance therapy**

Because pyrimethamine-based regimens are not active against the tissue form of the parasite, discontinuation of treatment almost invariably results in recrudescence of encephalitis (Luft & Remington 1992), necessitating maintenance therapy. The simplest approach is to continue primary therapy at a lower dose or pyrimethamine–clindamycin (Table 1) (Centers for Disease Control and Prevention 2004). Alternative regimens include:

- pyrimethamine and sulphadiazine;
- pyrimethamine and atovaquone (alone or in combination);
- pyrimethamine with one of clarithromycin or azithromycin or dapsone.

This treatment should be continued for life or until the CD4+ T-lymphocyte count is consistently above 200 cells/µL in patients on HAART (Benson et al. 2004).

**CRYPTOCOCCAL MENINGITIS**

Cryptococcus neoformans is a dimorphic fungus that is acquired from the environment by inhalation. Although there are three varietal forms, virtually all HIV-1 associated cryptococcal infections are caused by C. neoformans var neoformans.

**Epidemiology**

Cryptococcal meningitis is the most common manifestation of systemic fungal infection and the third most frequent neurological complication in patients with AIDS (Leenders et al. 1994; Sanchez-Portocarrero & Perez-Cecilia 1997; Oursler et al. 1999). 5–10% of HIV-infected patients will develop it as an AIDS defining illness (Fessler et al. 1998). The incidence has declined substantially with the use of HAART. The disease typically affects patients with a CD4+ T-lymphocyte count of < 50 cells/µL.

**Pathology**

It is not clear whether cryptococcal meningitis occurs as a result of dissemination of acute infection, or reactivation of latent infection. Immunoreconstitution secondary to HAART may unmask latent infection and precipitate meningitis (Woods et al. 1998). The organism reproduces by budding and develops a large polysaccharide capsule that inhibits phagocytosis and may impair leucocyte migration (Laurenson et al. 1998). Pathological examination reveals basal non-exudative chronic meningitis. Microabscesses and cryptococcomas may develop, usually in the basal ganglia region. Co-infection with other opportunistic pathogens has also been described (Silber et al. 1998). For unknown reasons, raised intracranial pressure (ICP) occurs in > 50% of HIV-infected patients with cryptococcal meningitis, without necessarily any accompanying hydrocephalus or cerebral oedema (Fessler et al. 1998; Saag et al. 2000).

**Clinical features**

The disorder usually presents as a subacute meningitis or meningoencephalitis. Patients develop fever, headache, altered mental status, nausea and vomiting. Classical meningeal signs such as neck stiffness and photophobia occur in approximately one-third of patients (Saag et al. 2000), and focal neurological signs and seizures in about 10% (Fig. 3) (Wright et al. 1997). Disseminated disease with pulmonary involvement and/or skin lesions is relatively common.

**Diagnosis**

Definitive diagnosis is based on culture and identification of the organism from the CSF. The opening pressure is usually elevated, > 200 mm CSF in 75% of patients. CSF changes are rela-
atively minor (mononuclear pleocytosis but usually no more than 20 cells/mm³, raised protein, low glucose), and may even be normal (Katz et al. 1989; Levy & Rothholtz 1997). The India ink stain shows encapsulated yeasts and has 80% sensitivity (Fig. 4) (Gal et al. 1987; Wang & Carm 2001; Metta et al. 2002). CSF should be tested for cryptococcal antigen and a titre above 1 : 8 is considered presumptive evidence of infection (Zeind et al. 1996). Serum cryptococcal antigen is positive in > 99% of cases of AIDS-related cryptococcal meningitis, usually at titres above 1 : 1024 (Saag et al. 2000). Up to 75% of patients with HIV-associated cryptococcal meningitis have positive blood cultures.

**Radiological features**

Brain scans may be normal in 50% of patients. The most common abnormality is hydrocephalus but there may be other non-specific changes that mimic those of tuberculous meningitis. Occasionally, cryptococcomas may be seen (Post et al. 1985; Rodesch et al. 1989; Khan et al. 1996; Boska et al. 2004).

