Human immunodeficiency virus associated opportunistic infections of the central nervous system

M. E. Torok

Clinical Research Fellow, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, 190 Ben Ham Tu, District 5, Ho Chi Minh City, Vietnam; E-mail: etorok@hcm.vnn.vn
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 replicate within any nucleated cell, then encyst in 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

Immunodeficiency virus associated opportunistic system infections

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 predominant 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

Figure 1 Diagnostic algorithm for HIV-associated CNS infections. CRAG, cryptococcal antigen; ZN, Ziehl-Neelsen.

Figure 2 CT brain scan showing contrast-enhancing ring lesion in the right frontal lobe in cerebral toxoplasmosis. © JN Day.

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/ μ L. 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 sulphonamides. 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 1 Treatment for HIV-associated CNS infections

Opportunistic infection	Initial treatment	Continuation phase	Comments
Cerebral toxoplasmosis (<i>Toxoplasma gondii</i>)	Pyrimethamine (75–100 mg, daily oral) + sulfadiazine (1–1.5 g oral qds) for 6 weeks.	Pyrimethamine (25–75 mg oral daily) + sulfadiazine (500–1000 mg oral qds), for life or until CD4 count remains > 200 in patients on HAART.	Pyrimethamine causes bone marrow suppression; folic acid, 10–15 mg/day is given to prevent this. For patients with sulfa allergy use alternative second drug, e.g. clindamycin.
Cryptococcal meningitis (<i>Cryptococcus neoformans</i>)	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.	Fluconazole 200 mg oral daily, for life, or until CD4 count remains > 100 in patients on HAART.	Regular lumbar punctures are often required to relieve symptomatic raised intracranial pressure.
Tuberculous meningitis (<i>Mycobacterium tuberculosis</i>)	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 <i>and</i> ethambutol 15–25 mg/kg/day (max 1.6 g) oral <i>or</i> streptomycin 15 mg/kg/day (max 1 g) im for 2 months.	Rifampicin 10 mg/kg/day (max 600 mg) oral and isoniazid 5 mg/kg/day (max 300 mg) oral for 10 months.	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).
Primary central nervous system lymphoma (Epstein Barr virus)	No specific treatment.		Radiotherapy improves symptoms, slightly improves survival. HAART prolongs survival.
Progressive multifocal leucoencephalopathy (JC virus)	No specific treatment.		Cytosine arabinoside and cidofovir have been investigated.
CMV encephalitis (Cytomegalovirus)	No specific treatment.		Ganciclovir± foscarnet have been investigated.

Adjunctive 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/ μ L 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/ μ L.

Pathology

It is not clear whether cryptococcal meningitis occurs as a result of dissemination of acute infection,

or reactivation of latent infection. Immune reconstitution 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 a 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-

Figure 3 Right VI cranial nerve palsy in a patient with cryptococcal meningitis. © JN Day.

tively 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 flucytosine 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

There is increasing evidence that secondary prophylaxis can be discontinued in patients who respond to HAART

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

of < 10% and a mycological response of approximately 70% (van der Horst *et al.* 1997; Saag *et al.* 2000). The addition of flucytosine 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 flucytosine are effective in treating HIV-associated disease but are more toxic than amphotericin and flucytosine, 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 flucytosine 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 flucytosine 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).

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 (Beren-guer *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; Thwaites *et al.* 2002b). Furthermore, the impact of HIV infection on response to treatment and outcome remains uncertain, as most studies have been too small to demonstrate significant differences in case fatality and have only reported in-hospital assessments (Beren-guer *et al.* 1992; Dube *et al.* 1992; Yechoor *et al.*

1996; 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

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).

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

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 (Moore *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 anti-tuberculous 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 rifamycins 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 size or a regimen 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 LMP-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 (Raez *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 (Grulich 1999; Conti *et al.* 2000). AIDS-related PCNSL is associated with a CD4 T-lymphocyte count of < 50 cells/ μ L (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).

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 supendymal 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'Malley *et al.* 1994; Ruiz *et al.* 1994; Lorberboym *et al.* 1996, 1998; Antinori *et al.* 1997; D'Amico *et al.* 1997; De La Pena *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 (PML) 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 β_2 -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; Cingolani *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

PML is a demyelinating disease of the CNS caused by the JC virus which is ubiquitous and usually acquired asymptotically 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

(Tornatore *et al.* 1992; Ferrante *et al.* 1995; Perrons *et al.* 1995) and can be reactivated during periods of immunosuppression.

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/ μ L, 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 (Karahalios *et al.* 1992; Fong & Toma 1995; Berger *et al.* 1998; Dworkin *et al.* 1999; Gagnault *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).

Figure 8 CT brain scan showing widespread white matter involvement in progressive multifocal leucoencephalopathy.

Diagnosis

The CSF may reveal a mild mononuclear pleocytosis (generally no more than 20 cells/ μ L), 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 (Taoufik *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 (Taoufik *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 (Gagnault *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; Gagnault *et al.* 1999; Inui

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/ μ L) 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; Burns *et al.* 1991; Kure *et 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 cidfovir 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 so 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 Manji, London.

