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Parasitic Central Nervous System Infections in Immunocompromised Hosts: Malaria, Microsporidiosis, Leishmaniasis, and African Trypanosomiasis

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Abstract

Immunosuppression associated with HIV infection or following transplantation increases susceptibility to central nervous system (CNS) infections. Because of increasing international travel, parasites that were previously limited to tropical regions pose an increasing infectious threat to populations at risk for acquiring opportunistic infection, especially people with HIV infection or individuals who have received a solid organ or bone marrow transplant. Although long-term immunosuppression caused by medications such as prednisone likely also increases the risk for acquiring infection and for developing CNS manifestations, little published information is available to support this hypothesis. In an earlier article published in *Clinical Infectious Diseases*, we described the neurologic manifestations of some of the more common parasitic CNS infections. This review will discuss the presentation, diagnosis, and treatment of the following additional parasitic CNS infections: malaria, microsporidiosis, leishmaniasis, and African trypanosomiasis.

As detailed in our previous article [1], the risk of acquiring fungal, viral, bacterial or parasitic infection is increased in patients receiving immunosuppressive therapy after transplantation and in people with advanced HIV infection. CNS infection occurs in 5%–10% of transplant recipients and up to 19% of patients with AIDS [2]. Patients with advanced HIV infection ($CD4^+$ cell count, <200 cells/mm^3) and patients who require high levels of immunosuppression because of graft rejection or graft-versus-host disease are at greater risk than others of developing opportunistic CNS infections. Although parasitic CNS infection can occur in any host, some infections are more common among patients undergoing specific types of transplantation (table 1). The clinical and radiographic manifestations of parasitic CNS infection are often similar in immunocompromised and immunocompetent hosts, but certain infections may blunt or enhance these manifestations in immunosuppressed hosts [3,4]. Although neurologic symptoms vary somewhat by infecting parasite, they are mainly determined by the location(s) of the infection within the CNS (table 2).

Evaluation of the immunosuppressed host presenting with neurologic symptoms or signs of infection should be guided by (1) the degree of immunosuppression, type of transplant received,

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or $CD4^+$ cell count, (2) the length of time since transplantation and the type of immunosuppressive therapy received (for transplant recipients), (3) the results of serological testing for infections endemic to the host's country of origin or transit, (4) concomitant systemic symptoms (especially pulmonary and gastrointestinal), and (5) neuroimaging findings (table 2). Diagnostic testing should then be directed toward detecting the organism or antibody response to the parasite (table 3). Eosinophilia in CSF or blood samples may be absent during parasitic CNS infection, especially during long-term infection [5].

Treatment of a parasitic infection should be guided by the local availability of medications, because some medications are not available in certain countries (table 4). In addition, *The Medical Letter* publishes periodic treatment guidelines for parasitic infections [6]. Because many individuals who are infected with HIV or who have received a transplant require medications that may alter or be altered by the medications used for treatment of parasitic infection, a pharmacist or other source should be consulted to assist with assessment for potential drug-drug interactions.

MALARIA

Malaria is caused by an intracellular protozoan transmitted via the bite of an infected female *Anopheles* mosquito. In humans, malaria can be caused by any of 4 *Plasmodium* species: *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium vivax*, or *Plasmodium malariae.* Although *P. vivax* is present in most areas of malaria endemicity, *P. falciparum* produces the highest mortality. The annual incidence of malaria is difficult to estimate, but recent estimates suggest that malaria causes 1.1–2.7 million deaths annually (predominantly among children living in sub-Saharan Africa) and that it infected >500 million people in 2002 [7–9]. The incidence of malaria is increasing because of a combination of drug and insecticide resistance, as well as because of social and environmental changes [10].

Malaria is not an opportunistic infection for HIV-infected people, but the effect of HIV infection on the natural history of malaria has not been completely defined. Although initial studies in areas where malaria and HIV infection are coendemic suggested no more than observed coexistence between these pathogens, subsequent studies detected not only an impact of HIV infection on the clinical course of malaria but also an impact of malaria on the clinical course of HIV infection [3,4,11,12]. For example, compared with people without HIV infection, HIV-infected people with malaria have a higher prevalence of fever, parasitemia, cerebral malaria, and severe or complicated malaria [5,13–18]. HIV-infected women with malaria are also more likely to become parasitemic and to have higher parasite density than are HIV-uninfected women [19,20]. Similar findings have been documented in nonpregnant women and in men, and the clinical severity of malaria worsens with advanced immunosuppression [21–23].

