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CENTRAL NERVOUS SYSTEM INFECTION DURING IMMUNOSUPPRESSION

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Abstract

The central nervous system (CNS) is susceptible to bacterial, viral, and fungal infections. Suppression of the immune system by human immunodeficiency virus (HIV) infection or immunosuppressive therapy after transplantation increases susceptibility to CNS infection and modifies the presentation, diagnosis, and recommended treatment of various CNS infections. This chapter discusses how suppression of the host immune status modifies the presentation, diagnosis, and treatment of selected CNS infections.

IMMUNOSUPPRESSION ASSOCIATED WITH HIV INFECTION

Neurologic illness occurs in 40% to 60% of HIV-infected people.[87] Infection of the CNS may occur during any stage of HIV infection, but opportunistic infection occurs only during late-stage infection, when the CD_4 count falls below 200 cells/dL.[114] Opportunistic infection may affect the brain or spinal cord, and onset may be acute, subacute, or chronic. The most common opportunistic CNS infections and neoplasms are: *Toxoplasma* encephalitis (TE), cryptococcal meningitis, primary CNS lymphoma (PCNSL), progressive multifocal leukoencephalopathy (PML), AIDS dementia complex (ADC, also known as HIV-associated dementia), and cytomegalovirus (CMV) encephalitis.[10] Focal brain lesions occur in up to 17% of people with AIDS and are most often caused by TE, PML, or PCNSL.[6] Since the introduction of potent antiretroviral therapy (previously called highly active antiretroviral therapy, or HAART), the incidence of TE and PCNSL has decreased, whereas the incidence of PML has increased.[5, 21, 98, 107]

IMMUNOSUPPRESSION ASSOCIATED WITH TRANSPLANTATION

Neurologic complications occur in 30% to 60% of people receiving solid organ transplantation and in 12% to 70% of people receiving bone marrow transplantation (BMT). Complications include infection of the CNS, encephalopathy, seizure, stroke, and peripheral neuropathy.[47, 61, 109] Infection of the CNS occurs in 5% to 10% of transplant patients and most often manifests as brain abscess, encephalitis, or meningitis.[42] *Aspergillus fumigatus*, *Listeria monocytogenes*, and *Cryptococcus neoformans* are the most common causes of CNS infections in post-transplant patients.

Immunosuppressive therapy reduces cell-mediated immunity to prevent rejection of transplant and graft versus host disease (GVHD), but this immunosuppression increases risk of infection by fungi, viruses (especially herpesviruses), bacteria, and parasites. In addition, some immunosuppressive agents, notably cyclosporine and tacrolimus (FK-506), can cause CNS

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leukoencephalopathy or peripheral neuropathy that can mimic CNS infection.[57, 125] Patients who receive autologous BMT (stem cells from patient's bone marrow or peripheral blood) are much less likely to develop CNS infection than patients who receive allogeneic BMT (stem cells from an HLA-matched donor).[61]

Susceptibility to CNS infection after transplantation changes over time.[42, 109] During the initial month, CNS infection is most often caused by common bacterial pathogens or opportunistic pathogens present in either the transplant environment (e.g., *Aspergillus species*), or host (e.g., *Mycobacterium tuberculosis*). At 1 to 6 months, immunosuppression is at its highest, resulting in increased susceptibility to CNS infection by the herpesviruses, especially CMV and Epstein-Barr virus (EBV), fungi, and atypical bacteria. Finally, after 6 months, reduction of immunosuppression is accompanied by decreased susceptibility to CNS infection. If a patient requires continued high levels of immunosuppression because of rejection of graft or GVHD, increased susceptibility to opportunistic CNS infection will persist. Most cases of PML and cryptococcal meningitis occur 6 months post-transplantation.

CLINICAL MANIFESTATIONS

Most opportunistic CNS infections and neoplasms are associated with headache, fever, meningismus, altered level of consciousness, or focal neurologic deficit. The presence of one or more of these symptoms should alert the medical care provider to the possibility of CNS infection. In people with AIDS, a normal ("non-focal") neurologic examination can be present with PML, cryptococcal meningitis, HIV-associated dementia, or CMVE. Bacterial or viral meningitis can occur at any stage of HIV infection and is typically accompanied by fever.

After transplantation, immunosuppressive therapy reduces the inflammatory response to infection, thus blunting typical symptoms of CNS infection.[71] Unlike immunocompetent patients with CNS abscess, post-transplant patients usually manifest with only headache, altered mental status, or fever, without focal neurologic deficits.[42, 65] Focal neurologic deficits, when present, are most often seen with toxoplasmosis, aspergillosis, PML, or other fungal abscesses. Clinical and radiologic features of a CNS lesion may distinguish between the various opportunistic infections and neoplasms (Tables 1 and 2).

DIAGNOSIS

Evaluation of potential CNS infection should include neuroimaging with computerized tomography (CT) scanning or magnetic resonance imaging (MRI) with and without administration of an intravenous contrast agent. Characteristic lesion location and contrast enhancement pattern can determine the most likely infection or neoplasm (Table 3).

