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Review

Central nervous system infections in individuals with HIV-1 infection

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Opportunistic infections of the central nervous system (CNS) are common complications of advanced immunodeficiency in individuals with human immunodeficiency virus type 1 (HIV-1) infection. Neurological disease is the first manifestation of acquired immunodeficiency syndrome (AIDS) in 10% to 20% of symptomatic HIV-1 infection. Prompt diagnosis and treatment of such disorders is critical. Also, in the era of highly active antiretroviral therapy (HAART), these disease states have changed in presentation and epidemiology. Therefore, we review the epidemiology, pathogenesis, clinical features, diagnosis, and management of five common central nervous system disorders in individuals with HIV-1 infection: toxoplasma encephalitis, primary central nervous system lymphoma, cryptococcal meningitis, cytomegalovirus encephalitis, and progressive multifocal leukoencephalopathy. *Journal of NeuroVirology* (2002) **8,** 158–167.

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Toxoplasma encephalitis

Cerebral toxoplasmosis is the most common cerebral mass lesion in patients with AIDS (Simpson and Tagliati, 1994). In the United States, the seroprevalence for *Toxoplasma gondii* in HIV-1-infected individuals is estimated to be 10% to 40% (Luft and Remington, 1992; Cohen, 1999). The frequency of symptomatic toxoplasma encephalitis (TE) in seropositive HIV-1-infected patients varies from about one fourth to one half of cases in the absence of antimicrobial prophylaxis (Cohen, 1999).

Toxoplasmosis is a parasitic disease that is prevalent worldwide and the majority of primary cases are asymptomatic. Cerebral toxoplasmosis is due to reactivation of latent infection as a result of progressive loss of cellular immunity. Although uncommon, cases of TE in patients with AIDS who are seronegative for *T. gondii* have been reported (Renold *et al*, 1992; Cohen, 1999). In most instances TE develops when the CD4+ T-lymphocyte count falls below 100 cells/μL.

Toxoplasma gondii is an obligate intracellular protozoan that exists in three forms: the oocyst, the tissue cyst, and the tachyzoite. The definitive host of *T. gondii* is the cat. Cats excrete oocysts which sporulate and become infectious tissue cysts. Undercooked pork and lamb are frequently implicated in transmission to humans. The ingested cysts release tachyzoites in the host's intestine. These enter the bloodstream, disseminate, and replicate within any nucleated cell, and destroy new cells until an effective immune response develops. Surviving parasites then encyst in various tissues, with a predeliction to localize in brain, myocardium, lung, skeletal muscle, and retina. The organism remains quiescent for the life of the host, with emergence of clinical infection occurring if the host develops compromise of cellular immunity.

The predominant neuropathologic feature of cerebral toxoplasmosis is a multifocal necrotizing encephalitis. The most common sites of these lesions are the frontal and parietal regions of the brain,

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particularly the cortico-medullary junctions and the basal ganglia. The lesions may also occur in the temporal and occipital regions, cerebellum or thalamus. Both gray and white matter may be involved.

The most frequent clinical manifestations of TE in HIV-1-infected patients are headache, confusion, fever, and lethargy. Seizures may be an initial manifestation; 50% to 60% of patients complain of or demonstrate focal neurological signs (Murray, 1999). Occasionally, TE may also present as a diffuse encephalitis (Renold *et al*, 1992).

Cerebrospinal fluid (CSF) examination in HIV-1-infected patients with TE may be normal, or may demonstrate pleocytosis, an elevated protein level, or hypoglycorrhachia. Serum anti-toxoplasma antibodies are usually detectable in patients with TE, but the changes in antibody titer are unreliable in determining acute reactivation or for following the course of TE (Sadler *et al*, 1998a). Determination of intrathecal production of *T. gondii* antibody may be a useful adjunct in the diagnosis of TE (Potasman *et al*, 1988). The use of polymerase chain reaction (PCR) amplification of *T. gondii* DNA in CSF is a moderately sensitive, but highly specific assay for the diagnosis of TE (Cingolani *et al*, 1996). Computed tomographic (CT) scanning and magnetic resonance imaging (MRI) findings typically include multiple (more than five) lesions with ring contrast enhancement, surrounding edema, and mass effect (Sadler *et al*, 1998a). MRI appears to be more sensitive than CT scan in diagnosing TE (Levy and 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 characteristic of TE (Pierce *et al*, 1995; Ruiz *et al*, 1997). The definitive diagnosis requires direct demonstration of the tachyzoite form of the parasite in involved tissues or in the blood or other fluids.

