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REVIEW ARTICLE

NEUROPARASITIC PROTOZOAL INFECTIONS – REVIEW ARTICLE

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ABSTRACT

Central nervous system infections by protozoa constitute a problem of increasing importance throughout the world. This is partially due to the globalization of our society, tourists and business people being more frequently exposed to parasitic infection in tropical countries than in moderate climate countries. Knowledge of epidemiology, initial clinical signs and symptoms, diagnostic procedures as well as specific chemotherapeutic therapies and adjunctive therapeutic strategies is of utmost important in all of these infections and infestations of the nervous systems, be it by protozoa. This article discusses the clinical presentation, diagnosis, and treatment for some of the more common infections of the nervous system caused by protozoans: *Naegleria fowleri*, *Acanthamoeba spp, Balamuthia mandrillaris, Toxoplasma gondii, Trypanosoma cruzi, Trypanosoma brucei rhodesiense, Trypanosoma brucei gambiense and Plasmodium falciparum.*

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INTRODUCTION

Global emergence of central nervous system (CNS) associated infections is currently being recognized. Pathogenic viruses, bacteria, fungi and protozoa are infecting the human CNS resulting in widespread diseases. Protozoal infections, though endemic to certain regions are also seen outside their original geographical areas, probably facilitated by the increase in international travel and migration of people from their native countries. Global variances including climate changes and pollution have led to changes in these pathogenic organisms (Chimelli, 2011). Despite the implementation of preventive measures to minimize the prevalence of parasitic infections in the most of underdeveloped countries and many of the developing countries, human parasites still account for inestimable loss of life, widespread morbidity and retardation of economic development (Winn *et al.,* 2006). These protozoal infectious diseases are largely known, particularly because immune-suppression associated with HIV infection, solid organ or bone marrow transplant with long-term immune - suppression caused by medications, occurrence of more severe clinical manifestations and failure to respond to specific treatments. For a number of protozoa, CNS is one of the many systems involved; however, this localization may often be the severe and not compatible with the survival of the patient (Chimelli, 2011).

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This review focuses on protozoal parasitic infections in the CNS that are causing and/or associated with significant morbidity and mortality in acute neurological diseases and chronic neurodegenerative conditions. Associations of protozoal infections with major CNS diseases are not traditionally considered but we have included these infections. In this way, this review extends our awareness and understanding of the involvement of infection in the concomitant pathogenesis of CNS disease.

Pathogenesis

The brain's first and perhaps foremost important line of defense is called the blood-brain barrier (BBB) which has a primary function to prevent hydrophilic micromolecules and macromolecules in the blood from entering the extracellular space of the CNS but a select few hydrophobic molecules and hormones. Choroid plexus and pre-optic recess lack the BBB, but usually employ other barriers similar to the BBB such as the blood-cerebrospinal fluid barrier or the blood-retinal barrier (Chimelli, 2011). If pathogens in one way or another manage to penetrate the BBB, they must then contend primarily with microglia (Chimelli, 2011). Thus, one can say that brain is far from a "safe zone" for an invading parasite. Neuropathogenic protozoa have evolved strategies to breach the BBB and invade CNS (Elsheikha and Khan, 2010; Bruschi and Pinto, 2013).

Table 1. Protozoa that may infect CNS (Chimelli, 2011; Winn *et al.,* 2006)

Cerebral abscess		*Entamoeba histolytica Toxaplasma gondii*
Encephalitis	Primary amoebic meningoencephalitis	*Naegleria fowleri*
	Granulomatous amoebic encephalitis	*Acanthamoeba spp*
		Balamuthia mandrillaris
	Acute/ subacute/ chronic encephalitis	*Toxoplasma gondii*
		Trypanosoma cruzi
		Trypanosoma brucei rhodesiense
		Trypanosoma brucei gambiense
Encephalopathy		*Plasmodium falciparum*

Table 2. Strategies used by protozoa to traverse across the BBB (Elsheikha and Khan, 2010; Bruschi and Pinto, 2013)

Sr. No.	Strategies	Mechanism
1	Paracellular route	Involves protozoa crossing of the BBB between the endothelial cells, by degrading the tight junction proteins
2	Transcellular route	Involves penetration of protozoa through the brain microvascular endothelial cells (BMEC) while maintaining its integrity
3	Trojan horse mechanism	By means of infected immune cells like phagocytes.
4	Injury to the cerebral endothelium	Resulting in the disintegration of the BBB
5	Matrix metalloproteinases	By disruption of the BBB and increasing its permeability