Evaluation of a solitary ring-enhancing CNS mass lesion in a patient with AIDS should be guided: 1) CD_4 count; 2) serologic status to *T. gondii* and *C. neoformans;* 3) findings on neurologic examination, and; 4) presence or absence of headache or fever. Lumbar puncture may be useful for differentiating between TE and PCNSL (Fig. 1). If the CD_4 count is greater than 200 cells/mL, opportunistic CNS infection or neoplasm is unlikely, and the differential diagnosis should include bacterial, fungal, or mycobacterial abcesses, syphilitic gumma, and stroke.

Evaluation of a CNS mass lesion in a post-transplant patient should be guided by: 1) time since transplantation; 2) immunosuppressive therapy being received; 3) serologic status to *T. gondii* and *C. neoformans;* 4) concomitant pulmonary or gastrointestinal (GI) symptoms; and, 5) findings on chest radiograph or CT scanning. Pulmonary infection usually precedes or accompanies CNS infection by *A. fumigatus, C. neoformans, Nocardia asteroides, M.*

tuberculosis, and the endemic mycoses.[65, 109] Type of transplantation received is associated with increased risk for certain CNS infections (Table 4).

INVASIVE DIAGNOSTIC TESTS

Lumbar puncture (LP) should be considered in any person presenting with new-onset headache, fever, or mental status change. If the patient is obtunded or comatose, or a focal deficit neurologic deficit is present, neuroimaging should be performed before LP. If a space-occupying CNS lesion is present in the posterior fossa or causes midline shift, LP should be avoided because CNS herniation could result.[2] Cerebrospinal fluid (CSF) testing should include cell count with differential, glucose, protein, bacterial culture, and VDRL. Other tests that should be considered include fungal cultures, cryptococcal polysaccharide capsular antigen (CrAg), and polymerase chain reaction (PCR) assays. If symptoms or brain imaging are consistent with herpesvirus infection or PML, PCR assay for the associated viral pathogen should be requested. The sensitivity and specificity of most PCR assays are high (Table 5). In people with AIDS, an elevated level of β_2 microglobulin in the CSF (greater than 3.8 mg/l) is specific, but not sensitive for the diagnosis of HIV-associated dementia.[20, 99] In post-transplant patients, presumptive diagnosis of CNS mass lesion may be made through pathogen identification in culture or biopsy from abnormal pulmonary or gastrointestinal tissue.[23, 65] Unfortunately, PCR assays of the CSF are not yet adequate for diagnosis of fungal or *M. tuberculosis* infection of the CNS.

BRAIN BIOPSY

The most common causes of focal CNS lesions in people with AIDS are toxoplasma encephalitis and PCNSL. The differential diagnosis also includes fungal or atypical bacterial abscess, cryptococcoma, syphilitic gumma, tuberculoma, cerebrovascular disease, and neoplasms other than PCNSL.[58] Stereotactic brain biopsy (SBB) of a CNS lesion may be necessary for certain clinical scenarios: if a solitary CNS lesion is accompanied by negative toxoplasmosis serology; if a contrast-enhancing lesion is atypical for TE or does not respond to anti-toxoplasma treatment; if a new lesion develops during anti-toxoplasma maintenance treatment; or if histopathologic diagnosis is required for entry into an experimental treatment protocol.[28, 31, 72] If CNS herniation is imminent, open biopsy and decompression should be considered, unless the patient is terminal or has previously requested no intervention. Stereotactic brain biopsy provides a diagnosis for 88% to 98% of contrast-enhancing lesions, and 67% of nonenhancing lesions.[28, 58] Studies of how SBB affects treatment and outcome of CNS disease have demonstrated that biopsy results can influence treatment decisions that can increase life expectancy.[28, 70, 72]

Complications of SBB occur in 3% to 12% of patients with HIV infection and include hemorrhage, neurologic deficits, seizures, and infection. Mortality occurred in 2% to 8% of patients.[7, 28, 53, 58, 72] These rates are slightly higher than rates associated with SBB in people without HIV infection.[16, 80, 94, 133]

In post-transplant patients, most focal CNS infections are caused by *Aspergillus sp.*, *Candida sp.*, or other fungal species. One study of 58 cases of brain abscess after bone marrow transplantation noted that only nine (16%) underwent brain biopsy. All nine biopsies provided the correct diagnosis.[65] Of note, of the 29 cases of *Aspergillus* brain abscess confirmed by autopsy, 27 (87%) had concomitant pulmonary aspergillosis and 10 (33%) had *Aspergillus* identified on culture of lung tissue, sputum, or chest-tube drainage. In addition, of 19 patients with candidal brain abscess, 12 (63%) were fungemic at the time of diagnosis. In summary, identification of the causative organism of brain abscess in post-transplant patients can often be obtained by fungal blood culture or histopathologic examination of secretions or tissue from the respiratory tract, without SBB.

DIAGNOSIS AND TREATMENT OF SPECIFIC INFECTIONS

Identical pathogens can cause different symptoms and variations in recommended treatment of CNS infection, according to whether the patient is immunocompromised because of AIDS or transplantation (Table 6). This section describes these variations associated with specific pathogens.