At present, treatment of TE is usually initiated upon presumptive diagnosis. Such a diagnosis is considered appropriate in patients with less than 200 CD4+ T-lymphocyte cells/μL, anti-toxoplasma IgG antibody in the serum, consistent clinical features, characteristic neuroimaging studies, and response to empiric anti-toxoplasma therapy (Murray, 1999). Brain biopsy is recommended for patients who present with a diagnostic dilemma or do not fulfill the criteria for presumptive treatment.

The mainstay for treatment of TE is combination chemotherapy. The agents of choice at present are sulfadiazine in synergistic combination with pyrimethamine. The most common side effect of pyrimethamine is dose-related bone marrow suppression which is countered by folinic acid supplementation. Unfortunately, up to 40% of patients with AIDS and TE are unable to complete a course of therapy because of adverse reactions to sulfonamides (Danneman *et al*, 1992).

Patients who are unable to tolerate sulfonamides can be treated with a combination of clindamycin and pyrimethamine. The relative efficacy of the pyrimethamine-clindamycin combination was shown to be approximately equal to that of pyrimethamine-sulfadiazine in a randomized trial (Danneman *et al*, 1992). Potential use of clindamycin as a single agent has not been established. Use of azithromycin alone or in combination with pyrimethamine has been reported (Saba *et al*, 1993; Wiselka *et al*, 1996). Studies with other drugs such as dapsone and atovaquone have demonstrated variable results (Murray, 1999).

Because pyrimethamine-sulfadiazine and pyrimethamine-clindamycin are active against the tachyzoite form of *T. gondii*, but not the tissue cyst form, discontinuation of therapy after the initial six weeks of treatment almost invariably results in recrudescence of encephalitis (Luft and Remington, 1992). Continuation of the acute therapeutic regimen as the maintenance regimen is usually the simplest approach to maintenance therapy. The preferred regimens are pyrimethamine with sulfadiazine or pyrimethamine with clindamycin. Other regimens include pyrimethamine-sulfadoxine, pyrimethamine alone, atovaquone alone, or pyrimethemine with either atovaquone, clarithromycin, azithromycin, or dapsone (Murray, 1999).

Primary prophylaxis is recommended for *T. gondii* seropositive HIV-1-infected patients with CD4+ T-lymphocyte counts of 100 cells/μL or less. The currently suggested prophylactic antimicrobials are trimethoprim-sulfamethoxazole or pyrimethamine plus dapsone. The optimal regimen with these drugs has not been defined. Discontinuation of primary prophylaxis has been shown to be safe in *T. gondii* seropositive HIV-1-infected patients who have responded to HAART with a sustained rise in CD4+ T-lymphocyte counts to at least 200 cells/μL or 14% of the peripheral lymphocyte count, and who have remained so for at least 12 weeks (Furrer *et al*, 2000).

Cryptococcal meningitis

Cryptococcal meningitis (CM) is the most common manifestation of systemic fungal infection in HIV-1-infected patients and is the third most frequent neurological complication in patients with AIDS (Leenders *et al*, 1997; Sanchez-Portocarrero and Perez-Cecilia, 1997; Oursler *et al*, 1999). Five percent to ten percent of HIV-1-infected patients will develop CM as an AIDS-defining illness (Fessler *et al*, 1998). In about 40% of patients with CM, it may be the initial manifestation of HIV-1 infection (Wright *et al*, 1997). CM usually affects patients with CD4+ T-lymphocyte counts of less than 100 cells/μL. Oursler *et al* found that sex, race, and opportunistic infections did not significantly alter the risk of CM in HIV-infected patients (Oursler *et al*, 1999).