In a cross-sectional study of HIV-infected adults with acute falciparum malaria in Malawi, plasma HIV levels were higher for HIV-infected people with parasitemia than for HIV-infected people without parasitemia [24]. This study was followed by a prospective cohort study which found that HIV-infected people with malaria had significantly elevated HIV loads [25]. The increases were greatest for people with fever, a parasite density of ≥2000 parasites/μL, and a $CD4^+$ cell count of >300 cells/μl; for these patients, a mean log increase of 0.82 (95% CI, 0.55–1.10) was observed. Such an increase could theoretically accelerate disease progression or increase the risk of HIV transmission [26–28].

Malaria has been transmitted by infected donor organ and bone marrow, but the effect of immunocompromised conditions other than HIV infection on the natural history of malaria has not been defined [29,30]. Malaria has been manifest in people receiving corticosteroids and in

African black-footed penguins receiving dexamethasone, but additional information regarding outcomes is not available [31–33].

The clinical presentation of malaria ranges from asymptomatic to severe and is largely dependent on host immune status and infecting *Plasmodium* species. The host immune status is determined by age, previous parasite exposure, and degree of endemicity of malaria in the environment. Children and pregnant women are at greater risk than others for developing severe or fatal disease. Typical symptoms in a host with no previous parasite exposure include fever, chills, headache, myalgias and arthralgias, diarrhea and vomiting, and other nonspecific signs and symptoms.

Cerebral malaria is a well-known complication of severe malaria and is defined as an unarousable state of unconsciousness, accompanied by the presence of asexual parasitemia (most often due to *P. falciparum*). Cerebral malaria is usually preceded by several days of nonspecific feverish symptoms, but it may occur within 24 h after development of the first symptoms. Episodic fevers may be accompanied by diaphoresis, headache, malaise, arthralgias, myalgias, nausea, or dizziness. Generalized seizures occur in 20%–50% of patients, most often in people infected with *P. falciparum* [34]. In children, seizures are typically recurrent and often focal. Coma may develop subacutely or precipitously after a generalized seizure and typically lasts 1–3 days. Hypoglycemia and prolonged postictal unresponsiveness are common during malaria and should be excluded as causes of a comatose state. Signs of increased intracranial pressure, such as papilledema and meningismus, are uncommon [35]. Cranial nerve dysfunction (such as horizontal or vertical nystagmus, ocular bobbing, or sixth nerve palsy) and decerebrate posturing are occasionally present [36–38]. In addition to the acute-phase manifestations of cerebral malaria, others have described a neurologic syndrome that may develop weeks or months after resolution of the acute phase of the infection. This syndrome, known as postmalaria neurological syndrome, by definition occurs in the absence of parasitemia and most frequently includes seizures, cognitive dysfunction, and psychiatric manifestations [39,40]. Although severe malaria, including cerebral malaria, has been reported following transplantation and in HIV-infected people, it is not clear that the incidence of cerebral malaria is elevated in either population. In early studies, rates of cerebral malaria among people with and people without HIV infection were reported to be both elevated and decreased for both groups, depending on the study [41,42]. A subsequent larger study involving 310 patients with malaria recently found that severe malaria was more common among HIV-infected people than among others (47% vs. 30%) and that severe malaria was more often associated with coma for HIV-infected people than for others (16% vs. 8%) [17].

The exact pathogenic mechanism of cerebral malaria has not been well established, but an autopsy study of fatal cases of cerebral malaria in children suggests that cerebral malaria is likely to be caused by the sequestration of RBCs containing *Plasmodium* trophozoites and meronts within cerebral capillaries and venules [43]. Petechial hemorrhages and endothelial activation are present in brains of people who die with cerebral malaria [44]. Impairment of the blood-brain barrier, as well as axonal injury and impairment of axonal transport, have been implicated as possible causes of CNS dysfunction [45,46].