Toxoplasmosis

Reactivation of previously acquired infections is responsible for the majority of opportunistic CNS infections caused by *T. gondii.* In the United States, 10% to 40% of people with AIDS are latently infected with *T. gondii*, as determined by presence of serum anti-toxoplasma immunoglobulin G (IgG) antibodies. In France, the seroprevalence of anti-toxoplasma IgG in people with AIDS is 80%. One-third of people with serum anti-toxoplasma IgG antibodies will develop TE. The absence of serum anti-toxoplasma IgG or IgM antibodies does not exclude the diagnosis of TE.[93, 111] The incidence of TE is reduced in people who take trimethoprim/sulfamethoxazole (TMP/SMZ) or dapsone/pyrimethamine as prophylaxis against PCP.[22, 26]

In post-transplant patients, toxoplasmosis presents as either primary infection, when a donor organ containing encysted *T. gondii* is transplanted into a seronegative recipient, or as reactivation of latent infection.[92] CNS toxoplasmosis is typically associated with disseminated infection. Prophylactic treatment with TMP/SMX for 6 months after transplantation reduces the risk of infection by *T. gondii, L. monocytogenes*, *N. asteroides*, and *Pneumocystis carinii.* Patients who are seropositive to *T. gondii*, and heart transplant recipients are at greater risk of developing infection by *T. gondii* and typically receive higher dosages of TMP/SMZ.[103]

Cryptococcal Meningitis

Cryptococcus neoformans is a ubiquitous yeast that causes meningitis in 7% of people with AIDS living in the United States and 30% of those living in Africa.[30] In people with cryptococcal meningitis, CrAg is detectable in 99% of serum samples and 91% of CSF samples; therefore, a negative serum CrAg virtually excludes the diagnosis of cryptococcal meningitis.[113]

In post-transplant patients, the lungs are typically the portal of entry for cryptococcal infection, but pulmonary symptoms may not manifest until after the infection has disseminated. Disseminated infection to the skin, skeletal system, urinary tract, or the CNS is also common.[42] The majority of cases of *C. neoformans* infection occur 6 months or more after transplantation. As opposed to patients with AIDS, who require life-long prophylaxis after treatment for *C. neoformans* infection, post-transplant patients only require treatment for active infection.[74] Prophylactic fluconazole reduces the risk of infection by *C. neoformans* and *Candida species.*

Herpesvirus Family

The herpesvirus family includes herpes virus type 1 (HSV-1) and type 2 (HSV-2), CMV, EBV, varicella-zoster virus (VZV), and human herpesviruses 6 (HHV-6) and 8 (HHV-8). All these viruses may persist in the human host, in either ganglia (HSV-1 and -2, VZV) or in lymphocytes (CMV, EBV, HHV-6, and -8). Herpesviruses are the most frequent causes of infections in the post-transplant patient. Symptomatic infection can occur with primary infection or reactivation of latent infection. Prophylactic treatment with acyclovir reduces the risk of infection by HSV, VZV, CMV, and EBV.[46, 136]

Herpes Simplex Viruses—HSV-1 causes 10% to 20% of CNS encephalitides and has a mortality rate of greater than 70% if untreated.[44, 137] HSV-2 causes genital herpes infection and is associated with neonatal encephalitis and recurrent benign lymphocytic meningitis in adults.[91, 110, 135]

Polymerase chain reaction is the test of choice for diagnosis of her pes simplex infections.[83, 131] The sensitivity of PCR decreases if antiviral treatment has been given for more than 1 week.[9] In people with AIDS, HSV-1 can present as encephalitis and or disseminated infection. In post-transplant patients, prophylactic antiviral medication is typically prescribed, so HSV infection is uncommon. When HSV encephalitis occurs in a post-transplant patient, the clinician should be alert for acyclovir-resistant HSV.

Epstein-Barr Virus—In the immunocompetent host, EBV is associated with a variety of neurologic syndromes, including mononucleosis, encephalitis, aseptic meningitis, Guillain-Barré syndrome, and Bell's palsy.[63] In post-transplant patients and in people with AIDS, EBV infection can be a primary infection or reactivation of latent infection. The clinical presentation of primary infection is similar to that of infectious mononucleosis, with pharyngitis, fever, lymphadenopathy, and hepatosplenomegaly.

In people with AIDS, EBV is associated with nearly 100% of PCNSL.[8, 33, 67] Primary CNS lymphomas represent reactivation of latent infection. The presence of serum antibodies against EBV does not correlate with an increased incidence of PCNSL.[29]

In post-transplant patients, EBV is associated with meningoencephalitis and an abnormal proliferation of lymphoid cells known as post-transplant lymphoproliferative disorders (PTLD).[8, 11, 49, 67] PTLD occurs in less than 1% of renal transplant recipients, 1% to 2% of bone marrow transplant recipients, 2% to 4% of liver allograft recipients, and up to 10% of heart–lung transplant recipients. Twenty-eight percent of patients with PTLD have CNS involvement, typically presenting as mental status change, hemiparesis, or other focal neurologic deficit. The incidence of PTLD is highest in the first year after transplantation and most often occurs in patients who were EBV-seropositive before transplantation. Diagnosis of PTLD is confirmed by demonstration of abnormal lymphoid proliferation in biopsy material or body fluid. The presence of serum EBV DNA correlates with an increased risk of development of PTLD.[88]