Cryptococcus neoformans is an encapsulated fungus which is acquired from the environment via

inhalation. The organism reproduces by budding and develops a large capsule in the tissues. This capsule inhibits phagocytosis and may impair leukocyte migration (Laurenson *et al*, 1997). It is not established whether CM occurs as a result of dissemination of newly acquired infection or represents reactivation of latent infection. Enhanced immune function secondary to HAART may unmask latent infection and precipitate clinically apparent meningitis (Woods *et al*, 1998). Pathologic examination reveals a basilar, nonexudative chronic meningitis. Microabscesses, usually in the basal ganglia region, as well as cryptococcomas, may also develop. Coinfection of CM with other oppportunistic pathogens has been described (Silber *et al*, 1998).

CM usually presents solely with neurologic manifestations, without evidence of systemic infection. The onset and duration of CM are variable. The signs and symptoms of meningitis in immunocompetent patients, such as nuchal rigidity and/or meningismus and photophobia, have not been shown to correlate well with CM in a study population of HIV-1-infected patients (Friedman *et al*, 1995). Patients often present with nonspecific complaints such as headache, fever, altered mental status, nausea, and vomiting. Focal neurologic signs and seizures occur in about 10% of patients (Wright *et al*, 1997). Elevated intracranial pressure (ICP) occurs in excess of 50% of HIV-1-infected patients with CM (Saag *et al*, 2000), without accompanying hydrocephalus or cerebral edema. The pathophysiology of increased ICP has not been fully elucidated in this condition (Fessler *et al*, 1998).

Diagnosis of CM in HIV-1-infected patients rests on demonstration of the organism in the CSF. The CSF changes are relatively minor, and in some cases the CSF is normal. CSF examination may reveal increased protein and depressed glucose levels. In approximately 70% of the patients, the CSF white cell count is below 20 cells/mm^3, and the pleocytosis is almost always mononuclear (Levy *et al*, 1997). The opening pressure on lumbar puncture is often elevated. India ink smear of CSF is a valuable supportive test for diagnosis, with a sensitivity ranging between 75% to 85%. CSF should be tested for cryptococcal antigen, and a titer above 1:8 is considered presumptive evidence of the infection (Zeind *et al*, 1996). Serum cryptococcal antigen is positive in more than 99% of cases of AIDS-related CM, usually at titers more than 1:2048 (Saag *et al*, 2000). The definitive diagnosis of CM is based on culture of the organism in CSF. Neuroimaging studies are useful to confirm the diagnosis of obstructive hydrocephalus.

Poor prognostic factors for CM in HIV-1-infected patients include positive blood cultures, altered mental status, CSF antigen titer above 1:1024, positive CSF India ink smear, CSF white cell count below 20/mm^3, and elevated CSF pressure (Zeind *et al*, 1996; Price *et al*, 1997; Oursler *et al*, 1999).

Intravenous amphotericin B combined with 5-flucytosine is the initial treatment of choice for two week induction therapy. Fluconazole is recommended for consolidation therapy for 8 weeks, or until CSF cultures are negative (Saag *et al*, 2000). Lipid formulations of amphotericin B appear to be efficacious and less nephrotoxic (Leenders *et al*, 1997). Fluconazole plus flucytosine may be an alternative for induction therapy. Even after successful therapy, relapse occurs in 25% to 60% of patients unless long-term maintenance therapy is used (Saag *et al*, 1999). Fluconazole is the mainstay of therapy in this setting, and is superior to itraconazole for secondary prophylaxis (Saag *et al*, 1999). Amphotericin B is an alternative for maintenance therapy. The addition of granulocyte-macrophage colony stimulating factor (GM-CSF) to standard antifungal therapy may provide a useful therapeutic option in HIV-1-infected patients with CM associated with raised ICP and CSF leukopenia (Price *et al*, 1997). The placement of lumbar drains and lumbar peritoneal shunts is indicated in patients with elevated ICP refractory to more conservative measures such as serial lumbar punctures (Fessler *et al*, 1998).

Primary prophylaxis for CM in HIV-1-infected patients is not recommended. Some studies support the concept that life-long secondary prophylaxis for CM may be safely discontinued in HIV-1-infected patients treated with HAART for at least 6 months who have experienced an increase in CD4+ T-lymphocyte counts above 100 cells/μL and a plasma viral load reduction below 200 copies of HIV-1 RNA/mL (Martinez *et al*, 2000).