REFERENCES

- Abgrall S, Rabaud C & Costagliola D (2001) Incidence and risk factors for toxoplasmic encephalitis in human immunodeficiency virus-infected patients before and during the highly active antiretroviral therapy era. *Clinical Infection and Disease*, **33**, 1747–55.
- Albrecht H *et al.* (1998) Highly active antiretroviral therapy significantly improves the prognosis of patients with HIV-associated progressive multifocal leukoencephalopathy. *Aids*, **12**, 1149–54.
- Ammassari A *et al.* (1998) Changing disease patterns in focal brain lesion-causing disorders in AIDS. *Journal of Acquired Immune Deficiency Syndrome & Human Retrovirology*, **18**, 365–71.
- Anduze-Faris BM *et al.* (2000) Induction and maintenance therapy of cytomegalovirus central nervous system infection in HIV-infected patients. *Aids*, **14**, 517–24.
- Antinori A *et al.* (1997) Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology*, **48**, 687–94.
- Arribas JR *et al.* (1995) Level of cytomegalovirus (CMV) DNA in cerebrospinal fluid of subjects with AIDS and CMV infection of the central nervous system. *Journal of Infection and Disease*, **172**, 527–31.
- Arribas JR *et al.* (1996) Cytomegalovirus encephalitis. *Annals of Internal Medicine*, **125**, 577–87.
- Ashby M & Grant H (1955) Tuberculous meningitis treated with cortisone. *Lancet*, **268**, 65–6.
- Baldeweg T & Catalan J (1997) Remission of progressive multifocal leukoencephalopathy after antiretroviral therapy. *Lancet*, **349**, 1554–5.
- Baqi M, Kucharczyk W & Walmsley SL (1997) Regression of progressive multifocal encephalopathy with highly active antiretroviral therapy. *Aids*, **11**, 1526–7.
- Baumgartner JE *et al.* (1990) Primary central nervous system lymphomas: natural history and response to radiation therapy in 55 patients with acquired immunodeficiency syndrome. *Journal of Neurosurgery*, **73**, 206–11.
- Benson CA *et al.* (2004) Treating Opportunistic Infections Among HIV-Exposed and Infected Children: Recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR Recommendations and Report*, **53**(RR-15), 1–112.
- Berenguer J *et al.* (1992) Tuberculous meningitis in patients infected with the human immunodeficiency virus. *New England Journal of Medicine*, **326**, 668–72.
- Berger JR *et al.* (1987) Progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. A review of the literature with a report of sixteen cases. *Annals of Internal Medicine*, **107**, 78–87.
- Berger JR & Mucke L (1988) Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. *Neurology*, **38**, 1060–5.
- Berger JR *et al.* (1998) Progressive multifocal leukoencephalopathy in patients with HIV infection. *Journal of Neurovirology*, **4**, 59–68.
- Berger JR & Major EO (1999) Progressive multifocal leukoencephalopathy. *Seminars in Neurology*, **19**, 193–200.
- Berman SM & Kim RC (1994) The development of cytomegalovirus encephalitis in AIDS patients receiving ganciclovir. *American Journal of Medicine*, **96**, 415–9.
- Bhargava S, Gupta AK & Tandon PN (1982) Tuberculous meningitis – a CT study. *British Journal of Radiology*, **55**, 189–96.
- Blumberg HM *et al.* (2003) American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *American Journal of Respiratory Critical Care Medicine*, **167**, 603–62.
- Bonington A *et al.* (2000) TB PCR in the early diagnosis of tuberculous meningitis: evaluation of the Roche semi-automated COBAS Amplicor MTB test with reference to the manual Amplicor MTB PCR test. *Tuberculous Lung Disease*, **80**, 191–6.
- Boska MD *et al.* (2004) Advances in neuroimaging for HIV-1 associated neurological dysfunction: clues to the diagnosis, pathogenesis and therapeutic monitoring. *Current HIV Research*, **2**, 61–78.
- Bower M *et al.* (1999) Treatment outcome in presumed and confirmed AIDS-related primary cerebral lymphoma. *European Journal of Cancer*, **35**, 601–4.
- Brambilla AM *et al.* (1999) Remission of AIDS-associated progressive multifocal leukoencephalopathy after cidofovir therapy. *Journal of Neurology*, **246**, 723–5.
- Brouwer AE *et al.* (2004) Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet*, **363**, 1764–7.
- Bullock MR & Welchman JM (1982) Diagnostic and prognostic features of tuberculous meningitis on CT scanning. *Journal of Neurology, Neurosurgery, & Psychiatry*, **45**, 1098–101.
- Burns DK, Risser RC & White CL 3rd (1991) The neuropathology of human immunodeficiency virus infection. The Dallas, Texas, experience. *Archives of Pathological Laboratory Medicine*, **115**, 1112–24.
- Centers for Disease Control and Prevention. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2004, **53**, no. RR-15.
- Chamberlain MC & Kormanik PA (1999) AIDS-related central nervous system lymphomas. *Journal of Neurooncology*, **43**, 269–76.
- Chowdhury M *et al.* (1992) Evidence that a sequence similar to TAR is important for induction of the JC virus late promoter by human immunodeficiency virus type 1 Tat. *Journal of Virology*, **66**, 7355–61.