Cytomegalovirus—In the immunocompetent host, CMV infection can be asymptomatic or can present as a mononucleosis-like syndrome or as Guillain-Barré syndrome.[38, 132] In people with AIDS, CMV can cause polyradiculitis, myelitis, encephalitis, or multifocal neuritis.[56, 69, 77] These complications are uncommon in an era of potent antiretroviral therapy. As opposed to the lymphocytic pleocytosis seen with other viral infections of the CNS, CMV infection produces a polymorphonuclear pleocytosis, particularly in individuals with polyradiculitis.[32, 33, 60]

In the post-transplant patient, CMV is an uncommon cause of encephalitis or Guillain-Barré syndrome but is often associated with pulmonary infection and graft rejection.[43, 62] Higher CMV viral loads in blood of solid organ and bone marrow transplant recipients are associated with higher likelihood of CMV-related diseases.[62]

Varicella-Zoster Virus—Varicella-zoster virus is the causative agent of varicella (chickenpox) and herpes zoster (shingles). Other CNS complications associated with VZV infection include post-varicella cerebellitis, meningoencephalitis (including the Ramsay Hunt syndrome), vasculopathy, and acute aseptic meningitis.[4, 41, 51, 73] In people with HIV

infection, CNS complications of VZV infection, most notably herpes zoster, occur more frequently than in the general population.[130]

In the post-transplant patient, primary infection with VZV can rapidly disseminate to multiple organs, including the CNS, and therefore requires emergency treatment when identified. In one study, 5.5% of bone marrow transplant recipients developed VZV infection during a 10-year period: 62% had zoster, and 32% had disseminated, visceral, or CNS infection.[68] Those patients who developed disseminated, visceral, or CNS infection did so within 7 months of transplantation. Compared with immunocompetent people, post-transplant patients with zoster are more likely to develop post-herpetic neuralgia.[120]

Human Herpesvirus-6—Human herpesvirus-6 (HHV-6) is the causative agent of roseola infantum (exanthem subitum) and has been associated with subacute leukoencephalitis, focal encephalitis, chronic myelopathy, and febrile convulsions.[27, 79, 96, 100, 139] In patients with AIDS, HHV-6 can cause pneumonitis and encephalitis. In addition, HHV-6 can coinfect HIV-infected cells and may be a cofactor in the acceleration of HIV infection.[78, 95]

Infection by HHV-6 occurs in 38% to 60% of bone marrow transplant patients and 31% to 55% of solid organ transplant patients. In bone marrow transplant patients as well as in organ transplant patients, HHV-6 infection has been associated with bone marrow suppression, interstitial pneumonitis, and encephalitis.[39, 124] Reactivation of latent infection is responsible for most cases of infection, but transmission of virus from donor tissue can occur.

JC Virus—The majority of people in the United States have serum antibodies against JC virus, a papova virus that causes PML.[29] PML is a subacute progressive demyelinating disease of the CNS that most commonly occurs in people with AIDS, but can also occur in post-transplant patients. The clinical presentation of PML in post-transplant patients is similar to that of patients with AIDS. Unlike other viral infections of the CNS, PML usually presents many months or years after transplantation. Reactivation of latent JC virus infection causes PML and can be detected by PCR assay in the CSF of 92% of patients with PML.[102] Detection of JCV DNA in the urine or blood is not predictive of PML.[81] One study of patients with AIDS showed a negative correlation between CSF JCV DNA concentration and survival. Those patients with PML and greater than $5\log_{10}$ JCV equivalents/mL CSF died within 8 months of diagnosis compared with those patients with less than $5\log_{10}$ JCV equivalents/mL CSF who survived at least 19 months.[128]

Mycobacterium Tuberculosis—Mycobacterium tuberculosis can cause meningitis, tuberculoma, brain abscess, myelopathy, or radiculopathy. Tuberculosis of the CNS can occur at any stage of HIV infection, and is often intracerebral and accompanied by anergy to skin testing.[17, 50] Patients with CNS tuberculosis typically have an insidious onset of headache, fever, and malaise, followed by meningismus, cranial nerve deficits, and mental status changes.[14] People with AIDS who have a focal CNS lesion without focal neurologic signs are more likely to have TE than CNS tuberculosis.[122] Stroke may occur when *M. tuberculosis* infects the intracranial arteries, most commonly in the anterior circulation.[85]

In post-transplant patients, the incidence of *M. tuberculosis* infection is uncommon but is higher than in the general population.[117] Infection of the CNS may present as meningitis, with headache, fever, and cranial nerve deficits, or less commonly as parenchymal infection.[25] Most cases of *M. tuberculosis* infection represent reactivation of latent disease and occur more than 6 months after transplantation. If infection occurs within weeks or months of transplantation, primary infection or active disease at time of transplantation should be suspected.[104, 117]

SUMMARY

The CNS is susceptible to bacterial, viral, and fungal infections. Examination of the level and type of immunosuppression, in addition to the clinical and radiologic findings at the time of diagnosis, can help the clinician determine the most likely etiology of infection. Treatment of active infection, as well as prophylactic treatment to prevent active infection, varies with type of immunosuppression.