**Treatment**

Treatment is with intravenous amphotericin B in combination with fluconazole for 2 weeks, followed by fluconazole for 8 weeks (Table 1) (Saag et al. 2000; Benson et al. 2004). This approach is associated with a case fatality of < 10% and a mycological response of approximately 70% (van der Horst et al. 1997; Saag et al. 2000). The addition of fluconazole does not improve immediate outcome but reduces the risk of relapse (van der Horst et al. 1997; Saag et al. 2000). Lipid formulations of amphotericin are efficacious and less nephrotoxic, but considerably more expensive and their optimal doses have not been determined (Leenders et al. 1997). Itraconazole is an alternative to fluconazole as follow-on therapy, although less effective (Wang et al. 1995; Saag et al. 1999).

Fluconazole and fluconazole are effective in treating HIV-associated disease but are more toxic than amphotericin and fluconazole, and only recommended in patients who are unable to tolerate or who are unresponsive to standard treatment (Larsen et al. 1994). One study has shown that amphotericin and fluconazole have superior fungicidal activity to amphotericin alone, amphotericin plus fluconazole, or triple therapy (Brouwer et al. 2004). A larger comparative study of combination anti-fungals with clinical outcomes is underway.

Raised ICP may cause clinical deterioration despite microbiological response (van der Horst et al. 1997; Graybill et al. 2000). For this reason, the Infectious Diseases Society of America (IDSA) recommends daily lumbar punctures to reduce symptomatic raised ICP. Lumbar drains or lumbar–peritoneal shunts may be useful in patients with raised ICP refractory to serial lumbar punctures (Fessler et al. 1998).

Treatment failure is defined as clinical deterioration despite appropriate therapy, lack of improvement after 2 weeks of appropriate therapy, or relapse after initial clinical response. A repeat lumbar puncture should be performed to assess CSF pressure and constituents. The optimal therapy for those with treatment failure is unknown. Higher doses of fluconazole in combination with fluconazole may be helpful. Voriconazole has in vitro activity against Cryptococcus spp. and may be an alternative.

Even after successful therapy, relapse occurs in 25–60% of patients unless long-term maintenance therapy is used. Fluconazole is superior to itraconazole in this setting (Saag et al. 1999). An alternative maintenance therapy is intermittent amphotericin, but this is less effective (Powderly et al. 1992). There is increasing evidence that secondary prophylaxis can be discontinued in patients who respond to HAART (Martinez et al. 2000; Vibhagool et al. 2003).

**Figure 4** India ink stain of cerebrospinal fluid showing encapsulated cryptococci.
TUBERCULOUS MENINGITIS

Tuberculous meningitis (TBM) is the most severe form of infection with *Mycobacterium tuberculosis*, causing death or disability in more than half of those affected (Garg 1999). HIV infection increases an individual’s risk of developing all forms of tuberculosis, in particular extra-pulmonary disease including TBM (Bergenguer et al. 1992).

Pathology

Tubercle bacilli enter the host lung by inhalation of infectious droplet nuclei and invade the pulmonary alveolar macrophages. Local infection develops within the lung and disseminates to the regional lymph nodes producing the ‘primary complex’. During this stage, there may be a short but significant bacteraemia that can seed tubercle bacilli to other organs in the body. In those who develop TBM, bacilli seed to the meninges or brain parenchyma forming subpial and subependymal Rich foci (Rich & McCordock 1933). Rupture of a Rich focus into the subarachnoid space heralds the onset of meningitis. Three processes produce the neurological complications: adhesion formation, an obliterative vasculitis, and an encephalitis or myelitis (Dastur et al. 1995). Oedema can be marked throughout both cerebral hemispheres, contributing to raised intracranial pressure and consequent neurological deficit.

Clinical features

The clinical features of TBM are non-specific and include fever, headache, neck stiffness, coma, cranial nerve palsies and urinary retention with a lymphocytic CSF, raised protein and low glucose (Fig. 5). A recent retrospective study of 251 Vietnamese adults identified five features that were predictive of TBM as opposed to bacterial meningitis: age, duration of history, blood white cell count, CSF white cell count and CSF neutrophil percentage. A diagnostic rule developed from these features was 88% sensitive and 79% specific when applied to a further 75 patients (Thwaites et al. 2002a). This rule has yet to be validated in HIV-infected patients.

There are limited data describing the influence of HIV infection on TBM (Karstaedt et al. 1998; Katrak et al. 2000). A recent prospective study (Thwaites, personal communication) showed that HIV infection did not alter the neurological presentation of TBM, although survival was significantly reduced.