- Ciacci JD *et al.* (1999) Lymphoma of the central nervous system in AIDS. *Seminal Neurology*, **19**, 213–21.
- Cingolani A *et al.* (1996) PCR detection of *Toxoplasma gondii* DNA in CSF for the differential diagnosis of AIDS-related focal brain lesions. *Journal of Medical Microbiology*, **45**, 472–6.
- Cingolani A *et al.* (1998) Minimally invasive diagnosis of acquired immunodeficiency syndrome-related primary central nervous system lymphoma. *Journal of the National Cancer Institute*, **90**, 364–9.
- Cinque P *et al.* (1995) Ganciclovir therapy for cytomegalovirus (CMV) infection of the central nervous system in AIDS patients: monitoring by CMV DNA detection in cerebrospinal fluid. *Journal of Infection and Disease*, **171**, 1603–6.
- Cinque P *et al.* (1996) Polymerase chain reaction on cerebrospinal fluid for diagnosis of virus-associated opportunistic diseases of the central nervous system in HIV-infected patients. *Aids*, **10**, 951–8.
- Cinque P *et al.* (1997) Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *Aids*, **11**, 1–17.
- Cinque P, Casari S & Bertelli D (1998) Progressive multifocal leukoencephalopathy, HIV, and highly active antiretroviral therapy. *New England Journal of Medicine*, **339**, 848–9.
- Clifford DB *et al.* (1999) HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology*, **52**, 623–5.
- Cohen BA (1999) Neurologic manifestations of toxoplasmosis in AIDS. *Seminars in Neurology*, **19**, 201–11.
- Collazos J *et al.* (1999) Contrast-enhancing progressive multifocal leukoencephalopathy as an immune reconstitution event in AIDS patients. *Aids*, **13**, 1426–8.
- Conti S *et al.* (2000) Differential impact of combined antiretroviral therapy on the survival of Italian patients with specific AIDS-defining illnesses. *Journal of Acquired Immune Deficiency Syndrome*, **25**, 451–8.
- Cote TR *et al.* (1996) Epidemiology of brain lymphoma among people with or without acquired immunodeficiency syndrome. AIDS/Cancer Study Group. *Journal of the National Cancer Institute*, **88**, 675–9.
- Crofton J (1987) The prevention and management of drug-resistant tuberculosis. *Bulletin of the International Union of Tuberculous Lung Disease*, **62**, 6–11.
- D'Amico A *et al.* (1997) Diagnostic accuracy and predictive value of 201Tl SPET for the differential diagnosis of cerebral lesions in AIDS patients. *Nuclear Medical Communications*, **18**, 741–50.
- Dastur DK, Manghani DK & Udani PM (1995) Pathology and pathogenetic mechanisms in neurotuberculosis. *Radiological Clinical North America*, **33**, 733–52.
- De La Pena RC, Ketonen L & J Villanueva-Meyer (1998) Imaging of brain tumors in AIDS patients by means of dual-isotope thallium-201 and technetium-99m sestamibi single-photon emission tomography. *European Journal of Nuclear Medicine*, **25**, 1404–11.
- De Luca A *et al.* (1996) Improved detection of JC virus DNA in cerebrospinal fluid for diagnosis of AIDS-related progressive multifocal leukoencephalopathy. *Journal of Clinical Microbiology*, **34**, 1343–6.
- De Luca A *et al.* (1999a) Clinical and virological monitoring during treatment with intrathecal cytarabine in patients with AIDS-associated progressive multifocal leukoencephalopathy. *Clinical Infection and Disease*, **28**, 624–8.
- De Luca A *et al.* (1999b) Response to zidovudine after failure of antiretroviral therapy alone in AIDS-associated progressive multifocal leukoencephalopathy. *Neurology*, **52**, 891–2.
- De Luca A *et al.* (2000) The effect of potent antiretroviral therapy and JC virus load in cerebrospinal fluid on clinical outcome of patients with AIDS-associated progressive multifocal leukoencephalopathy. *Journal of Infection and Disease*, **182**, 1077–83.
- Donahue BR, Sullivan JW & Cooper JS (1995) Additional experience with empiric radiotherapy for presumed human immunodeficiency virus-associated primary central nervous system lymphoma. *Cancer*, **76**, 328–32.
- Donald PR & Seifart HI (1989) Cerebrospinal fluid concentrations of ethionamide in children with tuberculous meningitis. *Journal of Pediatrics*, **115**, 483–6.