Primary central nervous system lymphoma

Primary central nervous system lymphoma (PCNSL) is an extranodal, non-Hodgkin's B-cell type neoplasm. In HIV-1-infected patients, the incidence of this neoplasm is 1000–3900 times more common (Raez *et al*, 1998) than in the general population. At present, PCNSL occurs in 2%–5% of patients with AIDS, and is the second most frequent space-occupying lesion of the brain after central nervous system toxoplasmosis (Arribas *et al*, 1995a). These lymphomas typically occur in HIV-1-infected individuals with CD4+ T-lymphocyte counts less than 50 cells/μL. In HIV-1-infected patients, the finding of PCNSL is considered an independent criterion for the diagnosis of AIDS.

In patients with AIDS, the age of presentation of PCNSL is usually in the fourth decade (Ruiz *et al*, 1997). Men are more commonly affected than women (ratio 9:1) (Fine and Mayer, 1993). The majority of these tumors are located supratentorially. Lymphomatous meningitis is estimated to occur in 25% of patients with AIDS and PCNSL (Chamberlain and Kormanik, 1999). Single or multiple lesions may be present. Autopsy studies have revealed that PCNSL associated with HIV-1 infection is virtually always multifocal, even when solitary lesions are seen

radiographically (McGowan and Shah, 1998). PCNSL is rarely associated with systemic lymphoma at the time of diagnosis. Large cell lymphoma and immunoblastic lymphomas are the most common histologic types in AIDS-related PCNSL.

The Epstein-Barr virus (EBV) is almost always found in tumor specimens from patients with AIDS-related PCNSL (Flinn and Ambinder, 1996). AIDS-related PCNSL expresses EBV nuclear antigen and viral protein LMP-1. EBV-infected B-cells can undergo monoclonal expansion in the presence of immune dysregulation, and the reduction of CD4+ T-lymphocyte cell count may allow EBV-infected B-cell proliferation (McGowan and Shah, 1998).

The clinical presentation of PCNSL in patients with AIDS usually consists of altered mental status, focal neurologic deficits, seizures, or evidence of increased intracranial pressure, with symptoms present for a mean of approximately two months prior to presentation (Sparano, 1995). Patients with HIV infection in whom PCNSL is suspected should promptly be evaluated with CT or MRI of the brain. The tumor may enhance in a ring or homogeneous pattern on contrast-enhanced CT and MRI. MRI is more specific than contrast enhanced CT in distinguishing cerebral toxoplasmosis from PCNSL. Approximately 10% of patients with AIDS-related CNS lymphoma have disease that is not evident on contrast-enhanced CT scanning (Sparano, 1995).

Empiric anti-toxoplasma therapy represents the first-line approach to most HIV-1-infected patients with focal brain lesions. Currently, brain biopsy is reserved for patients who fail empiric therapy for toxoplasmosis, individuals with negative toxoplasma titers, and those who present with lesions atypical for toxoplasmosis. Since brain biopsy is sometimes deferred by both patients and neurosurgeons, there is a need for noninvasive diagnostic methods for PCNSL (Cingolani *et al*, 1998).

SPECT imaging is now frequently accepted as a diagnostic aid in this setting, especially after failure of empiric therapy for toxoplasmosis (Raez *et al*, 1998). A ratio of lesion activity to contralateral brain activity greater than 1.0 is compatible with PCNSL, whereas a ratio of less than 1.0 is compatible with nonneoplastic causes (Ruiz *et al*, 1997; Raez *et al*, 1998). Similarly, PET scanning accurately differentiated lymphoma from non-lymphoma diagnoses in 17 of 18 patients with AIDS and central nervous system mass lesions in one trial (Pierce *et al*, 1995). Finally, proton magnetic resonance spectroscopy is yet another noninvasive modality that has shown promise in distinguishing the etiology of brain lesions in patients with AIDS (Chang *et al*, 1995). With the current imaging modalities available, an accurate diagnosis and differentiation between PCNSL and infectious brain lesions can be accomplished in the majority of the cases (Ruiz *et al*, 1997).