The diagnosis of malaria requires an index of suspicion based on the patient's exposure history and clinical presentation. Giemsa staining of thick and thin blood smears can detect parasitemia and identify malarial species. Serological tests (ParaSight-F and Immunochromotographic Malaria *P. falciparum* test) are available, but false-positive test results are common [47]. Confirmation of cerebral malaria requires an unarousable state of unconsciousness, accompanied by the presence of asexual parasitemia (most often *P. falciparum*) and exclusion of other causes of an unconscious state, such as hypoglycemia, postictal sedation, or other CNS infection [48]. Brain CT may demonstrate cerebral edema during cerebral malaria, as evidenced

by effacement of the cortical sulci and small or slit-like ventricles, and when this finding is accompanied by hypoattenuation of the basal ganglia or cerebellum, it portends poor prognosis [49,50]. MRI of the brain for patients with cerebral malaria has revealed diffuse swelling with or without edema, as well as multifocal cortical or subcortical lesions that may be enhanced after gadolinium administration [40,51,52]. Imaging analysis of a patient with acute cerebral malaria demonstrated multiple areas of high signal intensity on diffusion-weighted imaging with decreased signal on apparent diffusion coefficient maps, consistent with stroke [53]. Adnormal imaging findings can resolve if the patient recovers. Transtentorial herniation is a common finding on CT or MRI in fatal cases of cerebral malaria. MRI of patients with postmalaria neurologic syndrome, which is similar to acute demyelinating encephalomyelitis, may reveal enhancing, multifocal white matter abnormalities in the brain, brainstem, and posterior fossa that improve as symptoms resolve [40].

Choice of treatment should be guided by the *Plasmodium* species prevalent in the region where infection was acquired and the severity of malaria, and treatment should be initiated immediately after diagnosis is confirmed or when malaria is highly suspected. Chloroquine-resistant *P. falciparum* is present in Southeast Asia, the Amazon region of South America, and certain areas of sub-Saharan Africa. In these areas, quinine with doxycycline, mefloquine, or newer antimalarial drugs (e.g., artemisinian derivatives) should be used [54]. For the traveler with suspected cerebral malaria due to chloroquine-resistant *Plasmodium* or *Plasmodium* with unknown resistance, initial treatment should include intravenous quinidine. The availability of drugs and the parasite burden also influence treatment strategy, as does age and reproductive status. Because of the complicated nature of treating malaria, local treatment guidelines and *The Medical Letter* should be consulted [6,55]. Steroids should not be administered to patients with cerebral malaria, because they have been associated with worse outcome [48,56]. In addition, although anticonvulsants are indicated for patients with cerebral malaria who develop seizures, routine prophylactic use of anticonvulsants may be associated with worse outcome [57,58].

Poor prognosis is associated with longer duration of seizures, presence of retinal hemorrhages, coma, presence of hypoattenuation on CT images of the brain, hypoglycemia, and anemia [35,59]. Neurologic deficits may resolve quickly, slowly, or not at all: ataxia usually resolves rapidly, whereas hemiparesis or cortical blindness usually requires months to resolve. Children who develop spastic quadriparesis or vegetative state usually die. Residual neurologic sequelae occur in ~10% of immunocompetent people and may include epilepsy and cognitive, behavioral, and language deficits, as well as hemiparesis, blindness, and ataxia [58,60]. The effect of immunosuppression on the incidence of long-term neurologic sequelae is not known.

MICROSPORIDIOSIS

Microsporidia are single-celled, obligate intracellular parasites under consideration for reclassification from protozoa to fungi [61]. More than 20 genera of microsporidium are pathogenic in mammals, with *Encephalitozoon* species affecting immunosuppressed populations more commonly than other species [62]. Three species of *Encephalitozoon* are known to cause disseminated disease in humans: *Encephalitozoon intestinalis* (also known as Septata intestinalis), Encephalitozoon hellem, and Encephalitozoon cuniculi [63]. Several other species have caused disseminated disease, including Trachipleistophora species (Trachipleistophora hominis and Trachipleistophora anthropopthera), Pleistorphora species (Pleistorphora ronneafiei and others), and Brachiola species (Brachiola vesicularum and Brachiola algerae). Of these, the *Trachiplesitophora* species have been associated with encephalitis and death. In humans, microsporidium can be transmitted via contaminated water or air droplets and via the fecal-oral route [64,65]. Sexual transmission of *Encephalitozoon* species may also occur [66]. Microsporidia possess a unique mechanism of infection: these

parasites produce resilient spores with a polar apparatus capable of piercing a host cell and injecting infectious sporoplasm into the cytoplasm [67].