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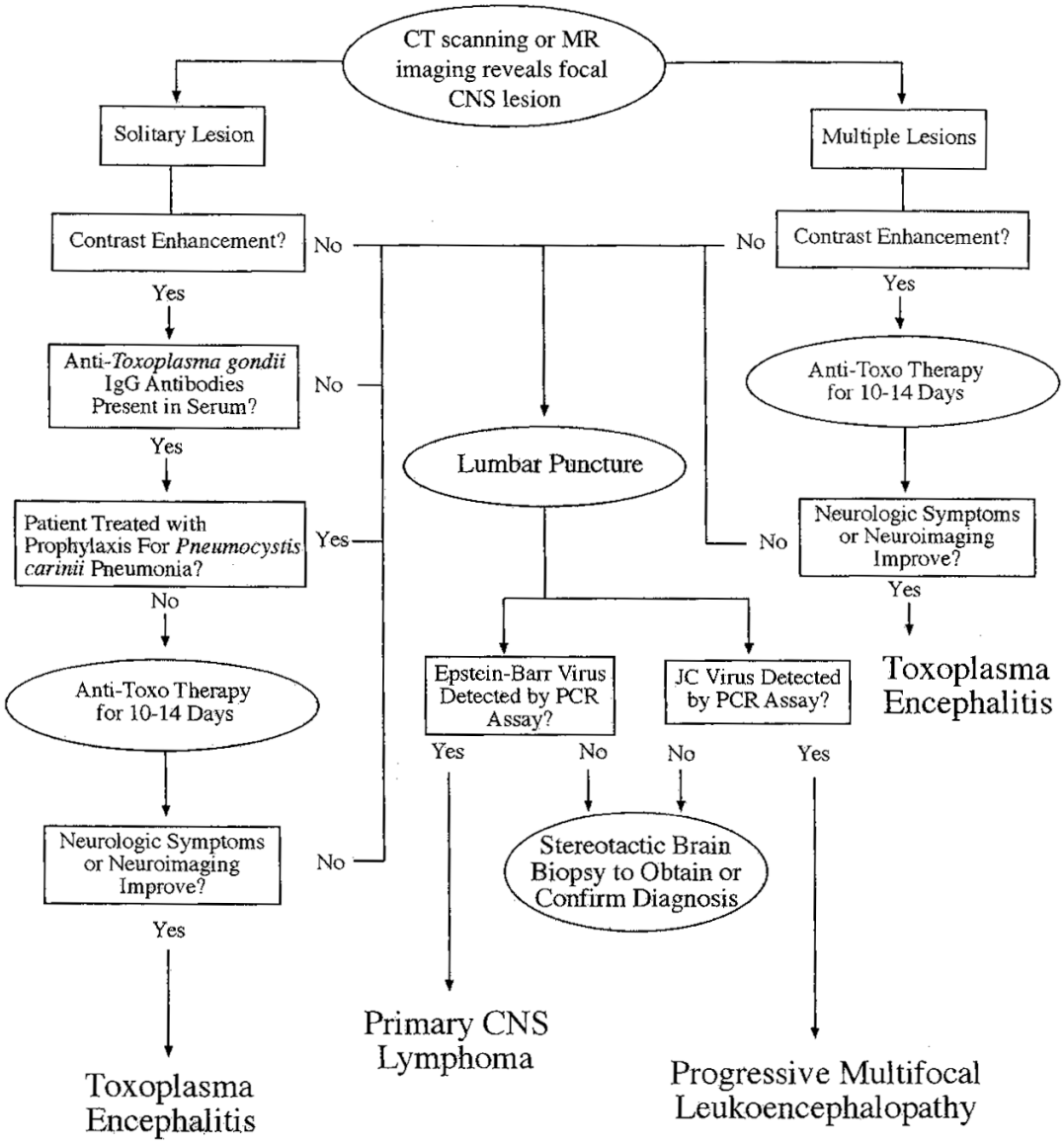

Figure 1.
Algorithm for evaluation of central nervous system lesions in the HIV-infected patient.

