# Focal Neurological Disease in Patients with Acquired Immunodeficiency Syndrome

**Daniel J. Skiest**

Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas



**Focal neurological disease in patients with acquired immunodeficiency syndrome may be caused by various opportunistic pathogens and malignancies, including *Toxoplasma gondii,* progressive multifocal leukoencephalopathy (PML), cytomegalovirus (CMV), and Epstein-Barr virus–related primary central nervous system (CNS) lymphoma. Diagnosis may be difficult, because the findings of lumbar puncture, computed tomography (CT), and magnetic resonance imaging are relatively nonspecific. Newer techniques have led to improved diagnostic accuracy of these conditions. Polymerase chain reaction (PCR) of cerebrospinal fluid specimens is useful for diagnosis of PML, CNS lymphoma, and CMV encephalitis. Recent studies have indicated the diagnostic utility of new neuroimaging techniques, such as single-photon emission CT and positron emission tomography. The combination of PCR and neuroimaging techniques may obviate the need for brain biopsy in selected cases. However, stereotactic brain biopsy, which is associated with relatively low morbidity rates, remains the reference standard for diagnosis. Highly active antiretroviral therapy has improved the prognosis of several focal CNS processes, most notably toxoplasmosis, PML, and CMV encephalitis.**

HIV is a neurotropic virus that affects the CNS at the earliest stages of infection. The prevalence of neurological disease in symptomatic HIV-infected patients has been estimated to be 39%–70% [1–4]. In a recent review of 390 autopsies of patients with AIDS, abnormal pathologic characteristics were found in 63% of brains [5]. The effects of HIV on the nervous system may be primary or secondary (table 1). This review will focus on the focal CNS complications of HIV.

It was recognized early in the HIV epidemic that diagnosis of focal CNS manifestations by use of noninvasive methods was difficult. Recently, several new techniques, including PCR and new neuroimaging techniques (single-photon emission CT and positron emission tomography), have been developed that have led to improved diagnostic accuracy of the focal CNS manifestations of AIDS.

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Reprints or correspondence: Dr. Daniel J. Skiest, University of Texas Southwestern Medical Center, Div. of Infectious Diseases, 5323 Harry Hines Blvd., Dallas, TX 75390-9113 (daniel.skiest@UTSouthwestern.edu).

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## OPPORTUNISTIC INFECTIONS

### Toxoplasmosis

*Toxoplasma gondii,* an intracellular parasite, has traditionally been the most common etiologic agent in focal CNS disease in patients with AIDS [3, 6]. However, the relative incidence of toxoplasmosis may be decreasing. In one study, the incidence of *T. gondii* as a cause of focal brain lesions decreased from 72% in 1991 to 19% in 1996 [7].

Humans may become infected by ingesting oocysts excreted in cat feces (in cat litter or soil) or by ingesting undercooked meat (pork and lamb) containing tissue cysts [8, 9]. In patients with AIDS, toxoplasmic encephalitis is primarily due to reactivation of latent infection. Most patients (>80%) who develop disease have CD4 cell counts of <100 cells/$\mu$L (range of medians for all patients, 34–50 cells/$\mu$L) [9–12].

**Table 1. Neurological complications of HIV infection.**

| Primary processes | Secondary processes |
|---|---|
| HIV dementia | Toxoplasmosis |
| Vacuolar myelopathy | Progressive multifocal leukoencephalopathy |
| Cerebrovascular disease | Primary CNS lymphoma |
| Inflammatory demyelinating polyneuropathy | *Cryptococcus neoformans* infection |
| Aseptic meningitis | Cytomegalovirus encephalitis |
| Distal symmetrical polyneuropathy | Cytomegalovirus polyradiculopathy |
| Mononeuritis multiplex | Tuberculous meningitis |
| Myopathy | Neurosyphilis |
| | *Nocardia* infection |
| | *Aspergillus* infection |

The incidence of toxoplasmosis in patients with AIDS varies according to country because of the varied seroprevalence of toxoplasmosis in different regions and among different socioeconomic groups. In the United States, the seroprevalence varies from 3% to 30%, whereas in France, 73%–90% of the population is infected [11]. Studies from before the era of highly active antiretroviral therapy (HAART) estimated that ~5%–47% of latently infected persons would develop CNS toxoplasmosis [8, 9, 11].

***Pathology.*** The lesions associated with toxoplasmosis begin as a focus of encephalitis and progress to parenchymal abscesses with necrosis and surrounding inflammation. Tachyzoites are usually located at the periphery of the lesions. Lesions may be unifocal or multifocal and can vary in size from microscopic to quite large. Lesions are most commonly located in the parietal or frontal lobes and at the corticomedullary junction, basal ganglia, thalamus, and pituitary gland [11, 13, 14].