Radiological features

More than half the patients with TBM have a chest X-ray consistent with active or previous pulmonary tuberculosis (Girgis et al. 1998). A small proportion of patients have a miliary appearance. The CT brain scan features of TBM are: hydrocephalus (more common in children than adults), basal meningeal enhancement and tuberculomas (Fig. 6). Other features include parenchymal enhancement, cerebral infarcts, and focal and diffuse brain oedema (Bhargava et al. 1982; Bullock & Welchman 1982; Teoh et al. 1989; Hsieh et al. 1992; Kumar et al. 1996; Ozates et al. 2000).

Diagnosis

The diagnosis of TBM depends on the detection of *M. tuberculosis* in CSF by microscopy or culture. Despite the advent of molecular methods, the demonstration of acid-fast bacilli in CSF is the gold standard.

Figure 5 Right III cranial nerve palsy in a patient with tuberculous meningitis.

Figure 6 CT or MRI brain scan showing tuberculomas as ring-enhancing lesions.

Figure 7 Ziehl–Neelsen smear of cerebrospinal fluid showing acid-fast bacilli (pink).
the CSF by the Ziehl–Neelsen stain remains the cornerstone of diagnosis (Fig. 7). Early studies reported about 90% sensitivity of detection by this method (Stewart 1953; Kennedy & Fallon 1979), but these figures have proved difficult to match in routine diagnostic laboratories. Factors that may influence detection include volume of CSF (at least 10 mL are required), speed of sample processing, and meticulous examination of the smear for at least 30 min (Thwaites et al. 2004a). Culture of M. tuberculosis from the CSF is the diagnostic gold standard but takes too long to guide early diagnosis and treatment. M. tuberculosis may be cultured in 3–6 weeks on solid media or, more rapidly, in liquid media. Newer and more rapid culture methods, e.g. microscopic observation drug susceptibility (MODS) assay, may become useful (M oore et al. 2004).

Because of the limitations of traditional culture methods, molecular methods of detecting M. tuberculosis DNA and identifying drug resistance genes have been developed. Although the sensitivity of PCR appears to be similar to that of a meticulously performed CSF smear (Bonington et al. 2000; Thwaites et al. 2004b), the specificity is highly variable. Thus, a positive result should be interpreted within the clinical context before initiating treatment.

Treatment

Despite the availability of highly effective antituberculous chemotherapy, the outcome from TBM still remains poor (Girgis et al. 1998; Hosoglu et al. 2002). Factors associated with poor outcome include convulsions, coma, delayed or interrupted treatment, and HIV infection (Hosoglu et al. 2002).

The treatment of HIV-associated TB is similar to that of other forms of tuberculosis, involving an intensive phase, followed by a continuation phase. However, there are several important differences:

- the potential for drug interactions between rifampicin and anti-retrovirals;
- paradoxical reactions that may be interpreted as clinical worsening;
- the potential for developing acquired rifampicin resistance when treated with highly intermittent therapy (Blumberg et al. 2003).

For TBM, the optimal drug regimen and duration of each phase are uncertain. The British Thoracic Society (BTS) and the IDSA both recommend that all patients start on isoniazid, rifampicin and pyrazinamide (Joint Tuberculosis Committee of the British Thoracic Society 1998; Blumberg et al. 2003). The choice of the fourth drug in the intensive phase is more difficult. The BTS recommend streptomycin or ethambutol, the IDSA recommend ethambutol, whereas some centres, notably in South Africa, advocate ethionamide (Donald & Seifart 1989).

HIV-infected patients are more likely to have multidrug-resistant tuberculosis (MDR TB), the treatment of which presents formidable challenges. For MDR pulmonary TB, the World Health Organization (WHO) recommends an aminoglycoside, ethionamide, pyrazinamide and ofloxacin for the initial phase of treatment (Crofton 1987). At present, there are no specific recommendations for MDR TBM, and initial treatment should be broad and include five or six drugs until drug susceptibility results become available. The optimal duration of treatment for TBM is also unknown. While the BTS and IDSA both recommend 12 months, a systematic review has concluded that 6 months of anti-tuberculous drugs is probably sufficient, provided the likelihood of drug resistance is low (van Loenhout-Rooyackers et al. 2001).