Table 1

DISTINGUISHING FEATURES OF NEUROLOGIC DISORDERS ASSOCIATED WITH HIV INFECTION

Etiology	CD_4 Count (cells/mm^3)	Common Clinical Features	Neuroimaging Findings by MRI or CT Scanning	Diagnosis
Fungal Infections				
Cryptococcal meningitis	<200	Fever; bilateral headache; altered mental status; meningeal signs (photophobia, nuchal rigidity)	Normal; meningeal enhancement or enhancing lesion (cryptococcoma) may be present	Presence of CrAg in serum and CSF; positive CSF culture of *C. neoformans;* positive CSF india ink test
Parasitic Infections				
Toxoplasma encephalitis	<200	Fever; unilateral or bilateral headache; altered mental status; seizures; focal neurologic deficit: hemiparesis, ataxia, facial weakness	Solitary or multiple ring-enhancing lesions located in the basal ganglia, deep white matter or hemispheric grey-white junction; MRI more sensitive than CT scanning and may detect more lesions	Serum *anti-Toxoplasma* IgG antibody usually present; definitive diagnosis by identification of trophozoiites on brain biopsy, but presumptive diagnosis by radiologic and clinical improvement after 10–14 days of *anti-Toxoplasma* therapy
Viral Infections				
Progressive multifocal leukoencephalopathy (JC Virus)	<100	Unilateral or bilateral headache; visual field deficit; subacute onset of hemiparesis or other focal neurologic deficits; seizures	Solitary or multiple nonenhancing white matter lesions on CT scanning or MRI; lesions most often in parieto-occipital region; on MRI, lesions hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging	CSF PCR for JC virus is sensitive and specific; brain biopsy
Primary CNS Lymphoma (Epstein-Barr Virus)	<100	Unilateral or bilateral headache; focal neurologic deficit; seizures	Solitary or multiple ring- or homogeneously enhancing lesions; may see nodular ventricular lesions or lesions that cross the midline	CSF PCR for Epstein-Barr virus is sensitive and specific; brain biopsy
AIDS dementia complex	<200	Impaired memory and concentration; psychomotor slowing; apathy or withdrawal	Atrophy; on CT scanning diffuse white matter hypodensity; on MRI white matter hyperintense on T2-weighted imaging; no contrast-	Clinical diagnosis; CSF β_2 microglobulin >3.8 mg/l specific, but not sensitive

Etiology	CD_4 Count (cells/mm^3)	Common Clinical Features	Neuroimaging Findings by MRI or CT Scanning	Diagnosis
			enhancing lesions	
Bacterial Infections				
M. tuberculosis of CNS	Any	Insidious onset of headeache, fever, and malaise, followed by meningismus, cranial nerve deficits, and mental status changes. Involvement of intracranial arteries may result in stroke.	Ring-enhancing or nonenhancing lesions, or normal. Patients with focal lesions without focal neurologic signs are more likely to have TE than CNS TB. HIV-infected people more often have intracerebral mass lesions.	CSF notable for lymphocytic pleocytosis, hypoglycorrhachia, increased protein, or elevated ADA. AFB smear positive in 37% of initial CSF exam, but 87% if four serial CSF samples examined. Anergy to tuberculin skin testing is common

Compiled from:[8, 10, 36, 102, 111, 112, 114, 122, 130]

Table 2

DISTINGUISHING FEATURES OF SELECT CNS INFECTIONS ASSOCIATED WITH TRANSPLANTATION

Etiology	Period of Greatest Risk	Common Clinical Features	Neuroimaging Findings on MRI or CT Scanning	Diagnosis
Fungal Infections				
Aspergillus fumigatus	< 1 month	Usually accompanied by pulmonary or gastrointestinal disease	Multiple nonenhancing hypodense lesions in hemispheric grey-white junction or basal ganglia	Identification of branching, often septate hyphae, or positive culture for *A. fumigatus* in brain tissue or from other site (e.g., lungs) with characteristic brain imaging findings
Candida species		Usually accompanied by disseminated disease and fungemia	Often normal	Identification of *Candida species* in brain tissue or CSF
Cryptococcus neoformans	> 6 months	Fever; headache; altered mental status	Normal; meningeal enhancement or enhancing lesion(cryptococcoma) may be present	Positive CSF culture of *C. neoformans;* (CrAg) in CSF
Parasitic Infections				
Toxoplasma encephalitis		Fever; headache; altered mental status; seizures; focal neurologic deficit: hemiparesis, ataxia, facial weakness	Solitary or multiple ring-enhancing lesions located in the basal ganglia, deep white matter or hemispheric grey-white junction	Serum *anti-Toxoplasma* IgG antibody usually present; definitive diagnosis by identificatior of trophozoiites on brain biopsy
Viral Infections				
CMV	1–6 months	Mental status changes, psychomotor slowing, cranial nerve palsies, retinitis	Nodular, enhancing ventriculoencephalitis	CSF PCR for CMV sensitive and specific; brain biopsy
HHV-6	< 3 months	Mental status changes, seizures, cranial nerve deficits	Focal or diffuse encephalitis	Primary infection is distinguished from reactivation by absence of serum IgG; viremi (either by blood culture or PCR of plasma, serum or CSF) diagnostic of active infection.
VZV	< 6 months	Disseminated infection; Zoster; encephalitis: may present without cutaneous involvement; headache, confusion and somnolence,	May be a mixture of ischemic or hemorrhagic infarcts and demyelinating lesions, often at grey-white matter junction	CSF PCR for VZV is sensitive and specific; brain biopsy
(PTLD) (Epstein-Barr Virus)	> 6 months	Mental status change, hemiparesis, or other focal neurologic deficit	Focal lesion with variable enhancement; may have associated hemorrhage or leptomeningeal spread	CSF PCR for Epstein-Barr virus sensitive and specific; brain biopsy More than 500 copies of EBV per 10^5 lymphocytes correlates with diagnosis
Progressive multifocal leukoencephalopathy (JC Virus)	> 6 months	Mental status changes, visual field deficits, focal neurologic deficit	Solitary or multiple nonenhancing white matter lesions on CT scanning or MRI lesions most often in parieto-occipital region	CSF PCR for JC virus is sensitive and specific; brain biopsy