***Clinical manifestations.*** Typically, patients have a subacute presentation over several weeks. Signs and symptoms are usually limited to the CNS and include headache (in 49%–55% of patients), fever (in 41%–47%), psychomotor or behavioral changes (in 37%–38%), confusion (in 15%–52%), lethargy (in 12%–43%), hemiparesis (in 39%–49%), seizures (in 24%–29%), ataxia (in ~30%), and cranial nerve palsies (in 17%–28%) [10, 11]. Up to 10% of patients may present with a diffuse encephalitis without any visible focal lesions [14].

***Neuroradiology.*** The typical CT and MRI findings in patients with toxoplasmosis are $\geq$2 ring-enhancing lesions with surrounding edema. However, radiographic findings can vary: up to 27%–43% of patients have a single lesion seen on imaging studies [10–12, 15]. On T1-weighted MRI, the lesions appear as focal areas of low signal intensity that enhance (usually ring enhancing) with gadolinium. T2-weighted MRI lesions have relatively high signal intensity.

Standard tests of CSF specimens are rarely diagnostic, because the findings for patients with toxoplasmosis are nonspecific. Testing of CSF specimens may reveal elevated levels of protein, mild lymphocytic pleocytosis, and, occasionally, hypoglycorrhachia; but often, the findings are normal [11].

Most patients with CNS toxoplasmosis have serological evidence of infection. Immunofluorescence antibody tests and ELISA are most commonly used by clinical laboratories. Because infection with *T. gondii* is widespread, a positive result on a serological test alone does not establish the diagnosis. However, a negative result essentially excludes the diagnosis of toxoplasmosis, because <3%–6% of patients with toxoplasmosis will have negative results of serological tests [16–19]. The value of intrathecal antibodies against *T. gondii* is debatable. One study suggested that they have a high specificity but a sensitivity of only 69% [20]. To date, PCR of spinal fluid samples for *T. gondii* DNA has been disappointing. In general, the test has had a reasonable specificity of 96%–100%, but the sensitivity is only 50% [21–24].

***Diagnosis.*** The definitive diagnosis of toxoplasmosis requires demonstration of tachyzoites in a biopsy specimen of the brain. However, in practice, most patients with multiple ring-enhancing lesions who have a positive result on serological testing of serum for *Toxoplasma* species are treated empirically. Most patients respond promptly to appropriate therapy. Of the patients who eventually improve, 86% will show clinical improvement by day 7 of treatment and 95% will show radiographic improvement by day 14 of treatment [10, 12]. If no improvement is seen within 2 weeks of starting treatment, alternative diagnoses should be considered. Corticosteroids should generally be given only to patients with significant mass effect, because their administration may result in transient improvement of lymphomatous lesions, thus making it difficult to assess response to empirical therapy.

***Treatment.*** Treatment of toxoplasmosis in patients with AIDS is successful in >70%–85% of patients [10–12, 25, 26]. The treatment of choice for toxoplasmic encephalitis is the combination of pyrimethamine plus sulfadiazine, which act by inhibiting dihydrofolate reductase and tetrahydrofolate synthetase, respectively [12, 27, 28]. Folinic acid is added to prevent

the hematopoietic toxicity of pyrimethamine. In the pre-HAART era, median duration of survival with treatment was ~10 months [11]. In patients unable to tolerate sulfadiazine, pyrimethamine plus clindamycin is a reasonable, albeit somewhat less effective, alternative [11, 25, 26].

Induction therapy is given for 6 weeks, followed by maintenance therapy with lower doses of the same regimen. For patients who experience excellent virological and immunological responses to HAART, there is accumulating evidence that both primary prophylaxis and maintenance therapy can eventually be discontinued with little or no risk of relapse [29–31]. However, specific recommendations have yet to be promulgated.

### Progressive Multifocal Leukoencephalopathy (PML)

PML is characterized by demyelinating lesions in the CNS. The prevalence of PML in patients with AIDS is 0.9%–1.8%, and PML is found in 2.4%–5.3% of patients with AIDS at postmortem examination [3–5, 32–34]. One recent study suggests that, although the incidence of other neurological complications has decreased in the HAART era, the incidence of PML has remained relatively steady [35].

***Pathogenesis.*** PML is caused by the JC virus (JCV), a DNA-containing papovavirus that infects up to 90% of the general population and that is usually acquired asymptomatically in childhood or early adulthood. The virus remains latent in lymphoid tissue and the kidney but can be activated during periods of immunosuppression. Studies suggest that an interaction between HIV and JCV may potentiate the clinical expression of JCV reactivation [33, 36].

***Pathology.*** The characteristic findings of PML are multifocal demyelination, hyperchromatic enlarged oligodendrocytic nuclei, and enlarged bizarre astrocytes with lobulated hyperchromatic nuclei. Immunohistochemistry, in situ hybridization, and electron microscopy can be used to demonstrate the viral inclusions in oligodendroglial cells [33, 36, 37]. Demyelinating lesions can occur in any part of the white matter, but they occur most commonly in the frontal, parietal, and occipital lobes. The posterior fossa may be involved.