Toxoplasma gondii Encephalitis

Epidemiology: Globally, about a third of the world's population is chronically infected with *Toxoplasma gondii* which infects most species of warm blooded animals. Members of family Felidae, are the only known definitive hosts and serve as main reservoirs (Prandota, 2009; Montoya *et al.,* 2010; Tilles, 2014). Principle routes of transmission include- (1) Zoonotic - Directly from ingestion of infective oocysts in food or water contaminated with cats feces or Indirectly, from ingestion of the raw or undercooked meat of animals (2) Transplancental - Vertical transfer to fetus from a mother infected during pregnancy (Winn *et al.,* 2006; Montoya *et al.,* 2010) (3) Organ transplant recipients, which may become infected by receiving an organ from a *Toxoplasma*-positive donor. Rarely, people can also become infected by receiving infected blood via transfusion. Laboratory workers who handle infected blood can also acquire infection through accidental inoculation (Berger , 1995; Montoya *et al.,* 2010).

Pathogenesis: Following ingestion of oocysts, tachyzoites are released in small intestine and first invade the mucosal epithelial cells, from which they enter the circulation, and then are widely distributed in body. As immune response develops, tachyzoites become less active and form tissue cysts in multiple organs which are responsible for residual infection and persist primarily in the brain, skeletal and heart muscle. Loss of cellular immunity then causes reactivation of quiescent infection (Winn *et al.,* 2006; Montoya *et al.,* 2010). All cases of toxoplasmic encephalitis develop as a result of haematogenous spread. In vivo and vitro studies indicate parasite breach the BBB by (1) Trojan horse mechanism, i.e., leucocyte-facilitated entry, and/or (2) Paracellular route, i.e., between the endothelial cells by targeting tight junction proteins (Elsheikha and Khan, 2010).

Clinical findings (Montoya *et al.,* 2010): Patients may have headache, disorientation, drowsiness, hemiparesis, reflex changes and convulsions, and many become comatose (Hill and Dubey, 2002). *Toxoplasma* associated psychiatric sequelae like schizophrenia and other forms of severe psychiatric disorders have been reported in few studies (Kamerkar and Davis, 2012). Damage to CNS is characterized by multiple foci Multiple brain abscesses is the most characteristic feature in patients with AIDS. A diffuse form has been described with widespread microglial nodules without abscess formation in the gray matter of the cerebrum, cerebellum, and brain stem which rapidly progresses to death. Leptomeningitis is infrequent and when present, occurs over adjacent areas of encephalitis. Spinal cord necrotizing lesions are seen at autopsy in approximately 6% of patients.

Diagnosis: Clinical signs of toxoplasmosis are non-specific and are not characteristic for a definite diagnosis. Toxoplasmosis in fact mimics several other infectious diseases. Demonstrations of tachyzoites in CSF establish the diagnosis of acute infection or reactivation. PCR amplification for detection of *T. gondii* DNA successfully diagnosed cerebral toxoplasmosis using CSF (Montoya *et al.,* 2010; Hill and Dubey, 2002). CT scans show single or multiple bilateral cerebral lesions. An enlarging hypodense lesion that does not enhance is seen in MRI (Berger, 1995).

Treatment (Hill and Dubey, 2002): Pyrimethamine, Sulphadiazine are widely used but are useful only in acute toxoplasmosis and can't eradicate *T. gondii.* Follinic acid, Clindamycin, Atovaquone and Azithromycin are also used as anti toxoplasmic drugs. These drugs are effective against tachyzoites, but not against tissue cysts.

Cerebral Malaria (CM)

Epidemiology: The worldwide prevalence of malaria is in the neighborhood of 100 million; one million deaths occur in Africa alone. Most cases occur in refugees; principally from South East Asia (Winn *et al.,* 2006). Malaria is caused by *Plasmodium (P.)* transmitted by bite of infected female anopheline mosquito. Four species cause human disease: *P. falciparum, P. vivax, P. malariae, and P. ovale* (Chimelli, 2011). Only *P falciparum* causes cerebral malaria and it accounts for almost all deaths (Berger, 1995). In holoendemic areas of malaria, cerebral malaria occurs in children between 6 months and 5 years old, most commonly in children aged 3-4 years (Hommel and Gilles, 2010).