- Dooley DP, Carpenter JL & Rademacher S (1997) Adjunctive corticosteroid therapy for tuberculosis: a critical reappraisal of the literature. *Clinical Infection and Disease*, **25**, 872–87.
- Dube MP, Holtom PD & Larsen RA (1992) Tuberculous meningitis in patients with and without human immunodeficiency virus infection. *American Journal of Medicine*, **93**, 520–4.
- Dworkin MS *et al.* (1999) Progressive multifocal leukoencephalopathy: improved survival of human immunodeficiency virus-infected patients in the protease inhibitor era. *Journal of Infection and Disease*, **180**, 621–5.
- Elliot B *et al.* (1997) 2.5 year remission of AIDS-associated progressive multifocal leukoencephalopathy with combined antiretroviral therapy. *Lancet*, **349**, 850.
- Escobar JA *et al.* (1975) Mortality from tuberculous meningitis reduced by steroid therapy. *Pediatrics*, **56**, 1050–5.
- Ferrante P *et al.* (1995) PCR detection of JC virus DNA in brain tissue from patients with and without progressive multifocal leukoencephalopathy. *Journal of Medical Virology*, **47**, 219–25.
- Fessler RD *et al.* (1998) Management of elevated intracranial pressure in patients with Cryptococcal meningitis. *Journal of Human Immune Deficiency Syndromes and Human Retrovirology*, **17**, 137–42.
- Fine HA & Mayer RJ (1993) Primary central nervous system lymphoma. *Annals of Internal Medicine*, **119**, 1093–104.
- Fong IW & Toma E (1995) The natural history of progressive multifocal leukoencephalopathy in patients with AIDS. Canadian PML Study Group. *Clinical Infection and Disease*, **20**, 1305–10.
- Gaidano G, Carbone A & Dalla-Favera R (1998) Pathogenesis of AIDS-related lymphomas: molecular and histogenetic heterogeneity. *American Journal of Pathology*, **152**, 623–30.
- Gal AA, Evans S & Meyer PR (1987) The clinical laboratory evaluation of cryptococcal infections in the acquired immunodeficiency syndrome. *Diagnosis of Microbiological Infection and Disease*, **7**, 249–54.
- Garcia de Viedma D *et al.* (1999) Dual qualitative–quantitative nested PCR for detection of JC virus in cerebrospinal fluid: high potential for evaluation and monitoring of progressive multifocal leukoencephalopathy in AIDS patients receiving highly active antiretroviral therapy. *Journal of Clinical Microbiology*, **37**, 724–8.
- Garg RK (1999) Tuberculosis of the central nervous system. *Postgraduate Medical Journal*, **75**, 133–40.
- Gasnault J *et al.* (1999) Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy. *Journal of Neurovirology*, **5**, 421–9.
- Gasnault J *et al.* (2001) Zidovudine in AIDS-associated progressive multifocal leukoencephalopathy: a monocenter observational study with clinical and JC virus load monitoring. *Journal of Neurovirology*, **7**, 375–81.
- Girgis NI *et al.* (1983) The use of dexamethasone in preventing ocular complications in tuberculous meningitis. *Transactions of the Royal Society of Tropical Medical Hygiene*, **77**, 658–9.
- Girgis NI *et al.* (1991) Dexamethasone adjunctive treatment for tuberculous meningitis. *Pediatrics Infection and Disease Journal*, **10**, 179–83.
- Girgis NI *et al.* (1998) Tuberculosis meningitis, Abbassia Fever Hospital–Naval Medical Research Unit No. 3–Cairo, Egypt, from 1976 to 1996. *American Journal of Tropical Medical Hygiene*, **58**, 28–34.
- Giudici B *et al.* (2000) Highly active antiretroviral therapy and progressive multifocal leukoencephalopathy: effects on cerebrospinal fluid markers of JC virus replication and immune response. *Clinical Infection and Disease*, **30**, 95–9.
- Goldstein JD *et al.* (1991) Primary central nervous system lymphoma in acquired immune deficiency syndrome. A clinical and pathologic study with results of treatment with radiation. *Cancer*, **67**, 2756–65.
- Gozlan J *et al.* (1992) Rapid detection of cytomegalovirus DNA in cerebrospinal fluid of AIDS patients with neurologic disorders. *Journal of Infection and Disease*, **166**, 1416–21.