PML is generally a late manifestation of AIDS (median CD4 cell count, 35–104 cells/$\mu$L) [38–45]. However, a subset of patients (7%–25%) have CD4 cell counts of >200 cells/$\mu$L [32, 43, 45–47]. Signs and symptoms depend on the parts of the brain that are involved and include cognitive deficits, speech deficits, hemiparesis, difficulty with gait, and incoordination of limbs [33]. Visual disturbances, which occur in up to 30%–50% of patients with PML, include either homonymous hemianopsia, quadrantanopsia, or cortical blindness.

***Neuroradiology.*** CT reveals hypodense lesions of the white matter without mass effect or enhancement. MRI, which is more sensitive, reveals areas of hypointensity on T1-weighted images and increased intensity on T2-weighted images [45, 48]. Involvement of the gray matter may occur, but only in conjunction with white matter disease [48]. Lesions are usually multiple and bilateral, but patients may present with a single focus. The lesions may have a scalloped appearance on MRI because of involvement of subcortical white matter.

Routine CSF studies for PML are generally not diagnostic. CSF may reveal mildly elevated protein level and the presence of myelin basic protein, with a mild mononuclear pleocytosis (<20 cells/$\mu$L) [45].

JCV DNA can be detected by means of PCR of CSF specimens with a high degree of sensitivity (range, ~42%–100%; mean, ~80%) and specificity (~95%) [22, 49]. Because of the relatively high positive predictive value of the test, a patient with a positive PCR result who has a compatible radiological picture can be assumed to have PML. Conversely, a negative test result does not rule out PML. Clearance of JCV DNA from the CSF has been noted with a beneficial response to HAART and prolonged duration of survival [50, 51].

***Diagnosis.*** The differential diagnosis of PML includes HIV dementia and cytomegalovirus (CMV) encephalitis. Definitive diagnosis requires brain biopsy, but this can be deferred for a patient with characteristic signs and symptoms (cognitive deficits with focal findings), multiple nonenhancing white matter lesions, and a positive result for JCV on PCR of CSF specimens.

***Prognosis.*** Traditionally, the prognosis of PML has been poor, with a median duration of survival of 1–6 months after diagnosis [32, 41, 44, 45, 47]. However, a significant minority of patients (~8%) will have a more benign course, with remission and even spontaneous recovery [45]. Factors associated with longer survival are listed in table 2.

***Treatment.*** There is no proven effective treatment for PML. Anecdotal reports suggested a possible benefit of the nucleoside analogue, cytosine arabinoside, but subsequent reports have failed to confirm this [40, 42, 47]. The AIDS Clinical Trials Group conducted a 24-week prospective, randomized, controlled trial of cytosine arabinoside [40]. The study was

**Table 2. Factors associated with prolonged survival in patients with progressive multifocal leukoencephalopathy.**

| Factor |
|---|
| Receipt of highly active antiretroviral therapy |
| High CD4 cell count at time of diagnosis |
| Increase of CD4 cell count by >100 cells/$\mu$L |
| Low HIV load |
| Progressive multifocal leukoencephalopathy as initial AIDS diagnosis |
| Low JC virus levels in CSF |
| Clearance of JC virus from CSF |
| Lack of neurologic progression 2 months after diagnosis |

**NOTE.** From [32, 39, 46, 47, 52–55].

terminated prematurely, because no survival benefit was seen for patients receiving cytosine arabinoside.

Several anecdotal reports have suggested a benefit of cidofovir, a nucleotide analogue with in vitro anti-JCV activity, among patients with PML [52, 56–59]. Recently, a larger study failed to demonstrate a clinical benefit of cidofovir, despite clearance of JCV from the CSF [60]. Ongoing prospective studies should clarify whether cidofovir has efficacy in PML.

Numerous reports have documented improved survival rates among patients with PML who receive HAART [32, 38, 39, 43, 44, 46, 50, 53, 61–68]. Tassie et al. [68] retrospectively compared survival among 109 patients with PML who did not receive a protease inhibitor and 131 who did. They found that the 6-month survival rate of patients who received protease inhibitors was almost double that of those who did not [68]. It appears that the mechanism of HAART in PML is immunorestoration, as evidenced by the correlation with increased CD4 cell counts and survival as well as the demonstration that patients who receive HAART are able to clear JCV from CSF [38, 46]. Other potential treatments for PML are listed in table 3.

Thus, HAART has become the standard of care for patients with PML. However, occasionally, PML may develop in patients receiving HAART, and patients with PML may not improve neurologically despite a beneficial virological and immunologic response to HAART [39, 69, 70]. The immune reconstitution syndrome, which is characterized by an enhanced inflammatory response to an infectious agent in patients who respond well to HAART, has recently been described in patients with PML and is characterized by enhancing lesions on neuroimaging studies [71].