Etiology	Period of Greatest Risk	Common Clinical Features	Neuroimaging Findings on MRI or CT Scanning	Diagnosis
Bacterial Infections				
M. tuberculosis of CNS	< 1 month or > 6 months	Headache, fever, and malaise, meningismus, cranial nerve deficits, and mental status changes.	Ring-enhancing or nonenhancing lesions.	Lymphocytic pleocytosis, hypoglycorrhachia increased protein, or elevated ADA. AFB smear positive in 37% of initial CSF exam, but 87% if four serial samples examined.

Compiled from:[4, 40, 42, 52, 65, 100, 109]

Table 3

ETIOLOGIES OF CNS ABNORMALITIES NOTED WITH NEUROIMAGING STUDIES

Findings on Neuroimaging	Most Common Etiologies During HIV Infection	Less Common Etiologies	Most Common Etiologies After Transplantation	Less Common Etiologies
Mass lesion with ring enhancement (enhancement may be absent in post-transplant patient)	*Toxoplasma gondii* Epstein-Barr virus (primary CNS lymphoma) *Mycobacteria tuberculosis*	*Cryptococcus neoformans* Kaposi's sarcoma Metastatic or primary malignancy Bacterial or fungal abscess	*Aspergillus sp.* *T. gondii* *Nocardia sp.* Bacterial abscess	*Coccidiodes immitis* *Histoplasma capsulatum* Mucor sp. *Mycobacteria tuberculosis*
Non-enhancing lesion in white matter	PML	Multiple sclerosis Stroke	*Aspergillus sp.* Cyclosporine or FK-506 PML	Cranial irradiation Multiple sclerosis Stroke
Diffuse atrophy with non-enhancing white matter	AIDS dementia complex (also may see late enhancement of basal ganglia)	PML	Cranial irradiation	
Meningeal enhancement	*C. neoformans* HSV VZV Bacteria	Atypical bacteria	*L. monocytogenes* *C. neoformans*	*M. tuberculosis* *C. immitis*
Encephalitis	Typical viral pathogens	HHV-6	EBV VZV	HHV-6 CMV
Ventricular enhancement	CMV	Primary CNS lymphoma	CMV	
Normal	*C. neoformans*		*Candida species*	

Compiled from:[15, 17, 40, 65, 105, 108, 126, 134]

Table 4

PATHOGENS ASSOCIATED WITH TYPE OF TRANSPLANTATION

Type of Transplantation	Associated Pathogens	Comments
Heart	*T. gondi* EBV (PTLD)	At higher risk of perioperative cerebrovascular events
Lung	PTLD *Aspergillus sp.*	PTLD more common in patients with primary EBV infection
Liver	Enteric organisms *L. monocytogenes* *C. neoformans*	During first month after transplantation In the presence of chronic active hepatitis Also at higher risk of central pontine myelinolysis
Kidney	Gram-negative organisms CMV, EBV	During first month after transplantation Encephalopathy may be seen with acute rejection of transplant
Bone marrow	Herpes viruses	Also most common cause of infection in organ transplant recipients

Compiled from:[3, 64, 75, 76, 86, 106, 138]

Table 5

SENSITIVITY AND SPECIFICITY OF PCR ASSAYS FOR SELECTED OPPORTUNISTIC CNS INFECTIONS

Pathogen	Associated Syndrome	Sensitivity (%)	Specificity (%)
EBV	Primary CNS lymphoma	97	100
JC Virus	Progressive multifocal leukoencephalopathy	74–92	92–96
CMV	CMV ventriculitis and polyradiculopathy	80–100	75–100
Varicella-Zoster Virus	VZV encephalitis and Varicella-Zoster	Unknown	100
HSV-1	HSV encephalitis	>95	100
Mycobacterium tuberculosis	CNS tuberculosis	48–100	100

Compiled from: [8, 18, 24, 32, 33, 35, 54, 59, 82, 83, 89, 97, 102, 116, 119, 123]