A number of investigators have looked at the use of adjunctive corticosteroids in TBM, but many studies were limited by small sample sizes or regimens that did not contain rifampicin (Ashby & Grant 1955; O'Toole et al. 1969; Escobar et al. 1975; Girgis et al. 1983, 1991; Kumarvelu et al. 1994; Dooley et al. 1997). However, a recent large prospective randomized trial has shown a 23% reduction in case fatality, but not in neurological disability, in 545 Vietnamese patients with TBM treated with dexamethasone (0.3–0.4 mg/kg/day tapered over 6–8 weeks) (Thwaites et al. 2004c). In the 96 HIV-infected patients included in the study, dexamethasone appeared to be safe and showed a trend towards benefit, although this was not statistically significant.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Primary central nervous system lymphoma (PCNSL) is an extranodal non-Hodgkin's B-cell malignancy thought to be related to infection with Epstein Barr virus (EBV). EBV DNA can be found in lymphoma cells in nearly 100% of cases of AIDS-related PCNSL (Wang et al. 1995), and lymphoma cells also express EBV nuclear antigen and viral protein LM P-1.

Epidemiology

PCNSL is the second most common cause of
Despite the introduction of HAART, the prevalence of the PCNSL has not decreased to the same extent as other AIDS-related conditions

a focal brain lesion in AIDS patients after toxoplasmosis (Raiz et al. 1998). In the pre-HAART era, 4–7% of patients with neurological complaints had PCNSL diagnosed (Levy et al. 1985; McArthur 1987). Despite the introduction of HAART, the prevalence of PCNSL has not decreased to the same extent as other AIDS-related conditions (Gruilich 1999; Conti et al. 2000). AIDS-related PCNSL is associated with a CD4 T-lymphocyte count of <50 cells/µL (Fine & Mayer 1993; Ruiz et al. 1997; Bower et al. 1999).

Pathology

There are several mechanisms by which EBV infection may result in PCNSL, including the ability of EBV to transform B cells, immune dysregulation and uncontrolled B cell stimulation in late-stage HIV, depletion of EBV-specific CD8+ cells by HIV, and EBV-induced mutations in tumour suppressor genes (Wang et al. 1995; Gaidano et al. 1998; Ciacci et al. 1999).

Most tumours are located supratentorially and are single or, more commonly, multiple (Baumgartner et al. 1990; Fine & Mayer 1993; Ciacci et al. 1999). Lymphomatous meningitis is estimated to occur in 25% of patients (Chamberlain & Kormanik 1999). Almost all PCNSLs are of the high-grade B cell phenotype and follow an aggressive course. Disease outside the CNS is extremely uncommon.

Clinical features

The clinical features include altered mental status, hemiparesis, dysphasia, sensory findings, seizures, cranial nerve palsies and headache. Most patients have constitutional symptoms such as fever, night sweats and weight loss. The mean duration of symptoms before diagnosis is 22–54 days (So et al. 1986; Baumgartner et al. 1990; Goldstein et al. 1991; Fine & Mayer 1993; Chamberlain & Kormanik 1999). Almost all PCNSLs are of the high-grade B cell phenotype and follow an aggressive course. Disease outside the CNS is extremely uncommon.

Radiological features

Brain imaging may reveal single or multiple hypodense lesions that enhance with contrast (usually homogenous but sometimes ring-enhancing), and within exhibit mass effect with surrounding oedema (Fine & Mayer 1993; Ammassari et al. 1998). Lesions are located in the cerebrum, the basal ganglia, the cerebellum and, occasionally, the brain stem. The location of lesions adjacent to CSF pathways (e.g. periventricular, meningeal and corpus callosum) and supradural spread of lesions are characteristic. MRI may be more sensitive than CT in detecting lesions and at distinguishing PCNSL from cerebral toxoplasmosis.

Thallium-201 SPECT and PET have been used to differentiate PCNSL from infectious brain lesions in AIDS patients. Several studies have evaluated the use of thallium-201 SPECT in the diagnosis of PCNSL and have shown a sensitivity and specificity of about 90% (O’M alley et al. 1994; Ruiz et al. 1994; Lorberboym et al. 1996, 1998; Antinori et al. 1997; D’Amico et al. 1997; De La Pen a et al. 1998; Miller et al. 1998; Lee et al. 1999; Skiest et al. 2000). A few studies have used PET to evaluate intracranial mass lesions (Hoffman et al. 1993; Pierce et al. 1995; Villringer et al. 1995; Heald et al. 1996; O’Doherty et al. 1997). The largest of these suggested that lesions with low metabolic activity were due to toxoplasmosis or progressive multifocal leucoencephalopathy (PM L) whereas lesions with high metabolic activity were due to lymphoma (O’Doherty et al. 1997).