## CMV

CMV disease in AIDS is due to reactivation (usually retinitis or gastrointestinal disease) in patients with very low CD4 cell counts (<50 cells/$\mu$L) [72–74]. The prevalence of neurological disease may be underestimated, because CMV is present in the brain in 12%–40% of patients at autopsy [4, 34, 74–76]. It is common to have a concomitant CNS opportunistic process when CMV disease is diagnosed, which makes it difficult to determine the amount of disease specifically attributable to CMV. Most patients with neurological CMV disease have previously had CMV disease diagnosed at another site, such as retina [74, 77].

Most patients with CMV disease of the brain present with either diffuse micronodular encephalitis or ventriculoencephalitis. The former is characterized by multifocal, diffusely scattered micronodules, which are aggregates of macrophages and glial cells [76, 78]. Nodules and inclusions bearing cytomegalic cells are concentrated in gray matter and widely distributed in the cortex, basal ganglia, brain stem, and cerebellum [79]. Although these are frequently found on histopathologic examination, the clinical significance is not always clear.

Clinically, ventriculoencephalitis presents as a rapidly progressive delirium, cranial nerve deficits, nystagmus, and ataxia. The CSF usually has an elevated protein level, pleocytosis, and/or hypoglycorrhachia [75, 78]. In patients with isolated ventriculoencephalitis, the CSF pleocytosis consists mostly of mononuclear cells. In patients with concomitant radiculomyelitis, neutrophil predominance is seen [74]. MRI reveals progressive ventricular enlargement, periventricular enhancement, and increased periventricular signal on T2-weighted images.

***Diagnosis.*** Neither serological testing of plasma or CSF specimens nor culture of CSF specimens is useful in the diagnosis of CNS CMV disease [22]. In contrast, several studies have demonstrated utility of PCR testing of CSF samples for CMV [80–82]. The sensitivity of PCR for CMV has ranged from 33% to 100%, and the specificity has ranged from 42% to 100%; however, in the majority of studies, the sensitivity exceeded 80% and the specificity exceeded 90%. Patients with polyradiculopathy and/or venticuloencephalitis appear to have higher levels of CMV in the CSF [83–85]. PCR has become a very important diagnostic tool for CMV encephalitis.

***Treatment.*** In general, the prognosis is poor for patients who have CMV disease of the CNS diagnosed, with death occurring in 1–7 months [84–86]. Ganciclovir, the mainstay of

**Table 3. Potential treatments for progressive multifocal leukoencephalopathy.**

| Treatment | Mechanism | Efficacy |
|---|---|---|
| Cytosine arabinoside | Nucleoside analogue | No |
| Zidovudine | Antiviral | Unknown |
| IFN-$\alpha$ | Immunomodulating agent | Unknown |
| Cidofovir | Nucleotide analogue | Conflicting data |
| Analogues of camptothecin | DNA topoisomerase I inhibitor, blocks JC virus replication in vitro | Unknown |
| HAART | Immunorestoration, possible indirect antiviral effect | Yes |
| Antisense oligonucleotides | Binding to JC virus DNA | Unknown |

**NOTE.** HAART, highly active antiretroviral therapy.

treatment for CMV retinitis, reaches lower concentrations in the CSF and brain than it does in serum [79, 87], and it is associated with poor responses [75, 85]. Foscarnet, a pyrophosphate analogue with better CSF penetration, is synergistic with ganciclovir and has been used to treat retinitis and polyradiculopathy [79, 88–92]. An open-label study of combined foscarnet-ganciclovir therapy in 31 patients with neurological CMV disease revealed a median duration of survival of 94 days, compared with 42 days for a group of historical controls who had mostly received CMV monotherapy [74, 77]. Given the poor outcomes with monotherapy, combination therapy may be justified; however, prospective randomized data are needed. All patients who have a CMV neurological syndrome diagnosed should be treated with HAART, because extrapolating from CMV retinitis and other opportunistic infections, immune reconstitution may be associated with markedly improved outcomes.

## PRIMARY CNS LYMPHOMA

Primary CNS lymphoma is the second most common cause of focal brain disease in patients with AIDS. In the pre-HAART era, ~4%–7% of patients with neurological complaints had primary CNS lymphoma diagnosed [3, 93], whereas the postmortem rate of diagnosis was 0.6%–5.0% [4, 34, 94]. Some studies have suggested that the prevalence of non-Hodgkin's lymphoma has not decreased with the availability of HAART to the same extent as have other AIDS related conditions [95, 96].

***Pathology.*** Lesions usually occur supratentorially and are often multicentric, but solitary lesions occur in one-third to one-half of cases [97–100]. Almost all are of high-grade B cell phenotype and follow an aggressive course. The most common histology is either large-cell immunoblastic or small noncleaved cell [99, 100]. Lesions are characterized by perivascular involvement, high mitotic rates, and variable amounts of necrosis. Disease outside of the CNS is distinctly uncommon.

***Pathophysiology.*** The Epstein-Barr virus (EBV) genome can be found in lymphoma cells in nearly 100% of cases of AIDS-related primary CNS lymphoma [98, 101]. There are several factors by which EBV infection may result in lymphoma in AIDS, including the ability of EBV to transform B cells, immune dysregulation and uncontrolled B cell stimulation of late-stage HIV, depletion of EBV-specific CD8 T cells by HIV, and EBV-induced mutations in tumor-suppressor genes, such as *p53* [97, 101, 102].