- Grant IH *et al.* (1990) Toxoplasma gondii serology in HIV-infected patients: the development of central nervous system toxoplasmosis in AIDS. *Aids*, **4**, 519–21.
- Graybill JR *et al.* (2000) Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. *Clinical Infection and Disease*, **30**, 47–54.
- Grulich AE (1999) AIDS-associated non-Hodgkin's lymphoma in the era of highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndrome*, **21** (Suppl. 1), S27–S30.
- Hall CD *et al.* (1998) Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. *New England Journal of Medicine*, **338**, 1345–51.
- Heald AE *et al.* (1996) Differentiation of central nervous system lesions in AIDS patients using positron emission tomography (PET). *International Journal of STD AIDS*, **7**, 337–46.
- Hellerbrand C, Goebel FD & Disko R (1996) High predictive value of Toxoplasma gondii IgG antibody levels in HIV-infected patients for diagnosis of cerebral toxoplasmosis. *European Journal of Clinical Microbiological Infection and Disease*, **15**, 869–72.
- Hoffman JM *et al.* (1993) FDG-PET in differentiating lymphoma from non-malignant central nervous system lesions in patients with AIDS. *Journal of Nuclear Medicine*, **34**, 567–75.
- Holland NR *et al.* (1994) Cytomegalovirus encephalitis in acquired immunodeficiency syndrome (AIDS). *Neurology*, **44**, 507–14.
- Holloway RG & Mushlin AI (1996) Intracranial mass lesions in acquired immunodeficiency syndrome: using decision analysis to determine the effectiveness of stereotactic brain biopsy. *Neurology*, **46**, 1010–15.
- Holman RC *et al.* (1991) Epidemiology of progressive multifocal leukoencephalopathy in the United States: analysis of national mortality and AIDS surveillance data. *Neurology*, **41**, 1733–6.
- Hosoglu S *et al.* (2002) Predictors of outcome in patients with tuberculous meningitis. *International Journal of Tuberculous Lung Disease*, **6**, 64–70.
- Hsieh FY, Chia LG & Shen WC (1992) Locations of cerebral infarctions in tuberculous meningitis. *Neuroradiology*, **34**, 197–9.
- Inui K *et al.* (1999) Remission of progressive multifocal leukoencephalopathy following highly active antiretroviral therapy in a patient with HIV infection. *Brain and Development*, **21**, 416–9.
- Jacomot C *et al.* (1997) Intravenous methotrexate for primary central nervous system non-Hodgkin's lymphoma in AIDS. *Aids*, **11**, 1725–30.
- Janssen RS (1997) Epidemiology and neuroepidemiology of human immunodeficiency virus infection. In: *AIDS and the Central Nervous System* (ed. Levy RM), pp. 13–37. Lippincott-Raven, Philadelphia.
- Joint Tuberculosis Committee of the British Thoracic Society (1998) Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax*, **53**, 536–48.
- Kalayjian RC *et al.* (1993) Cytomegalovirus ventriculoencephalitis in AIDS. A syndrome with distinct clinical and pathologic features. *Medicine (Baltimore)*, **72**, 67–77.
- Karahalios D *et al.* (1992) Progressive multifocal leukoencephalopathy in patients with HIV infection: lack of impact of early diagnosis by stereotactic brain biopsy. *Journal of Acquired Immune Deficiency Syndrome*, **5**, 1030–8.
- Karstaedt AS *et al.* (1998) Tuberculous meningitis in South African urban adults. *Quarterly Journal of Medicine*, **91**, 743–7.
- Katrak SM *et al.* (2000) The clinical, radiological and pathological profile of tuberculous meningitis in patients with and without human immunodeficiency virus infection. *Journal of Neurological Science*, **181**, 118–26.
- Katz RL *et al.* (1989) Cerebrospinal fluid manifestations of the neurologic complications of human immunodeficiency virus infection. *Acta Cytologica*, **33**, 233–44.
- Kennedy DH & Fallon RJ (1979) Tuberculous meningitis. *Journal of the American Medical Association*, **241**, 264–8.