For HIV-infected people, increased rates of infection are associated with $CD4^+$ counts of <100 cells/mm^3 but are not associated with higher viral load [68]. Disseminated infection can occur when $CD4^+$ counts decrease to <50 cells/mm^3 [69,70]. Microsporidiasis has been reported following transplantation, but most cases are detected postmortem [71]. Disseminated infection with CNS involvement has been reported following kidney, pancreas, and bone marrow transplantation [71–74].

Primary infection usually begins in the intestines, lungs, or, possibly, bladder and may be asymptomatic [63]. Most microsporidium infections in immunocompetent hosts are asymptomatic, but rare cases of CNS involvement presenting with seizures have been reported [75,76]. The most common clinical manifestation of infection among HIV-infected people is diarrhea, and CNS infection occurs only during disseminated infection, often accompanied by microsporidial sinusitis or keratoconjunctivitis [77]. Although CNS symptoms are dependent on lesion location, seizures are a common manifestation [74].

Diagnosis of microsporidiasis is most often made by detection of organisms in body fluids or tissue biopsy specimens [78,79]. Electron microscopy or light microscopy can be used to speciate microsporidium, but electron microscopy is more successful than light microscopy [80]. Although shedding of microsporidia can be detected in urinary sediment up to 6 months before onset of symptoms, diagnosis is difficult during early infection, and collection of a 24-h urine sample increases the likelihood of detecting the organisms [81]. PCR of tissue biopsy samples is highly sensitive but is not widely available [82]. During CNS infection, spores are often present in peripheral blood [83,84]. CSF examination may demonstrate a neutrophilic pleocytosis and occasionally organisms [65,85]. Serological testing may not be reliable in late stages of HIV infection, because antibody levels are often decreased and difficult to detect [84]. Brain imaging usually reveals multifocal contrast-enhancing lesions in gray or white matter, and meningeal enhancement has been reported in a transplant recipient with CNS infection [65,74,86,87]. Biopsy of CNS lesions typically reveals necrosis and microsporidia spores [88].

Albendazole is effective for treatment of disseminated infection, but improvement may be transient [89]. For HIV-infected people, HAART provides the greatest chance for remission if the $CD4^+$ count increases to >100 cells/mm^3; people without an increase often develop a fatal course [68,90]. Other medications have not been successful for disseminated infection.

LEISHMANIASIS

Leishmaniasis is an obligate intracellular protozoan infection transmitted by the bite of a female sand fly [2]. In injection drug users, syringe sharing is another potential route of transmission, because *Leishmania* parasites have been detected in used syringes [91]. Leishmaniasis is endemic in 88 countries, and nearly 2 million people become infected each year [92]. More than 20 *Leishmania* species can infect humans, with most infections due to *Leishmania donovani* group, specifically *Leishmania infantatum* [93]. In countries where leishmaniasis is endemic, such as India, Nepal, Bangladesh, and Sudan, visceral disease is more commonly encountered in immunocompetent than in immunosuppressed hosts, but disseminated infection is more common in immunosuppressed hosts [94–96]. Among HIV-infected people, higher HIV load is associated with higher prevalence of *Leishmania* coinfection, and lower $CD4^+$ cell count is associated with visceral and disseminated forms of leishmaniasis [94,95]. Visceral disease is more common among people with $CD4^+$ cell counts of <300 cells/mm^3, but disseminated infection usually does not occur until the cell count is <50 cells/mm^3 [97]. Visceral leishmaniasis is the fourth most common AIDS-related infection in southern Spain

[97]. HAART decreases the incidence of visceral infection [98,99]. Leishmaniasis, including visceral disease, has also been reported in patients with immunosuppression following transplantation, in people receiving chronic corticosteroid treatment, and in people with blood dyscrasias [100–106].