***Diagnosis.*** Primary CNS lymphoma is a late manifestation of HIV that occurs in patients with very low CD4 cell counts (<50 cells/$\mu$L) [99, 103]. At the time of diagnosis, patients frequently have other manifestations of AIDS and often have a poor functional status [104, 105]. The presenting signs and symptoms of primary CNS lymphoma include altered mental status (e.g., confusion, memory loss, lethargy) in 48%–60% of cases; hemiparesis, dysphasia, or sensory findings, in 31%–78%; seizures, in 15%–41%; cranial nerve findings, in 10%–18%; and headache, in 5%–45% [98–100, 104, 105]. The majority of patients have B symptoms (e.g., fever, night sweats, weight loss) at the time of presentation. The mean duration of symptoms before diagnosis is 22–54 days [99, 106, 107].

***Neuroimaging.*** Either CT or MRI will reveal a single or multiple hypodense lesions, which enhance with contrast (usually homogenous, but sometimes ring enhancing) and exhibit mass effect with surrounding edema [7, 99]. Lesions that do not appear on a CT scan may be apparent on the more sensitive MRI. Lesions are located in the cerebrum, basal ganglia, cerebellum, and, occasionally, brain stem. Location of lesions adjacent to CSF pathways—for example, periventricular or meningeal, as well as the corpus callosum—and subependymal spread of lesions are characteristic findings.

Routine CSF evaluation is usually not helpful, except to exclude other diagnoses. The CSF findings often include an elevated protein level and mild pleocytosis with a mononuclear cell predominance, but these findings are nonspecific [105]. Cytological testing of CSF specimens is diagnostic in ~10%–30% of cases of non-Hodgkin's lymphoma in patients without AIDS, but it has lower sensitivity in patients with AIDS [99, 105].

The association of EBV with CNS lymphoma has resulted in a useful diagnostic test: PCR of CSF specimens for EBV [108, 109]. In 2 recent reviews, the sensitivity of PCR of CSF specimens for EBV ranged from 50% to 100% and the specificity ranged from 94% to 100% [22, 49]. In the majority of studies, the sensitivity exceeded 80% and had a high positive and negative predictive value [109]. Thus, PCR for EBV is now considered the standard of care in patients with focal-enhancing CNS lesions.

***Treatment.*** In the pre-HAART era, the median duration of survival for untreated patients with primary CNS lymphoma was quite poor (1–2.5 months) [99, 106, 107, 110]. Because, most often, the tumor is multifocal, complete surgical resection is usually not possible and does not improve prognosis.

For 50%–75% of patients, cranial whole-brain radiation (usual dose, 2000–4500 cGy) effectively shrinks the tumor and improves symptoms; however, most studies have documented a median survival benefit of only 1–3 months [99, 100, 103, 104, 106, 107, 111, 112]. In most studies, patients died of other causes related to their severe immunosuppression [105, 107].

The results of chemotherapy have been disappointing in the past, but with the improved treatment for HIV, chemotherapy may be a consideration in the future [104, 113]. The role of HAART in the treatment of primary CNS lymphoma is not clear. A single case report [114] and 1 small series [113] have suggested a longer duration of survival among patients who received a protease inhibitor compared with those who did not.

It is hoped—but not proven—that earlier diagnosis and the use of HAART will lead to better outcomes.

## OTHER CONDITIONS

Several other infections may occasionally present with focal lesions in HIV-infected patients, including *Nocardia* species, varicella-zoster virus, *Aspergillus* species, *Listeria monocytogenes, Treponema pallidum, Histoplasma capsulatum, Cryptococcus neoformans,* and *Mycobacterium tuberculosis.* The latter 3 organisms are more commonly causes of meningitis, but they may present as a focal process. *Cryptococcus* infection may involve the brain parenchyma in the form of cryptococcomas, which are collections of organisms, inflammatory cells, and mucoid material. Alternatively, *Cryptococcus* infection may result in nodules of the brain parenchyma or can involve perivascular and subarachnoid spaces (gelatinous pseudocyst) [115, 116]. Tuberculosis may present with either tuberculomas (granulomas) or abscesses. Tuberculomas may occur in any part of the brain and appear as ring-enhancing or nodular lesions on CT or MRI scans [116]. In contrast to tuberculomas, tuberculous abscesses contain numerous acid-fast bacilli and pus, tend to be larger and solitary, and appear similar to a bacterial abscess on imaging studies [115]. *Nocardia* infection often presents with multiple brain abscesses.