The CSF examination may reveal elevated protein levels, elevated β-2 microglobulin, and elevated lactate dehydrogenase (LDH). Pleocytosis and glucose levels are variable. Spinal fluid cytology reveals malignant cells late in the course of disease. The uniform association of the tumor with EBV led to the suggestion that EBV DNA in the CSF might serve as a tumor marker (Flinn and Ambinder, 1996). The temporal relationship between EBV DNA release in the CSF and the natural history of brain lymphoma is still unclear (Cingolani *et al*, 1998). The results of a series of patients with AIDS and PCNSL suggest that EBV DNA is likely to be detected in the CSF in patients who have widespread disease (Arribas *et al*, 1995a). The feasibility of simultaneous detection of CSF *Toxoplasma gondii* DNA and EBV DNA by a multiplex PCR assay has been demonstrated as well (Roberts and Storch, 1997).

The median survival of patients with AIDS and PCNSL is 3 to 4 months with treatment (Pierce *et al*, 1995; McGowan and Shah, 1998). External-beam radiation therapy is the most commonly employed therapeutic modality. The role of chemotherapy or combined modality therapy remains to be established. Young age, high performance status, and use of high-dose radiotherapy have been determined as predictors of survival (Corn *et al*, 1997). Changes in EBV DNA viral burden in CSF with response to chemotherapy for AIDS-related PCNSL correlated with patient survival (Antinori *et al*, 1999). An anecdotal report demonstrated success of EBV targeted therapy with hydroxyurea in two patients (Slobod *et al*, 2000). Long-term remission of AIDS-related PCNSL after treatment with HAART has been described (McGowan and Shah, 1998). Unfortunately, patients frequently succumb to other complications such as infection, even when the lymphoma can be controlled.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an often fatal, demyelinating disease of immunocompromised patients caused by the JC virus. Though once relatively uncommon, PML is now encountered more frequently, due mainly to the presence of HIV and AIDS. Though survival with PML remains low, the introduction of HAART now offers some hope in improving survival with PML.

PML was originally described in 1958 in patients with chronic leukemia and Hodgkin's disease (Astrom *et al*, 1958). The causative agent, a polyoma virus, was identified in 1971 from a patient with the initials JC (Padgett *et al*, 1971). This virus is ubiquitous, and is usually acquired during childhood. Serologic studies have determined that 70% to 90% of adults have been infected with JC virus (Major *et al*, 1992). The means of transmission of JC virus remains unclear, though the upper respiratory tract may be the initial site of infection and respiratory spread has been postulated (Monaco *et al*, 1998). Primary

infection has not been associated with clinical symptoms. During latency, the virus appears to reside in the kidney, CNS, and peripheral lymphocytes (Tornatore *et al*, 1992; Ferrante *et al*, 1995; Perrons *et al*, 1996; Vago *et al*, 1996). The onset of cell-mediated immune deficiency presumably allows the reactivated JC virus to then manifest as the clinical syndrome of PML.

The epidemiology of this disease has greatly changed since the first case of PML in an AIDS patient was reported in 1982. Prior to 1984, AIDS accounted for only 3% of the cases of PML, with most cases at that time due to underlying lymphoproliferative disorders (Krupp *et al*, 1985). By 1991, though, AIDS was the underlying condition in 72% of cases of PML (Holman *et al*, 1991). The prevalence of PML in patients with AIDS has ranged from 1% to 10% (Berger *et al*, 1987; Krupp *et al*, 1985; Petito *et al*, 1986; Kure *et al*, 1991), and it has been reported as an AIDS-defining illness in as many as 57% of patients presenting with PML (Fong *et al*, 1995). A recent retrospective study of PML in patients with HIV-1 infection found a male predominance (7.6:1) (Berger *et al*, 1998). The CD4+ T-lymphocyte count in HIV-1-infected patients with PML is typically <100 cells/μL, but PML has been reported in such patients with higher CD4+ T-lymphocyte counts (Fong *et al*, 1995; Berger *et al*, 1998).