Leishmaniasis can produce cutaneous, mucocutaneous, gastrointestinal, or visceral manifestations, and some *Leishmania* species have a predilection for producing one or more of these manifestations [107]. The host defense against *Leishmania* infection is an important determinant of the clinical presentation. Primary infection is usually limited to cutaneous involvement. HIV infection is associated with decreased response to treatment and recurrent infection [105,108]. Although HIV-infected people with visceral leishmaniasis often present with the classical triad of fever, hepatosplenomegaly, and pancytopenia, some present with only fever [109]. In HIV-infected people, symptomatic leishmaniasis may represent reactivation of latent infection rather than primary infection; consistent with this theory, some people develop symptoms years after leaving areas of endemicity [110]. Regardless of host immune status, the most common neurologic manifestation of leishmaniasis is peripheral neuropathy; CNS manifestations are uncommon, regardless of host immune status, but have been reported in immunosuppressed people, usually in conjunction with disseminated infection [111,112]. CNS involvement is believed to occur via extension of contiguous infection, most often from the paranasal sinuses; cranial nerve dysfunction and meningitis have been reported [113–116]. Optic nerve involvement has been reported following extension of conjunctival and sinus infection to the orbital apex, with invasion and erosion of adjacent bony structures [117]. Aside from painful peripheral neuropathies, an ascending demyelinating disease similar to Guillain-Barré syndrome has been reported, but it was largely localized to the peripheral nervous system [118,119].

Diagnosis of leishmaniasis may be made by direct identification of amastigotes in biopsy tissue, serological testing, or PCR. Although serological testing is both sensitive and specific in immunocompetent hosts, in HIV-infected hosts, antibody detection for visceral disease by ELISA or immunofluorescence assay has a sensitivity of only 40%–50% [120,121]. Up to 60% of HIV-infected people with leishmaniasis have amastigotes in serum samples, and amastigotes have been detected in CSF [94,122]. PCR may have a much higher yield, with some studies reporting 100% sensitivity [123,124]. Culture remains the gold standard for speciation, but PCR can be used for speciation in some laboratories. There are no neuroimaging findings specific to CNS leishmaniasis, but CT of the head may be useful for patients with ocular or sinus disease and potential bony invasion [117].

The treatments of choice for visceral leishmaniasis are miltefosine, sodium stibogluconate, or amphotericin B lipid complex, but miltefosine is not available in the United States. Many treatments can produce severe side effects, and most are parenteral [125]. Amphotericin B lipid complex has been used as first-line therapy for HIV-infected people [126]. Up to 30% of HIV-infected people with leishmaniasis experience relapse within 6 months after treatment, regardless of the treatment used; therefore, chronic suppressive therapy is recommended [127,128]. In HIV-infected people, treatment failure and resistance to standard medications are common, so combination therapy is often necessary [129]. Concomitant administration of HAART decreases the incidence of symptomatic visceral leishmaniasis [97].

AFRICAN TRYPANOSOMIASIS

Human African trypanosomiasis (HAT) can be caused by *Trypanosoma brucei gambiense* (in western and central Africa) or *T. brucei rhodesiense* (in eastern Africa) and is contracted from the bite of the tsetse fly (genus *Glossina*) [130]. Although the 2 *T. brucei* subspecies causing HAT are morphologically similar and produce clinically similar CNS symptoms during the

second stage of infection, *T. brucei rhodesiense* progresses from first stage to second stage over weeks rather than months or years [131]. Coinfection with HIV likely modifies the response to treatment but appears to have little if any effect on the clinical manifestations of HAT [132–134]. There are no reported cases of HAT in patients who have received organ or bone marrow transplants, perhaps because of limited disease surveillance and the infrequency of transplantation in these regions of Africa [130]. Although few cases of HAT have been reported outside of tropical Africa, with increasing migration and international travel, HAT is being observed more frequently in the Western Hemisphere [135].