## DIAGNOSIS

### Neuroimaging

MRI has greater sensitivity than does CT for toxoplasmosis, white matter disease (e.g., PML), and disease in the posterior fossa; thus, it is the preferred neuroimaging modality [117]. In most instances, white matter diseases, such as AIDS dementia complex and PML, can be differentiated from toxoplasmosis and lymphoma on the basis of clinical, laboratory, and radiographic data. Although certain radiographic characteristics favor lymphoma over toxoplasmosis, such as presence of a solitary lesion, location adjacent to the ventricle, subependymal spread, and homogenous rather than ring enhancement, considerable overlap occurs. Thus, the constellation of symptoms, physical findings, and findings of laboratory and neuroimaging studies is not sufficiently specific to reliably differentiate toxoplasmosis from CNS lymphoma [105, 116, 118, 119]. An additional limitation on routine neuroimaging techniques is the fact that often >1 process occurs simultaneously in patients with AIDS.

### The Role of Brain Biopsy

Studies have demonstrated the relatively poor predictive acumen of physicians in determining the etiology of brain lesions in HIV-infected patients. In 2 studies, the clinical diagnosis was incorrect 34%–48% of the time [15, 120]. Because of the limitations of noninvasive techniques, tissue diagnosis by means of examination of biopsy specimens of the brain remains the reference standard for diagnosis of focal brain lesions in patients with AIDS.

Several retrospective series, which have included a total of >600 patients, have evaluated the role of brain biopsy in patients with AIDS who have intracranial mass lesions (table 4) [15, 112, 120–128]. In practice, the most common technique is CT- or MRI-guided stereotactic biopsy, because it is associated with significantly lower morbidity than is craniotomy and because

**Table 4. The findings of studies investigating brain biopsy in patients with AIDS who have focal neurological disease.**

| Reference | No. of subjects | Percentage of patients with | | | | Definitive diagnosis | Major morbidity, %[a] | Mortality, %[b] |
|---|---|---|---|---|---|---|---|---|
| | | Lymphoma | PML | Toxoplasmosis | Other | | | |
| [3] | 50 | 28 | 28 | 26 | 18 | 96 | 8 | 0 |
| [15] | 251 | 33 | 30 | 15 | 16 | 94 | 3.2 | 2.8 |
| [120] | 26 | 42 | 15 | 23 | 12 | 96 | 4 | 4 |
| [121] | 13 | 31 | 23 | 38 | 15 | 85 | 8 | 0 |
| [122] | 25 | 36 | 24 | 8 | 12 | 80 | 4 | 0 |
| [123] | 23 | 39 | 22 | 30 | 4 | 88 | 0 | 8.7 |
| [124] | 20 | 15 | 35 | 25 | 15 | 70 | 5 | 0 |
| [125] | 12 | 50 | 25 | 0 | 17 | 92 | 8.3 | 0 |
| [126] | 26 | 46 | 23 | 15 | 8 | 92 | 11.5 | 0 |
| [127] | 25 | 40 | 8 | 40 | 4 | 92 | 0 | 0 |
| [128] | 158 | 51 | 17 | 6 | 14 | 86 | 3.7 | 3.1 |

**NOTE.** PML, progressive multifocal leukoencephalopathy.

[a] Defined as hemorrhage or permanent neurological deficits; does not include death.

[b] Biopsy-related mortality (death related to biopsy complication within 30 days of biopsy).