- Khan ZK *et al.* (1996) Cryptococcosis associated with HIV negative Indian patients and HIV positive Indian blood donors. *Zentralblatt fur Bakteriologie*, **283**, 360–74.
- Koralnik IJ, Du Pasquier RA & Letvin NL (2001) JC virus-specific cytotoxic T lymphocytes in individuals with progressive multifocal leukoencephalopathy. *Journal of Virology*, **75**, 3483–7.
- Krupp LB *et al.* (1985) Progressive multifocal leukoencephalopathy: clinical and radiographic features. *Annals of Neurology*, **17**, 344–9.
- Kumar R *et al.* (1996) Value of CT scan in the diagnosis of meningitis. *Indian Pediatrics*, **33**, 465–8.
- Kumarvelu S *et al.* (1994) Randomized controlled trial of dexamethasone in tuberculous meningitis. *Tuberculous Lung Disease*, **75**, 203–7.
- Kure K *et al.* (1991) Human immunodeficiency virus-1 infection of the nervous system: an autopsy study of 268 adult, pediatric, and fetal brains. *Human Pathology*, **22**, 700–10.
- Larsen RA *et al.* (1994) Fluconazole combined with flucytosine for treatment of cryptococcal meningitis in patients with AIDS. *Clinical Infection and Disease*, **19**, 741–5.
- Laurenson IF, Ross JD & Milne LJ (1998) Microscopy and latex antigen negative cryptococcal meningitis. *Journal of Infection*, **36**, 329–31.
- Lee VW *et al.* (1999) Intracranial mass lesions: sequential thallium and gallium scintigraphy in patients with AIDS. *Radiology*, **211**, 507–12.
- Leenders AC *et al.* (1994) Cryptococcal meningitis in HIV-infected patients. *Aids*, **8**, 1741–3.
- Leenders AC *et al.* (1997) Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. *Aids*, **11**, 1463–71.
- Levy RM, Bredesen DE & Rosenblum ML (1985) Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. *Journal of Neurosurgery*, **62**, 475–95.
- Levy RM & Rothholtz V (1997) HIV-1-related neurologic disorders. Neurosurgical implications. *Neuroimaging Clinics of North America*, **7**, 527–59.
- Lorberboym M *et al.* (1996) Rapid differential diagnosis of cerebral toxoplasmosis and primary central nervous system lymphoma by thallium-201 SPECT. *Journal of Nuclear Medicine*, **37**, 1150–4.
- Lorberboym M *et al.* (1998) Thallium-201 retention in focal intracranial lesions for differential diagnosis of primary lymphoma and nonmalignant lesions in AIDS patients. *Journal of Nuclear Medicine*, **39**, 1366–9.
- Luft BJ *et al.* (1984) Toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome. *Journal of the American Medical Association*, **252**, 913–7.
- Luft BJ & Remington JS (1992) Toxoplasmic encephalitis in AIDS. *Clinical Infection and Disease*, **15**, 211–22.
- Luft BJ *et al.* (1993) Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. Members of the ACTG 077p/ANRS 009 Study Team. *New England Journal of Medicine*, **329**, 995–1000.
- Major EO *et al.* (1992) Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JC virus-induced demyelinating disease of the human brain. *Clinical Microbiological Review*, **5**, 49–73.
- Martinez E *et al.* (2000) Discontinuation of secondary prophylaxis for cryptococcal meningitis in HIV-infected patients responding to highly active antiretroviral therapy. *Aids*, **14**, 2615–7.
- Maschke M *et al.* (2000) Incidence and prevalence of neurological disorders associated with HIV since the introduction of highly active antiretroviral therapy (HAART). *Journal of Neurology, Neurosurgery, & Psychiatry*, **69**, 376–80.
- Masliha E *et al.* (2000) Changes in pathological findings at autopsy in AIDS cases for the last 15 years. *Aids*, **14**, 69–74.
- McArthur J (1987) Neurologic manifestations of AIDS. *Medicine (Baltimore)*, **66**, 407–37.
- McCutchan JA (1995) Cytomegalovirus infections of the nervous system in patients with AIDS. *Clinical Infection and Disease*, **20**, 747–54.
- McGowan JP & Shah S (1998) Long-term remission of AIDS-related primary central nervous system lymphoma associated with highly active antiretroviral therapy. *Aids*, **12**, 952–4.