The clinical manifestations of HAT are divided into 2 stages. First-stage symptoms develop 1–3 weeks after the tsetse fly bite and are typically mild. Nonspecific symptoms, such as fever, headache, and malaise, are common, and patients may recall a chancre at the site of inoculation [136]. The second stage of infection is when CNS manifestations begin. *T. brucei rhodesiense* tends to be more aggressive than *T. brucei gambiense* and progresses to the second stage of disease within weeks to months [137]. Initial symptoms may include abnormal gait or speech, mental status changes, and abnormal movements [138]. Sleep disturbance is a classic feature of infection and is usually accompanied by lassitude and distractibility. The normal sleep-wake cycle is reversed, resulting in daytime somnolence and nocturnal insomnia [139]. Progression to late-stage infection may be rapid if due to *T. brucei rhodesiense* or progress over months if due to *T. brucei gambiense,* and it can produce a broad spectrum of neurologic symptoms, including sensori-motor abnormalities, seizures, or coma [137]. The clinical manifestation of infection does not appear to vary by host immune status [132–134].

Diagnosis of HAT is most often made by detection of trypansome-specific antibodies with the card agglutination test for trypanosomiasis. Positive card agglutination test results always requires parasitological confirmation, and CNS infection is confirmed by identification of trypanosomes and elevated WBC count in CSF samples [140]. Although detection of antitrypanosomal IgM in CSF and pleocytosis confirms CNS involvement, some investigators propose increasing the CSF WBC count threshold from >5 cells/μL to >20 cells/μL to improve specificity for CNS involvement [141]. Neuroimaging findings with CT are often normal, but MRI may reveal hypointensity in the basal ganglia [142].

Treatment with pentamidine and/or suramin is successful for early infection but not when CNS involvement is present [143]. Once trypanosomes have entered the CNS, melarsoprol is the only potentially effective treatment for both infections [144]. Eflornithine is effective for CNS infection with *T. b. gambiense,* but it is not available in the United States. No other medication effectively crosses the blood-brain barrier without producing significant toxicity [131]. With treatment, the mortality rate is 2%–7%; untreated, the infection is uniformly fatal [145]. Compared with immunocompetent people with HAT, HIV-infected people appear to have higher risk for treatment failure and worse outcome of both HAT and HIV infection [146, 147]. Treatment with suramin may prevent HIV from penetrating $CD4^+$ cells and inhibit reverse-transcriptase activity [143,148].

CONCLUSIONS

With the exception of cerebral malaria, most parasitic infections of the CNS are uncommon. During some years, outbreaks of endemic infections, such as HAT, may alter the expected epidemiologic characteristics of CNS infections. Although information regarding the effect of immunosuppression on the clinical manifestations and treatment efficacy of parasitic infection is sparse, available information suggests that both HIV infection and transplant-associated immunosuppression lessen the sensitivity of serological testing and increase the risk of disseminated infection and CNS involvement. Clinical manifestations of infection are most often similar to those observed in immunocompetent hosts. Involvement of the CNS typically

portends a poor prognosis. In HIV-infected people, parasitic coinfection usually adversely affects the natural history of HIV infection, but treatment of HIV infection may provide improvement of both conditions.

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Table 1

Transplant type and risk of parasitic infection.

Transplant	Disease	Comments
Heart	Leishmaniasis	Only 2 cases are reported in the literature
Lung	Leishmaniasis, microsporidiasis	Reported in persons living in or traveling to Mediterranean countries
Liver	Microsporidiasis	More common in pediatric transplant patients
Kidney and/or pancreas	Leishmaniasis, microsporidiasis, malaria	Disseminated leishmaniasis tends to occur between 6–12 months after transplantation; concurrent cytomegalovirus dissemination may be seen with microsporidial infection in renal transplantation; malaria has been transmitted via renal transplantation
Bone marrow	Leishmaniasis, microsporidiasis, malaria	Only reported in animal studies; malaria reported following receipt of a transplant from an infected donor

NOTE. Adapted from [29,30,71–74,96,106,149,150].

Table 2

Neurologic and neuroimaging findings associated with selected parasitic CNS infections.