Table 6

MEDICAL THERAPY OF SELECTED CNS INFECTIONS

Infection	Therapy	Dose and Duration	Comment
Cryptococcal meningitis	Amphotericin B and Flucytosine (5-FC) then Fluconazole	0.6–0.8 mg/kg/day IV for 14 days, or until headache, fever, nausea, and vomiting resolve 75–100 mg/kg/day PO 400 mg/day until CSF culture negative, then decrease to200 mg/day and continue for life	In patients with AIDS, fluconazole associated with delayed sterilization of CSF and more early deaths. If intracranial pressure increases, repeat lumbar punctures one to four times daily to remove15–30 mL of CSF, until opening pressure consistently normal. Flucytosine (5-FC) should be used concurrently with amphotericin B; may cause marrow suppression or leukopenia Lumbar puncture should be repeated after amphotericin B, then every 2 to 4 weeks, or sooner if clinical deterioration occurs. Once CSF culture is negative, fluconazole should be started. CSF CrAg can persist positive even if culture is negative, and should not guide therapy. If CSF CrAg titer rises above initial titer, repeat treatment with amphotericin Unlike patients with AIDS, who require prophylactic treatment after cryptococcal infection, post-transplant patients require treatment for only 2–6 weeks after clearance of CrAg
Toxoplasma encephalitis	Pyrimethamine and Folinic acid and Sulfadiazine or Clindamycin	100–200 mg load, then 75–100 mg/day PO 10–50 mg/day PO 4–8 g/day (100 mg/kg/day) PO divided into four doses 600–900 mg PO/IV qid.	Alternatives to sulfadiazine: 1) Atovaquone: 750 mg PO qid; 2) Clarithromycin: 1 g PO bid; 3) Azithromycin: 1 g load, then 500 mg/day. Consider sulfa desensitization for sulfa-allergic people Lifetime maintenance dose required for patients with AIDS: 1) Pyrimethamine: 25–50 mg/day; 2) Folinic acid: 10–50 mg/day; 3) Sulfadiazine: 1 g tid-qid, or

Infection	Therapy	Dose and Duration	Comment
			Clindamycin: 300–450 mg tid-qid Post-transplant patients receive prophylaxis with trimethoprim/sulfamethoxazole for 6 months
EBV-related neoplasms (Primary CNS lymphoma and post-transplant lymphoproliferative disorder)	Radiotherapy Chemotherapy	Whole-brain irradiation with 4,000 cGy with a “boost” of 1,000 to 2,000 cGy focused on the tumor bed Methotrexate (intravenous and intrathecal), thiotepa, and procarbazine.	Radiation or combined modality treatments prolong life by several months (27 days versus 119 days mean survival in persons receiving radiation therapy) Steroids (dexamethasone) may reduce edema associated with tumor. Mortality rate of PTLD is 50%. Reduced immunosuppressive therapy may improve outcome
Progressive multifocal leukoencephalopathy	Antiretroviral therapy	Potent antiretroviral therapy	No effective treatments. Anecdotal reports of efficacy of antiretroviral therapy; spontaneous remissions and prolonged survival in 5%–10%, but average life expectancy is usually months
(JC Virus)	Cytarabine	2 mg/kg/d for 5 days; may repeat single dose in six weeks	Cytarabine not effective in patients with AIDS, but may be effective in post-transplant patients. Reduction of immunosuppression can produce resolution of infection
Cytomegalovirus	Gancyclovir or Foscarnet	5 mg/kg BID or TID for 2–4 weeks (induction) then5 mg/kg/day 5–7 x/week (maintenance) 60 mg/kg q8H for 2–3 weeks (induction), then90–120 mg/kg/day IV6–7 x/week (maintenance)	There may be synergy if gancyclovir and foscarnet are used together. Resistance to gancyclovir has occurred in patients with polyradiculopath Poor prognosis associated with previous treatment for CMV retinitis, Karnofsky score less than 70, persistently positive CSF CMV PCR, persistent hypoglycorrhachia. Average life expectancy for CMVE or

Infection	Therapy	Dose and Duration	Comment
			polyradiculopathy is weeks to months Recommended treatment for severely affected patients: induction with gancyclovir and foscarnet, then monotherapy after 2 weeks of therapy if there is improvement in symptoms or lower quantitative CSF CMV PCR. Improvement of symptoms may take weeks to months
Human herpesvirus-6	Gancyclovir or Foscarnet	Dosing same as for CMV infection	Acyclovir not effective (similar to CMV, HHV-6 lacks thymidine kinase)
Varicella-zoster virus	Acyclovir Famciclovir Valacyclovir	10–14 mg/kg/QID 500 mg QID for 7 days 1g QID for 7 days	Primary infection: disseminated cutaneous or visceral infection, requires treatment with acyclovir VZV seronegative post-transplant patients should receive varicella-zoster immune globulin (VZIG) if exposed to persons with VZV infection
Tuberculosis of CNS	Isoniazid (INH) pyridoxine Rifampin Pyrazinamide (PZA) Streptomycin or Ethambutol	300 mg/day 50 mg/day 600 mg day 20–35 mg/kg/day 1 g/day 15–25 mg/kg/day	INH, rifampin and PZA are bacteriocidal, and all except rifampin penetrate noninflamed meninges into CSF. Corticosteroids should be considered for very ill patients. Four-drug therapy should be used if patient was previously treated for TB, or comes from area with high prevalence of drug resistance Full therapy for 2 months, then INH and rifampin for 4–16 months. Patients with less than 200 CD_4 cells/dL or more than 2 weeks of illness Previous initiating TB therapy has lower survival rates.

Compiled from:[1,12,13,19,34,37,45,48,55,66,77,84,90,101,115,118,121,129,140]