- Metta HA *et al.* (2002) Disseminated cryptococcosis in patients with AIDS. Clinical, microbiological, and immunological analysis of 51 patients. *Review of Argentinian Microbiology*, **34**, 117–23.
- Miller RF *et al.* (1998) Magnetic resonance imaging, thallium-201 SPET scanning, and laboratory analyses for discrimination of cerebral lymphoma and toxoplasmosis in AIDS. *Sexually Transmitted Infection*, **74**, 258–64.
- Miralles P *et al.* (1998) Treatment of AIDS-associated progressive multifocal leukoencephalopathy with highly active antiretroviral therapy. *Aids*, **12**, 2467–72.
- Moore DA *et al.* (2004) Microscopic observation drug susceptibility assay, a rapid, reliable diagnostic test for multidrug-resistant tuberculosis suitable for use in resource-poor settings. *Journal of Clinical Microbiology*, **42**, 4432–7.
- Moreno S *et al.* (1996) Cytarabine therapy for progressive multifocal leukoencephalopathy in patients with AIDS. *Clinical Infection and Disease*, **23**, 1066–8.
- Morgello S *et al.* (1987) Cytomegalovirus encephalitis in patients with acquired immunodeficiency syndrome: an autopsy study of 30 cases and a review of the literature. *Human Pathology*, **18**, 289–97.
- Murray H (1999) Toxoplasmosis. In: *AIDS Therapy* (ed. Saag M), p. 307–27. Churchill Livingstone, New York.
- Nuckols JD *et al.* (1999) Primary central nervous system lymphomas: a 30-year experience at a single institution. *Modern Pathology*, **12**, 1167–73.
- O'Doherty MJ *et al.* (1997) PET scanning and the human immunodeficiency virus-positive patient. *Journal of Nuclear Medicine*, **38**, 1575–83.
- O'Malley JP *et al.* (1994) Diagnosis of intracranial lymphoma in patients with AIDS: value of 201TI single-photon emission computed tomography. *American Journal of Roentgenology*, **163**, 417–21.
- O'Toole RD *et al.* (1969) Dexamethasone in tuberculous meningitis. Relationship of cerebrospinal fluid effects to therapeutic efficacy. *Annals of Internal Medicine*, **70**, 39–48.
- Oursler KA, Moore RD & Chaisson RE (1999) Risk factors for cryptococcal meningitis in HIV-infected patients. *AIDS and Research Human Retroviruses*, **15**, 625–31.
- Ozates M *et al.* (2000) CT of the brain in tuberculous meningitis. A review of 289 patients. *Acta Radiologica*, **41**, 13–7.
- Perrons CJ *et al.* (1995) Progressive multifocal leukoencephalopathy in patients with AIDS: detection of JC virus DNA in CSF and brain. *Genitourinary Medicine*, **71**, 35–40.
- Petito CK *et al.* (1986) Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. *Journal of Neuropathological Experimental Neurology*, **45**, 635–46.
- Pierce MA *et al.* (1995) Evaluating contrast-enhancing brain lesions in patients with AIDS by using positron emission tomography. *Annals of Internal Medicine*, **123**, 594–8.
- Porter SB & Sande MA (1992) Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *New England Journal of Medicine*, **327**, 1643–8.
- Post MJ *et al.* (1985) Cranial CT in acquired immunodeficiency syndrome: spectrum of diseases and optimal contrast enhancement technique. *American Journal of Roentgenology*, **145**, 929–40.
- Post MJ *et al.* (1999) Progressive multifocal leukoencephalopathy in AIDS: are there any MR findings useful to patient management and predictive of patient survival? AIDS Clinical Trials Group, 243 Team. *American Journal of Neuroradiology*, **20**, 1896–906.
- Potzman I *et al.* (1988) Intrathecal production of antibodies against *Toxoplasma gondii* in patients with toxoplasmic encephalitis and the acquired immunodeficiency syndrome (AIDS). *Annals of Internal Medicine*, **108**, 49–51.
- Powderly WG *et al.* (1992) A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. *New England Journal of Medicine*, **326**, 793–8.
- Raez LE *et al.* (1998) Natural history and prognostic factors for survival in patients with acquired immune deficiency syndrome (AIDS)-related primary central nervous system lymphoma (PCNSL). *Critical Reviews in Oncology*, **9**, 199–208.
- Raffi F *et al.* (1997) A prospective study of criteria for the diagnosis of toxoplasmic encephalitis in 186 AIDS patients. The BIOTOXO Study Group. *Aids*, **11**, 177–84.
- Renold C *et al.* (1992) Toxoplasma encephalitis in patients with the acquired immunodeficiency syndrome. *Medicine (Baltimore)*, **71**, 224–39.
- Revello MG *et al.* (1994) Diagnosis of human cytomegalovirus infection of the nervous system by pp65 detection in polymorphonuclear leukocytes of cerebrospinal fluid from AIDS patients. *Journal of Infection and Disease*, **170**, 1275–9.
- Rich AR & McCordock HA (1933) The pathogenesis of tuberculous meningitis. *Bulletin of the John Hopkins Hospital*, **52**, 5–37.
- Roberts TC & Storch GA (1997) Multiplex PCR for diagnosis of AIDS-related central nervous system lymphoma and toxoplasmosis. *Journal of Clinical Microbiology*, **35**, 268–9.
- Robotin MC *et al.* (2004) Clinical features and predictors of survival of AIDS-related non-Hodgkin's lymphoma in a population-based case series in Sydney, Australia. *HIV Medicine*, **5**, 377–84.
- Rodesch G *et al.* (1989) Nervous system manifestations and neuroradiologic findings in acquired immunodeficiency syndrome (AIDS). *Neuroradiology*, **31**, 33–9.
- Ruiz A *et al.* (1994) Use of thallium-201 brain SPECT to differentiate cerebral lymphoma from toxoplasma encephalitis in AIDS patients. *American Journal of Neuroradiology*, **15**, 1885–94.
- Ruiz A *et al.* (1997) Primary central nervous system lymphoma in patients with AIDS. *Neuroimaging Clinics of North America*, **7**, 281–96.
- Saag MS *et al.* (1999) A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clinical Infection and Disease*, **28**, 291–6.
- Saag MS *et al.* (2000) Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clinical Infection and Disease*, **30**, 710–18.
- Sacktor N *et al.* (2001) HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990–1998. *Neurology*, **56**, 257–60.
- Sacktor N (2002) The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. *Journal of Neurovirology*, **8** (Suppl. 2), 115–21.
- Sadler M, Brink NS & Gazzard BG (1998) Management of intracerebral lesions in patients with HIV: a retrospective study with discussion of diagnostic problems. *Quarterly Journal of Medicine*, **91**, 205–17.
- Salazar A *et al.* (1995) Cytomegalovirus ventriculoencephalitis in AIDS patients. *Scandinavian Journal of Infection and Disease*, **27**, 165–9.
- Sanchez-Portocarrero J & Perez-Cecilia E (1997) Intracerebral mass lesions in patients with human immunodeficiency virus infection and cryptococcal meningitis. *Diagnostic Microbiology and Infectious Diseases*, **29**, 193–8.
- Silber E *et al.* (1998) Dual infective pathology in patients with cryptococcal meningitis. *Neurology*, **51**, 1213–5.
- Simpson DM & Tagliati M (1994) Neurologic manifestations of HIV infection. *Annals of Internal Medicine*, **121**, 769–85.
- Skiest DJ *et al.* (2000) SPECT thallium-201 combined with Toxoplasma serology for the presumptive diagnosis of focal central nervous system mass lesions in patients with AIDS. *Journal of Infection*, **40**, 274–81.
- Skiest DJ & Crosby C (2003) Survival is prolonged by highly active antiretroviral therapy in AIDS patients with primary central nervous system lymphoma. *Aids*, **17**, 1787–93.
- Skolasky RL *et al.* (1999) HIV-associated primary CNS lymphoma and utility of brain biopsy. *Journal of Neurological Science*, **163**, 32–8.
- So YT, Beckstead JH & Davis RL (1986) Primary central nervous system lymphoma in acquired immune deficiency syndrome. a clinical and pathological study. *Annals of Neurology*, **20**, 566–72.