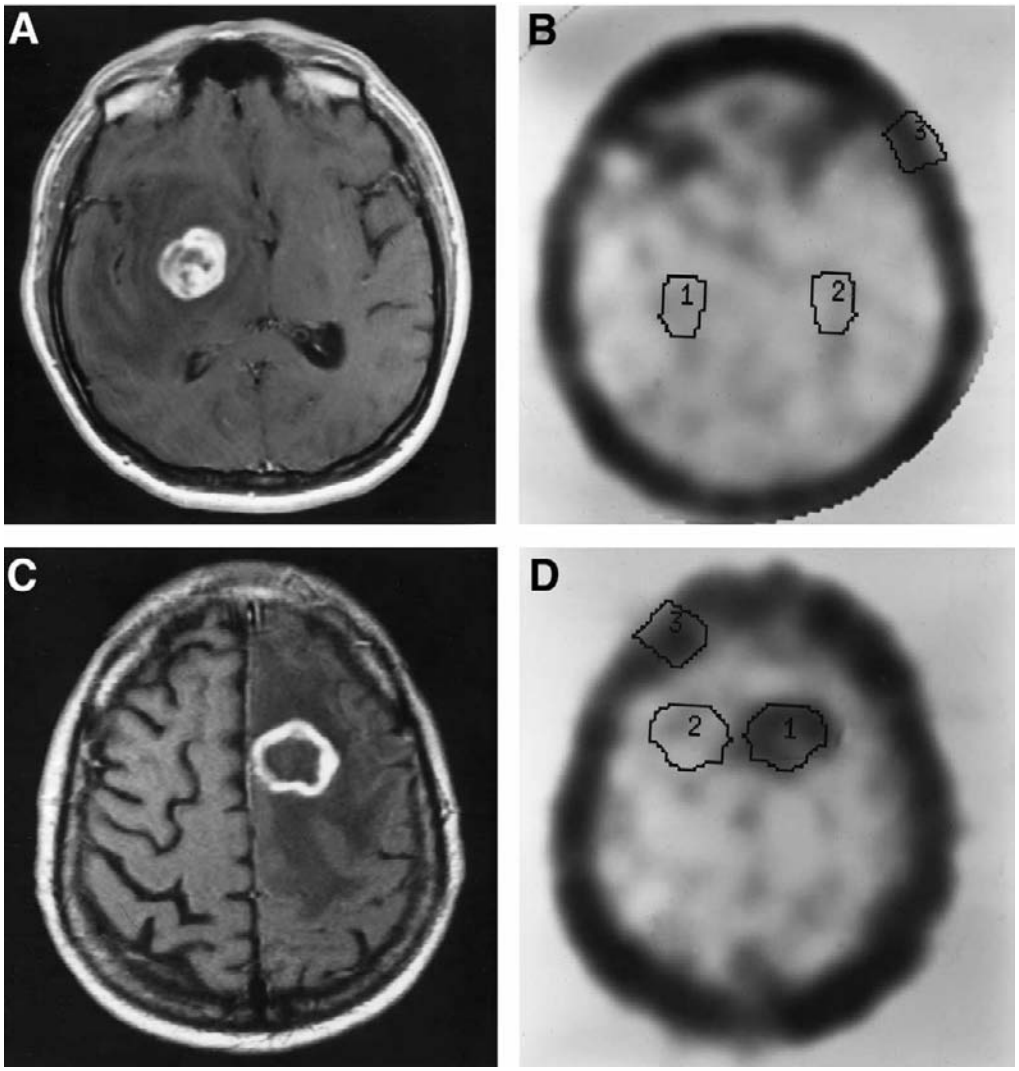


**Figure 1.** Single-photon emission CT (SPECT) thallium-201 images. *A,* Gadolinium-enhanced T1-weighted MRI of a patient who had CNS toxoplasmosis diagnosed. MRI reveals a single lesion that enhances with gadolinium. Surrounding brain edema is present. *B,* Cross-sectional SPECT thallium-201 image of the patient in panel *A* that shows lack of $^{201}$Tl uptake, consistent with toxoplasmosis or another nonmalignant cause. Superimposed numbers represent regions of interest drawn around the lesion *(1),* on contralateral normal brain *(2),* and on contralateral scalp *(3). C,* Gadolinium-enhanced T1-weighted MRI of a patient who had CNS lymphoma diagnosed. MRI reveals single lesion that enhances with gadolinium. Surrounding brain edema is present. *D,* Cross-sectional SPECT thallium-201 image of the patient in panel *C* that shows increased $^{201}$Tl uptake in region of interest, consistent with lymphoma. Superimposed numbers represent regions of interest drawn around lesion *(1),* on contralateral normal brain *(2),* and on contralateral scalp *(3).*

it usually provides adequate tissue. A definitive diagnosis was determined for >90% of patients who underwent biopsy in most studies. Of importance, diagnoses other than lymphoma, PML, or toxoplasmosis are identified in up to 18% of examinations of biopsy specimens. Of interest, in the largest study, 6% of patients had >1 diagnosis made from biopsy of a single brain lesion [15].

In general, the morbidity and mortality rates associated with brain biopsy have been low (table 4) and mostly related to the occurrence of hemorrhage at the operative site. Unfortunately, the procedure is invasive and places the surgical personnel at risk of occupational acquisition of HIV. Thus, other less invasive methods of diagnosis have been sought in recent years.

### Thallium-201 Single-Photon Emission CT (SPECT)

Thallium-201 SPECT has been used to differentiate CNS lymphoma from infectious causes of brain lesions (most commonly toxoplasmic encephalitis) in patients with AIDS. $^{201}$Tl (thallous chloride), a radioisotope, is a potassium analogue. Tumor cells, which have a high rate of metabolic activity, accumulate more

**Table 5. The findings of single-photon emission CT thallium-201 studies of patients with AIDS.**

| Reference | No. of subjects | Method of interpretation | Sensitivity, % | Specificity, % |
|---|---|---|---|---|
| [119] | 32 | Uptake ratios | 55 | 100 |
| [133] | 13 | Subjective | 100 | 86 |
| [134] | 37 | Uptake ratios | 100 | 100 |
| [135] | 18 | Uptake ratios | 100 | 90 |
| [136] | 37 | Uptake ratios | 75 | 96 |
| [137] | 49 | Subjective | 96 | 76 |
| [138] | 36 | Uptake ratios | 83 | 96 |
| [139] | 21 | Subjective | 100 | 80 |
| [140] | 31 | Uptake ratios | 92 | 89 |
| [141] | 38 | Uptake ratios | 86 | 83 |
| Total | 312 | | 92[a] | 89[a] |

[a] Weighted mean.

$^{201}$Tl (via active transport) than does surrounding normal tissue [129–132].