Disease	Neurologic manifestations	Neuroimaging findings	Comments
Malaria	Coma, seizures, cranial nerve dysfunction, cognitive dysfunction; neurologic syndrome after malaria	Cerebral edema, multifocal cortical or subcortical lesions that may be enhanced after gadolinium administration, high signal intensity on diffusion-weighted imaging and decreased signal on apparent diffusion coefficient maps	Severe malaria is more common among HIV-infected people than others
Trypanosomiasis	Mental status changes and sleep, motor, and speech disturbances	Hypointensity of the basal ganglia	HIV-infected people have higher risk for treatment failure and worse outcome of both HAT and HIV; no posttransplantation cases have been reported
Microsporidiasis	Multifocal deficits; seizures are common	Multiple ring enhancing lesions that can involve grey and white matter	CNS infection occurs only during disseminated infection; in HIV-infected people, it is often accompanied by microsporidial sinusitis or keratoconjunctivitis
Leishmaniasis	Peripheral neuropathy, cranial nerve dysfunction, meningitis, optic nerve involvement, Guillain-Barre syndrome	Usually normal	CNS manifestations are uncommon regardless of host immune status; the most common neurologic manifestation of leishmaniasis is peripheral neuropathy

NOTE. Adapted from [77,112–117,119,137,142,151,152]. HAT, human African trypanosomiasis.

Table 3

Diagnostic testing for selected parasitic CNS infections.

Variable	Malaria	Trypanosomiasis	Microsporidiasis	Leishmaniasis
Specimen				
Serum	Serological tests (ParaSight-F and Immunochromoto-graphic Malaria *Plasmodium falciparum* test) are available, but false positive tests are common	…	Spores are seen in serum samples only during massive dissemination	ELISA and immunofluorescence assay have low sensitivity, compared with PCR
CSF	…	WBC count 15 cells/ μL and organisms detected; CSF trypanosomal IgM may be helpful in early stages of disease	Spores can rarely be detected	…
Stool	…	…	Light microscopy of fecal samples to identify spores	…
Urine	…	…	Asymptomatic shedding can be detected in urinary sediment up to 6 months before renal failure or dissemination ensues	…
Skin scraping	…	…	…	In cutaneous form
Gold standard for diagnosis	Detection of parasites on thick and thin blood smears with Giemsa staining	Detection of organisms in CSF samples; card agggglutination trypanosomiasis test	Transmission electron microscopy may be useful for identification of species, but light microscopy is adequate for diagnosis	Culture of a biopsy specimen is required for speciation

NOTE. Adapted from [47,78,79,107,121,124,141].

Table 4

Treatment of selected parasitic CNS infections.

Disease	Treatment	Suppressive therapy required	Comments
Malaria	For suspected cerebral malaria due to *Plasmodium* species with chloroquine resistance or unknown resistance, treatment should include a 10-mg/kg iv loading dose of quinidine in normal saline for 1–2 h; then 0.02 mg/kg iv per min of quinidine until patient can swallow; then quinine tablets, administered at 30 mg/kg for3–7 days[a]	No	Use of steroids and prophylactic anticonvulsants in patients with cerebral malaria have been associated with worse outcome; elevated intracranial pressure should be treated with mannitol
Microsporidiosis	Albendazole 400 mg b.i.d.	Unknown	HAART therapy for HIV-positive patients
Trypanosoma rhodesiense infection	Melarsoprol 2–3.6 mg/kg per day for 3 days; after 7 days, 3.6 mg/kg per day for 3 days; repeat after 7 days	No	Early stage: intravenous suramin 100–200 mg (test dose), then 1 g iv administered on days 1, 3, 7, 14, and 21
Trypanosoma gambiense infection	Eflornithine 100 mg/kg q.i.d. for 2 weeks or melarsoprol 2.2 mg/kg q.d. for 10 days	No	Early stage: pentamidine 4 mg/kg im per day for 10 days or suramin 100–200 mg (test dose) iv, then 1 g iv administered on days 1, 3, 7, 14, and 21
Leishmaniasis	Sodium stibogluconate 20 mg/kg iv or im per day for 28 days or amphotericin B 0.5–1 mg/kg iv daily or every second day for up to 8 weeks or liposomal amphotericin B 3 mg/kg iv per day (days 1–5) and 3 mg/kg iv per day (days 14 and 21) or pentamidine 4 mg/kg iv or im daily or every second day for 15–30 doses	Yes	Amphotericin B is recommended for HIV-infected people and pregnant women

NOTE. Adapted from [6,37,38,48,55,57,77,105,108,144,145,149,153–156].

[a] For additional options, see [6].