Diagnosis

Routine examination of CSF is generally unhelpful except to exclude other diagnoses. The CSF findings are non-specific and include a mild pleocytosis (usually mononuclear) and raised β2-microglobulin, lactate dehydrogenase and protein levels. Cytological examination is positive in 10–30% of HIV-negative patients with non-Hodgkin’s lymphoma but has lower sensitivity in patients with AIDS (So et al. 1986; Fine & Mayer 1993). The association of EBV with PCNSL has led to the suggestion that EBV DNA in the CSF might serve as a tumour marker. This has resulted in the development of PCR-based diagnostic tests (Cinque et al. 1996; Cinigoli et al. 1998), with reported sensitivities and specificities of 50–100% and 94–100%, respectively (Cinque et al. 1997; Weber 1999). A multiplex PCR assay to detect simultaneously EBV DNA and T. gondii DNA has also been developed (Roberts & Storch 1997).

Treatment

In the pre-HAART era the median survival for untreated patients with PCNSL was 1–2.5 months (Goldstein et al. 1991; Fine & Mayer 1993; Cote et al. 1996; Nuckols et al. 1999). Surgical resection does not improve prognosis. External beam radiotherapy is the most commonly used treatment, shrinking the tumour and improving symptoms in 50–70% of patients. However, the median survival benefit is less than 3 months (Baumgartner et al. 1990; Fine & Mayer 1993; Donahue et al. 1995; Cote et al. 1996; Bower et al. 1999; Chamberlain & Kormanik 1999; Nuckols et al. 1999; Skolasky et al. 1999). Chemotherapy has been disappointing but may be a consideration in the future, with improvements in HIV therapy (Jacomet et al. 1997; Chamberlain & Kormanik 1999). Treatment with HAART appears to prolong survival in patients with PCNSL (Jacomet et al. 1997; McGowan & Shah 1998; Skiest & Crosby 2003; Robotin et al. 2004).

PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

PM L is a demyelinating disease of the CNS caused by the JC virus which is ubiquitous and usually acquired asymptomatically in childhood or early adulthood. Serological studies suggest that 70–90% of adults have been infected (Major et al. 1992). The virus remains latent in the kidney, lymphoid tissue and CNS.
Epidemiology
Prior to 1984, AIDS accounted for only 3% of PML cases, most being associated with underlying lymphoproliferative disorders (Krupp et al. 1985). By 1991, three-quarters of PML cases were HIV-associated (Holman et al. 1991). The prevalence of PML has ranged from 0.9 to 1.8% in AIDS patients and 2.4–5.3% at post-mortem (Levy et al. 1985; Krupp et al. 1985; Petito et al. 1986; Berger et al. 1987, 1998; Dworkin et al. 1999; Masliah et al. 2000). One study has suggested that although the incidence of other neurological complications has decreased in the HAART era, the incidence of PML remains static (Sacktor et al. 2001). The CD4+ T-lymphocyte count is typically <100 cells/µL, but may be higher (Berger et al. 1998; Fong & Toma 1995).

Pathology
The JC virus predominantly infects oligodendrocytes and astrocytes, resulting in cell lysis and demyelination. Multifocal demyelinating lesions may occur in any part of the white matter, but most commonly in the frontal, parietal and occipital lobes. Other affected areas include the grey matter, the brain stem, the cerebellar white matter and the white matter tracts of the cervical spinal cord (Thorner & Katz 2001). Immunohistochemistry, in situ hybridization and electron microscopy can be used to demonstrate viral inclusions in oligodendrocytes (Berger & Major 1999). A number of studies have suggested that an interaction between HIV and the JC virus may result in the development of PML (Tada et al. 1990; Chowdhury et al. 1992; Koralnik et al. 2001).

Clinical features
Because of its multifocal nature, PML may present with a wide variety of neurological symptoms. Clinical features include limb weakness and incoordination, abnormal gait, dysarthria, cognitive dysfunction and, less frequently, visual defects, sensory loss, seizures and vertigo. Fever and headache are usually absent. The clinical picture is one of focal neurological deficits, progressive dementia, coma and death. Traditionally the prognosis of PML is poor and most patients die within 1–6 months of diagnosis (Karhalios et al. 1992; Fong & Toma 1995; Berger et al. 1998; Dworkin et al. 1999; Gasnault et al. 1999), although prolonged survival has been reported in a small number of patients (Berger & Mucke 1988).