The JC virus predominantly infects oligodendrocytes and astrocytes, resulting in cell lysis and demyelination. A hallmark of PML is its multifocality. Though nearly all cases of PML involve the cerebral white matter, other affected areas can include gray matter, brain stem, cerebellar white matter and white matter tracts of the cervical spinal cord (Thorner and Katz, 2001). Pathologic specimens typically reveal multiple areas of demyelination. There are a decreased number of oligodendrocytes that may contain viral inclusions, oligodendrocytes with enlarged nuclei and nuclear inclusions, and reactive astrocytes with bizarre nuclei which may also contain viral particles.

A number of investigators have studied the interaction between JC virus and HIV-1 infection, with the intent of explaining why AIDS so frequently predisposes to PML. For example, JC virus-specific, cytotoxic T-lymphocytes, which are critical in controlling the JC virus, are absent in some patients with AIDS and PML (Koralnik *et al*, 2001). Others have shown that the HIV-1 *tat* protein may upregulate transcription of JC virus in glial cells (Tada *et al*, 1990; Chowdhury *et al*, 1993). Finally, it has been demonstrated that HIV-1 infection is capable of disrupting the blood–brain barrier (BBB), possibly facilitating entry of JC virus into the brain (Power *et al*, 1993; Hofman *et al*, 1994).

Because PML is a multifocal disease, a wide variety of neurologic symptoms can occur, and PML should be considered in any HIV-1-infected patient with neurologic symptoms. Typically the disease is one of focal neurologic deficits, progressive dementia, and eventual coma and death. Common signs and symptoms include mono- or hemiparetic limb weakness, gait abnormality, cognitive dysfunction, and dysarthria. Less frequently there may be seizures, sensory loss, vertigo, and visual impairment. Fever and headache are usually absent. Without intervention, most patients with PML will die within 4–6 months, though prolonged survival has been reported in a small number of patients, even in the pre-HAART era (Berger and Mucke, 1988).

Definitive diagnosis of PML is based on pathologic examination of brain tissue. Brain biopsy can provide tissue which will demonstrate the above-mentioned pathologic changes, and immunocytochemistry techniques can confirm the presence of JC virus in this tissue. Because this method of diagnosis is invasive, other less-invasive diagnostic methods, discussed next, are often utilized in combination with clinical findings to diagnose PML.

Radiographic imaging of the brain with CT or MRI can be helpful in the diagnosis of PML. MRI was found to be more sensitive than CT in detecting the extent of disease due to PML (Whiteman *et al*, 1993). Typically, multiple foci of low attenuation (by CT) or increased signal intensity (by MRI, T-2 weighted imaging) are noted in areas of white matter of the cerebral hemispheres, although other areas of the brain may be involved. There is usually no mass effect, and the lesions do not enhance with contrast. When contrast enhancement has been noted, it is usually faint and located at the rim of the lesion (Berger *et al*, 1998).

Routine analysis of the CSF is usually unhelpful in the diagnosis of PML. Evaluation of CSF for presence of the JC virus, however, can be very useful both diagnostically and prognostically. Polymerase chain reaction (PCR) for JC virus DNA in CSF, particularly when nested PCR is performed, has been shown to be both highly sensitive (90–100%) and specific (92–100%) for PML (DeLuca *et al*, 1996; Weber *et al*, 1994). In addition, quantitation of JC virus DNA in the CSF has been used as a prognostic marker in PML (with higher levels of JC virus DNA correlating with lower survival) as well as in monitoring response to therapy (Taoufik *et al*, 1998; DeLuca *et al*, 1999; Yiannoutsos *et al*, 1999).

Several antiviral agents have been evaluated for the treatment of PML. A large clinical trial evaluating the use of cytosine arabinoside, capable of inhibiting JC virus *in vitro*, proved disappointing in the treatment of PML (Hall *et al*, 1998). Cidofovir, an antiviral agent with *in vitro* activity against JC virus, has shown promising results in treating PML in some trials, but little benefit in other trials (Sadler *et al*, 1998b; Brambilla *et al*, 1999; DeLuca *et al*, 2000; Marra *et al*, 2001). Other agents, such as alpha-interferon, heparin sulfate, and topoisomerase inhibitors are being evaluated. At this time, none of the above agents have been evaluated adequately enough to show a clear benefit to treating PML.