- Stewart SM (1953) The bacteriological diagnosis of tuberculous meningitis. *Journal of Clinical Pathology*, **6**, 241–2.
- Tada H *et al.* (1990) Trans-activation of the JC virus late promoter by the tat protein of type 1 human immunodeficiency virus in glial cells. *Proceedings of the National Academy of Sciences of the USA*, **87**, 3479–83.
- Taoufik Y *et al.* (1998) Prognostic value of JC virus load in cerebrospinal fluid of patients with progressive multifocal leukoencephalopathy. *Journal of Infection and Disease*, **178**, 1816–20.
- Tassie JM *et al.* (1999) Survival improvement of AIDS-related progressive multifocal leukoencephalopathy in the era of protease inhibitors. Clinical Epidemiology Group. French Hospital Database on HIV. *Aids*, **13**, 1881–7.
- Teofilo E *et al.* (1998) Progressive multifocal leukoencephalopathy regression with highly active antiretroviral therapy. *Aids*, **12**, 449.
- Teoh R *et al.* (1989) Clinical correlation of CT changes in 64 Chinese patients with tuberculous meningitis. *Journal of Neurology*, **236**, 48–51.
- Thorner AR & Katz JT (2001) Progressive Multifocal Leukoencephalopathy. *Current Infective Disease Report*, **3**, 352–9.
- Thwaites GE *et al.* (2002a) Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. *Lancet*, **360**, 1287–92.
- Thwaites GE *et al.* (2002b) Isoniazid resistance, mycobacterial genotype and outcome in Vietnamese adults with tuberculous meningitis. *International Journal of Tuberculous Lung Disease*, **6**, 865–71.
- Thwaites GE, Chau TT & Farrar JJ (2004a) Improving the bacteriological diagnosis of tuberculous meningitis. *Journal of Clinical Microbiology*, **42**, 378–9.
- Thwaites GE *et al.* (2004b) Comparison of conventional bacteriology with nucleic acid amplification (amplified mycobacterium direct test) for diagnosis of tuberculous meningitis before and after inception of antituberculosis chemotherapy. *Journal of Clinical Microbiology*, **42**, 996–1002.
- Thwaites GE *et al.* (2004c) Dexamethasone for the treatment of tuberculous meningitis in adults and children. *New England Journal of Medicine*, **351**, 1741–51.
- Tornatore C *et al.* (1992) Detection of JC virus DNA in peripheral lymphocytes from patients with and without progressive multifocal leukoencephalopathy. *Annals of Neurology*, **31**, 454–62.
- Torok ME *et al.* (2005) Immediate or deferred antiretroviral therapy for central nervous system opportunistic infections? *Aids*, **19**, 535–6.
- van der Horst CM *et al.* (1997) Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *New England Journal of Medicine*, **337**, 15–21.
- van Loenhout-Rooyackers JH *et al.* (2001) Tuberculous meningitis: is a 6-month treatment regimen sufficient? *International Journal of Tuberculous Lung Disease*, **5**, 1028–35.
- Vibhagool A *et al.* (2003) Discontinuation of secondary prophylaxis for cryptococcal meningitis in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy: a prospective, multicenter, randomized study. *Clinical Infection and Disease*, **36**, 1329–31.
- Villringer K *et al.* (1995) Differential diagnosis of CNS lesions in AIDS patients by FDG-PET. *Journal of Computer Assisted Tomography*, **19**, 532–6.
- Wang CY, Snow JL & Su WP (1995) Lymphoma associated with human immunodeficiency virus infection. *Mayo Clinical Proceedings*, **70**, 665–72.
- Wang W & Carm AR (2001) Clinical manifestations of AIDS with cryptococcal meningitis. *Chinese Medical Journal (English)*, **114**, 841–3.
- Weber T (1999) Cerebrospinal fluid analysis for the diagnosis of human immunodeficiency virus-related neurologic diseases. *Seminal Neurology*, **19**, 223–33.
- Wolf DG & Spector SA (1992) Diagnosis of human cytomegalovirus central nervous system disease in AIDS patients by DNA amplification from cerebrospinal fluid. *Journal of Infection and Disease*, **166**, 1412–5.
- Wong B *et al.* (1984) Central-nervous-system toxoplasmosis in homosexual men and parenteral drug abusers. *Annals of Internal Medicine*, **100**, 36–42.
- Woods ML 2nd *et al.* (1998) HIV combination therapy: partial immune restitution unmasking latent cryptococcal infection. *Aids*, **12**, 1491–4.
- Wright D, Schneider A & Berger JR (1997) Central nervous system opportunistic infections. *Neuroimaging Clinical North America*, **7**, 513–25.
- Yechoor VK *et al.* (1996) Tuberculous meningitis among adults with and without HIV infection. Experience in an urban public hospital. *Archives of Internal Medicine*, **156**, 1710–6.
- Yiannoutsos CT *et al.* (1999) Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leukoencephalopathy. *Annals of Neurology*, **45**, 816–21.
- Zeind CS *et al.* (1996) Cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. *Pharmacotherapy*, **16**, 547–61.