Radiological features
CT reveals hypodense lesions of the white matter usually without mass effect or contrast enhancement (Fig. 8). When contrast enhancement does occur, it is usually faint and located at the rim of the lesion. MRI is more sensitive and reveals areas of low intensity on T1-weighted images and increased intensity on T2-weighted images (Berger et al. 1998; Post et al. 1999). Lesions are usually multiple and bilateral and may have a scalloped appearance because of involvement of the subcortical white matter. Involvement of the grey matter may occur but only in conjunction with white matter lesions (Post et al. 1999).

Diagnosis
The CSF may reveal a mild mononuclear pleocytosis (generally no more than 20 cells/µL), raised protein and the presence of myelin basic protein. PCR detection of JC virus DNA in the CSF is useful both diagnostically and prognostically with reasonable sensitivity (42–100%) and specificity (95%) (de Luca et al. 1996; Cinque et al. 1997; Weber 1999). Quantification of JC virus DNA in the CSF has been used as a prognostic marker as well as in monitoring response to therapy (Taoufi k et al. 1998; De Luca et al. 1999a; Garcia de Viedma et al. 1999; Yiannoutsos et al. 1999; Giudici et al. 2000). Definitive diagnosis requires a brain biopsy, but this is usually unnecessary in patients with characteristic clinical and radiological features, and a positive PCR for JC virus in the CSF.

Treatment
Several antiviral agents have been evaluated and initial reports suggested a possible benefit of cytosine arabinoside, a nucleoside analogue, but subsequent reports have failed to confirm this (Fong & Toma 1995; Moreno et al. 1996; Hall et al. 1998). Cidofovir, a nucleotide analogue with in vitro activity against JC virus, also appeared to be efficacious (Taoufi k et al. 1998; Brambilla et al. 1999; De Luca et al. 1999b). However, a larger study failed to demonstrate clinical benefit despite clearance of JC virus from the CSF (Gasnault et al. 2001).

Numerous reports have documented improved survival in patients with HIV-associated PML who receive HAART (Baldeweg & Catalan 1997; Baqi et al. 1997; Elliot et al. 1997; Albrecht et al. 1998; Cinque et al. 1998; Miralles et al. 1998; Teofilo et al. 1998; Clifford et al. 1999; Dworkin et al. 1999; Gasnault et al. 1999; Inui et al. 1992; Ferrante et al. 1995; Perrons et al. 1995) and can be reactivated during periods of immunosuppression.
et al. 1999; De Luca et al. 2000; Giudici et al. 2000). One study has shown that the survival in patients who received a protease inhibitor based HAART regimen was almost double that of patients who did not (Tassie et al. 1999). Immune restoration with improvement in CD4 count and clearance of JC virus from the CSF appears to be the underlying mechanism. Thus an effective HAART regimen is currently the mainstay of therapy for HIV-associated PML. However, occasionally PML may develop in patients receiving HAART, and patients with PML may not improve despite an immunological and virological response to HAART. The immune reconstitution inflammatory syndrome (unmasking of latent infection caused by HAART-induced restoration in immune function) has also been described in patients with PML (Collazos et al. 1999).

**CYTOMEGALOVIRUS ENCEPHALITIS**

Cytomegalovirus (CMV) is a DNA virus of the herpes virus family. Primary infection is common in childhood and may be asymptomatic, or presents with a mononucleosis syndrome. The virus becomes latent but may reactivate in the presence of cell-mediated immunosuppression. CMV disease usually occurs with advanced HIV infection (CD4+ T-lymphocyte count < 50 cells/µL) and may result in a number of clinical syndromes, e.g. retinitis, oesophagitis, adrenalitis, colitis, pneumonitis, encephalitis, polyradiculitis, myelitis and peripheral neuropathy.

**Epidemiology**

CMV infection of the brain is found in 12–40% of AIDS patients at post-mortem (Morgello et al. 1987; Burnset et al. 1991; Kureet al. 1991; Holland et al. 1994; Arribas et al. 1996). The significance of this finding is unclear since CMV encephalitis is a relatively rare clinical diagnosis. Furthermore, it is common to have other CNS opportunistic infections present at the time of diagnosis, which makes it difficult to determine the amount of disease specifically attributable to CMV. Most patients with neurological CMV disease have previously had CMV diagnosed at another site (Arribas et al. 1996; Anduze-Faris et al. 2000).