As mentioned before, the survival of patients with PML and AIDS without intervention is usually 4 to 6 months. Restoration of the immune system with HAART has had a profound effect on the survival rate and neurologic outcome of patients with PML and AIDS (Albrecht *et al*, 1998; Clifford *et al*, 1999; Dworkin *et al*, 1999). In one large, prospective trial of patients with AIDS and PML, a 63% decrease in risk of death was observed in patients treated with HAART containing a protease inhibitor, as compared with a 38% decrease in risk of death when treated with antiretroviral therapy that did not contain a protease inhibitor (Tassie *et al*, 1999). At this time, an effective HAART regimen is the mainstay of therapy for PML in patients with AIDS. Although the incidence of PML has increased with the AIDS epidemic, newer diagnostic techniques and improved antiretroviral therapy has enabled patients with this disease to be diagnosed quicker and to survive longer with PML.

Cytomegalovirus infection

Cytomegalovirus (CMV) infection of the central and peripheral nervous system in patients with HIV-1 infection and AIDS may result in various clinical syndromes. Encephalitis, polyradiculitis, and polyradiculomyelitis, and peripheral neuropathies due to CMV infection can occur. This section focuses on CMV infection of the CNS, namely CMV encephalitis.

CMV infection of the brain has been documented at autopsy in approximately 30% of patients with AIDS (Petito *et al*, 1986). The clinical significance of this finding, however, is unclear, since CMV encephalitis is a relatively rare clinical diagnosis in patients with HIV-1 infection (Gallant *et al*, 1992). The neuropathologic findings of CMV infection in the CNS have been well described (Morgello *et al*, 1987; Vinters *et al*, 1989). Common findings include microglial nodules, focal parenchymal necrosis, and necrotizing ventriculoencephalitis. CMV inclusion-bearing cells are usually present as well. CMV infection of astrocytes, neurons, and capillary endothelial cells can occur. Microglial nodules, consisting of astrocytes surrounding inclusion-bearing cells, are predominantly demonstrated in grey matter. Areas of focal necrosis can be found in brain parenchyma, the meninges, and in the case of ventriculoencephalitis, in the periventricular region.

CMV encephalitis usually occurs in patients with very low CD4+ T-lymphocyte counts (<50 cells/μL), and CMV infection is often present at other sites (retina, adrenal glands, gastrointestinal tract, or blood) at the time of presentation (Vinters *et al*, 1989; Kalayjian *et al*, 1993; Salazar *et al*, 1995). Two distinct clinical and neuropathological entities of CMV encephalitis have been described (Kalayjian *et al*, 1993; Holland *et al*, 1994). The first, encephalitis with dementia, is characterized by subacute dementia with periods of delirium, confusion, apathy, and focal neurologic deficits (Holland *et al*, 1994). Autopsy in these patients reveals diffuse microglial nodules in the grey matter of cortex, basal ganglia, brain stem, and cerebellum. The second form of CMV encephalitis is a ventriculoencephalitis. CMV infection of the ependymal cells lining the ventricles typically results in a rapidly progressive syndrome of delirium, cranial nerve deficits, and ventriculomegaly (Kalayjian *et al*, 1993). Neuropathologically, these patients have areas of necrosis in cranial nerves and the periventricular white matter. Encephalitis with dementia is reportedly the more common form of CMV encephalitis (McCutchan, 1995). Death due to CMV encephalitis usually results within 4 to 6 weeks of presentation (Kalayjian *et al*, 1993; Salazar *et al*, 1995).

The diagnosis of CMV encephalitis may involve multiple modalities. As mentioned, these patients are usually profoundly immunocompromised, and may have evidence of CMV infection at distal sites. For example, some patients with CMV encephalitis have had electrolyte abnormalities consistent with adrenal insufficiency, perhaps indicating concomitant CMV adrenalitis (Holland *et al*, 1994). Radiographically, diffuse areas of low attenuation in brain parenchyma may be noted on CT, and areas of increased signal intensity may be observed in T-2 weighted images on MRI (Walot *et al*, 1996). In cases of ventriculoencephalitis, ventriculomegaly may be present, and MRI may reveal increased signal intensity in the periventricular area, though it should be noted that these findings are not specific for CMV encephalitis. Similarly, the sensitivity of MRI in detecting CMV encephalitis, particularly in severe cases, may be quite poor (Clifford *et al*, 1996).