In SPECT, a region of interest corresponding to the lesion is compared visually to the contralateral brain or quantitatively to either the contralateral brain or the scalp (a lesion-uptake ratio is calculated). An area that demonstrates increased thallium retention compared with the surrounding brain (or scalp) is considered to be positive—that is, consistent with lymphoma (figure 1*C,* 1*D*). Lesions that do not retain thallium are considered negative—that is, not malignant (figure 1*A,* 1*B*).

Several studies have evaluated the utility of thallium-201 SPECT in distinguishing cerebral lymphoma from toxoplasmic encephalitis in patients with AIDS (table 5) [119, 133–144]. Although initial studies of thallium-201 SPECT showed a high sensitivity and specificity for the diagnosis of CNS lymphoma in patients with AIDS [133, 134], subsequent reports reported lower diagnostic accuracy. A compilation of the published studies revealed a mean sensitivity and specificity of 92% and 89%, respectively [119, 135–139, 141, 144–147].

The accuracy of thallium-201 SPECT can be affected by several factors, including size of the lesion, grade of the malignancy, presence of necrotic areas in the tumor [138], and location of lesions [133, 138]. False-negative results are more likely with smaller lesions (diameter, <6–8 mm), necrotic and hemorrhagic tumors, and lesions of low-grade malignancy [138, 144, 145]. In addition, tumors located near the base of the skull may be obscured by the normally high activity in this region [133, 144]. In contrast, nonspecific uptake has occasionally been demonstrated in lesions other than lymphoma. Corticosteroids do not appear to diminish the sensitivity of thallium-201 SPECT [145]. False-positive results may be less likely when lesion-uptake ratios are used instead of qualitative assessment [144].

### Positron Emission Tomography (PET)

PET uses a radiopharmaceutical, 18-fluorodeoxyglucose, which enters the cell and competes with glucose for the enzyme hexokinase. Malignant cells, which divide rapidly and have an enhanced rate of glycolysis, take up the glucose tracer at a higher rate than does the surrounding nonmalignant tissue. Thus, tumors appear hypermetabolic or "hot" when compared with surrounding normal tissue on PET. Lesion activity is measured by comparing the region of interest corresponding to the lesion with the contralateral cortex.

Relatively few studies of PET in patients with AIDS who have intracranial mass lesions have been published [148–153]. In the largest study, O'Doherty et al. [152] found that lesions with low metabolic activity were due to toxoplasmosis or PML and lesions with high activity were due to lymphoma. Other researchers have found similar results; however, in several studies, PML lesions have been either hypometabolic or hypermetabolic [148, 150, 151].

Although PET appears promising, a number of problems prevent its widespread use. First, the technology is not yet widely available, and in many cases, the cost of the test is prohibitive. Second, as noted, PML may occasionally demonstrate increased metabolic activity and, thus, it may simulate lymphoma. Finally, very small lesions may be below the level of detection of PET.

Typical patterns for $^{201}$Tl SPECT and PET are shown in table

**Table 6. Radiological patterns of CNS mass lesions in patients with AIDS.**

| Imaging technique | Toxoplasmosis | Lymphoma | PML |
|---|---|---|---|
| MRI findings | | | |
| Enhancement | Yes | Yes | No |
| Pattern | Ring | Homogenous or ring | — |
| Edema | Yes | Yes | No |
| SPECT thallium-201 | Cold | Hot | Cold |
| PET | Hypometabolic | Hypermetabolic | Hypometabolic[a] |

**NOTE.** PET, positron emission tomography; PML, progressive multifocal leukoencephalopathy; SPECT, single-photon emission CT.

[a] Usually hypometabolic, but occasionally hypermetabolic.

6. Each of these modalities has limitations and thus should not be relied on in isolation. Specific expertise is required for interpretation of these tests, and rigid diagnostic criteria have not yet been agreed upon. These tests are also costly. However, when used with other criteria, including serological testing for *Toxoplasma* species and CSF PCR for JCV, CMV, and EBV, they may provide valuable diagnostic information.

Although use of PCR has led to significant advances in the diagnosis of focal brain disease in patients with AIDS, there are limitations. In some cases, the test may be too sensitive. Development of quantitative PCR techniques may improve the specificity, by allowing clinically significant cutoff values. PCR for CMV is commercially available (Roche), but it has not been approved by the US Food and Drug Administration. The other aforementioned PCR tests have mainly consisted of locally developed "home brew" assays and are available in reference laboratories, but they also do not have US Food and Drug Administration approval.

The prognosis for several CNS opportunistic infections has been improved by HAART; however, focal neurological complications remain an important source of morbidity. New techniques, including PCR and neuroimaging, have improved diagnostic accuracy in patients with focal CNS disease and have been incorporated into diagnostic algorithms [19, 140, 154]. These new diagnostic tests now allow for the empirical treatment of some patients without the need for brain biopsy. However, until larger validation studies are completed, there will continue to be a subset of patients who require examination of a brain biopsy specimen for diagnosis, the only definitive diagnostic modality.

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