**Pathology**

The neuropathological findings of CMV infection of the CNS include microglial nodules (aggregates of glial cells and macrophages containing cytomegalic inclusion bodies), focal parenchymal necrosis and necrotizing ventriculoencephalitis.

**Clinical features**

Two distinct clinical and neuropathological forms of CMV encephalitis have been described (Mccutchan 1995). The first, encephalitis with dementia, is more common and characterized by subacute dementia with periods of delirium, confusion, apathy and focal neurological deficits (Holland et al. 1994). Autopsy in these patients reveals diffuse microglial nodules in the grey matter of the cortex, basal ganglia, brain stem and cerebellum. The second form, ventriculoencephalitis, presents with a rapidly progressive syndrome of delirium, cranial nerve deficits, nystagmus and ataxia (Kalayjian et al. 1993). Neuropathologically, these patients have areas of necrosis in cranial nerves and the periventricular white matter.

**Radiological features**

Radiographically, there may be diffuse areas of low attenuation in the brain parenchyma on CT and increased signal intensity on T2-weighted MR images. In patients with CMV ventriculoencephalitis, MRI reveals progressive ventricular enlargement and increased periventricular signal, but these findings are not specific for CMV encephalitis.

**Diagnosis**

CSF examination may show pleocytosis, raised protein and low glucose levels, but these changes are too variable and non-specific to be diagnostic (Kalayjian et al. 1993; Holland et al. 1994). Neither serological testing of plasma and CSF, nor CSF culture are useful (Cinque et al. 1997). However, several studies have demonstrated the utility of PCR detection of CMV DNA in the CSF. Although the sensitivity has ranged from 33% to 100% and the specificity from 42% to 100%, in most studies the sensitivity and specificity exceeded 80% and 90%, respectively (Gozlan et al. 1992; Wolf & Spector 1992; Revello et al. 1994). Quantification of CMV DNA in the CSF may be useful as a prognostic marker and serve as a means of monitoring response to antiviral therapy (Cinque et al. 1995; Arribas et al. 1995).

**Treatment**

Treatment of CMV encephalitis with antivirals has been disappointing. Indeed, CMV encephalitis may develop in patients undergoing treatment for CMV disease at other sites (Kalayjian et al. 1993; Berman & Kim 1994; Salazar et al. 1995). Ganciclovir, a guanosine analogue, is the mainstay of therapy but has poor CSF penetration, as well as renal and haematological toxicity, and is associated with poor response rates (Holland et al. 1994; Cinque et al. 1995). Foscarnet, a pyrophosphate analogue, has better CSF penetration and is synergistic with ganciclovir. One study of combined therapy with ganciclovir and foscarnet showed improved survival (median 94 days) compared with historical controls (42 days) (Anduze-Faris et al. 2000). Combination therapy or use of other antivirals such as cidovir may be of benefit, but data from randomized controlled trials are required. The impact of HAART has not been evaluated but it has been shown to be of benefit in patients with CMV retinitis.
SUMMARY
- Opportunistic infections of the central nervous system remain common complications of advanced HIV disease.
- The advent of HAART has reduced the incidence of these complications in the developed world, but they remain a common cause of morbidity and mortality in the developing world.
- Diagnosis is often presumptive and based on clinical features, as CSF abnormalities and radiological features are often non-specific.
- Molecular diagnostic assays exist, but these may be hampered by poor sensitivity and specificity, lack of availability outside specialist centres, and high cost.
- Diagnostic algorithms based on simple clinical and laboratory features need to be developed for use in resource-limited settings.
- Treatment of CNS opportunistic infections may be complicated because of the need to treat HIV infection in addition to the opportunistic infection; the evidence base for the present guidelines is imperfect.
- The optimum time to initiate HAART in patients presenting with CNS opportunistic infections remains unknown, and prospective data from randomized, controlled trials are urgently required.

ACKNOWLEDGEMENTS
M. E. Torok is a Wellcome Trust Research Training Fellow. I thank Jeremy Farrar for stimulating discussions and critical reading of the manuscript. This article was reviewed by Dr Hadi M anji, London.

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