Routine evaluation of the CSF in CMV encephalitis is usually unhelpful. Although pleocytosis, elevated protein, and hypoglycorrhachia may be present, these results are too variable and nonspecific to be considered diagnostic of CMV encephalitis (Holland *et al*, 1994; Cinque *et al*, 1998). Because isolation of CMV by culture of CSF is infrequent in CMV encephalitis, interest has focused on detection of CMV DNA (by PCR and branched-chain DNA assay) as an aid in the diagnosis. A positive predictive value of 92% and a negative predictive value of 95% was noted for CMV infection of the CNS when employing CMV DNA testing of CSF (by PCR) (Cinque *et al*, 1996). Quantitative analysis of CMV DNA in CSF may serve as a prognostic marker for severity of disease, and may also serve as a means of monitoring response to antiviral therapy (Cinque *et al*, 1995; Arribas *et al*, 1995b).

In general, treatment of CMV encephalitis with anti-CMV agents has been disappointing. In fact, several authors have reported the development of CMV encephalitis while undergoing treatment with antivirals for CMV infections at other sites (Kalayjian *et al*, 1993; Berman and Kim, 1994; Salazar *et al*,

Table 1 Major central nervous system infections during HIV-1 infection

Opportunistic infection	*Organism*	*Pathogenesis*	*Clinical presentation*	*Diagnosis*	*Therapy*
Toxoplasma encephalitis	*Toxoplasma gondii*	Multifocal necrotizing encephalitis	Headache, fever, altered mental status, focal deficits	Imaging studies, brain biopsy	Pyrimethamine plus sulfadiazine
Cryptococcal meningitis	*Crytococcus neoformans*	Basilar, non-exudative, chronic meningitis	Headache, fever, altered mental status	CSF* cryptococcal antigen, India ink stain	Amphotericin B plus flucytosine
Primary central nervous system lymphoma	Epstein-Barr virus	Monoclonal B-cell expansion	Altered mental status, focal deficits, seizures	Imaging studies, CSF* EBV DNA+, brain biopsy	Radiation, chemotherapy
Progressive multifocal leukoencephalopathy	JC virus	Multifocal cell lysis and demyelination	Focal deficits, progressive dementia	Imaging studies, CSF* JCV DNA†, brain biopsy	HAART#
CMV encephalitis	Cytomegalovirus	Focal necrosis, necrotizing ventriculoencephalitis, microglial nodules	Subacute dementia, rapid delirium, focal deficits	Imaging studies, CSF* CMV DNA††	Ganciclovir, foscarnet

*CSF: cerebrospinal fluid.
+ EBV DNA: Epstein-Barr virus DNA.
† JCV DNA: JC virus DNA.
†† CMV DNA: cytomegalovirus DNA.
# HAART: highly active antiretroviral therapy.

1995). Failures of therapy have been reported with ganciclovir, as well as foscarnet (Price *et al*, 1992; Holland *et al*, 1994; Cinque *et al*, 1998). Postulated reasons for failure of these agents include poor CNS penetration for these drugs, and the presence of viral resistance. Efficacy of other therapies for CMV encephalitis, such as the antiviral agent cidofovir, or the combination of ganciclovir with foscarnet, is currently being evaluated. Finally, the impact of HAART on CMV encephalitis will also require study.

In sum, CMV encephalitis is a relatively rare clinical disease and affects HIV-1-infected patients with very low CD4+ T-lymphocytes counts. The clinical presentation, radiographic findings, and routine CSF analysis may be nonspecific, and diagnosis may rely on detection of CMV DNA in the CSF. Therapy with current antiviral agents is often disappointing.

As discussed before, HAART has had an important impact on the epidemiology and outcome of CNS opportunistic infections (Table 1) in individuals with HIV-1 infection. Nevertheless, these disease states continue to occur, and physicians caring for such patients must be aware of the newer diagnostic modalities and therapeutic options in these conditions.

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