Pathogenesis (Elsheikha and Khan, 2010): Once a host is infected by the bite of a vector mosquito, the injected sporozoites enter the exo-erythrocytic cycle and then the erythrocytic cycle. Subsequently to avoid the resulting immune response of host, the parasites use variant surface glycoproteins (VSG) to shield themselves from host antibodies. After completion of each reproductive cycle a new VSG is expressed, preventing the specific response from properly targeting and eliminating the parasites. An important feature of *P. falciparum* is its cyto-adherence characteristic, which result in the sequestration of mostly parasitized erythrocytes in tissues, particularly in small blood vessels throughout the body and thus causing engorgement, hemorrhage, deformation and occlusion. Tumor necrosis factor (TNF) is thought to play a central role in the mechanism of cerebral malaria. Cytokines produced during a malarial infection (particularly IFN-γ and TNF) and possibly toxins released during schizont rupture stimulate macrophages to release high amounts of nitric oxide. Nitric oxide could pass through the BBB and act as a powerful inhibitor of neurotransmitter activity, landing the patient to unarousable coma. Though this mechanism is still not fully understood this may explain why recovery from such coma is so swift and complete.

Clinical findings (Berger, 1995; Hommel *et al.,* 2010): The earliest symptom is usually fever (37.5- 41^0 C) followed by failure to eat or drink. Vomiting and cough are common though diarrhea is unusual. The history of symptoms preceding coma may be very brief (1 or 2 days). Hypoglycemia is common in children below 3 years of age and in those with convulsions, hyperparasitemia or profound coma. In the later, corneal and vestibular – ocular reflexes may be absent. Extreme opisthotonos is sometimes seen. Some are in shock. Convulsions are common before or after the onset of coma. Neurological sequelae which occur in about 10% of children include hemiparesis, cerebral ataxia, cortical blindness, severe hypotonia, mental retardation, generalized spasticity and aphasia. Some develop cortical infarcts and cerebral venous or dural sinus thrombosis as part of a disordered coagulation. Bacterial co-infection may be observed, particularly in those with shock and it accounts for the majority of late deaths (Idro *et al.,* 2010).

Diagnosis: It is a clinical rather than a pathological diagnosis and should be considered in the differential diagnosis of any patient who has a febrile illness with impaired consciousness who lives in or has recently traveled to malaria endemic areas. (Chimelli, 2011) Giemsa staining of thick and thin blood smears can detect parasitemia and identify malarial species. Serological tests (Para Sight-F and Immunochromotographic Malaria *P. falciparum* test) are available, but false-positive test results are common (Kodisinghe *et al.,* 1997). Brain CT may demonstrate cerebral edema during cerebral malaria and when this finding is accompanied by hypo-attenuation of the basal ganglia or cerebellum, it suggests poor prognosis (Looareesuwan *et al.,* 1983; Patankar *et al.,* 2002). Transtentorial herniation is a common finding on CT or MRI in fatal cases of cerebral malaria (Mohsen *et al.,* 2000).

Treatment: Chloroquine sensitive strains are treated with 0.83mg/Kg body weight, by continuous IV infusion over 30 hours. Chloroquine resistant strains are treated with quinine 10 mg/Kg body weight, by continuous IV infusion over 4 hours, every 8 hours and may switch to oral quinine, 600 mg TDS on return to consciousness (Berger, 1995). Artemisinin-based combination therapies are now recommended by the WHO as first-line treatment of uncomplicated falciparum malaria in all areas where malaria is endemic. Parenteral artesunate is replacing quinine for the treatment of severe malaria (Mallewa *et al.,* 2014).

Trypanosomiasis

Trypanosomes are haemoflagellates that cause disease in large, but geographically restricted, parts of the world. There are three species of *Trypanosoma* (*T. brucei gambiense and rhodesiense and T. cruzi*), that affect man, all transmitted by blood-feeding insects. Though morphologically similar in their trypomastigote blood form, they give rise to quite different diseases in Africa and South America, African Trypanosomiasis (sleeping sickness) and American Trypanosomiasis (Chagas Disease) respectively (Walker and Zunt, 2005).

African Trypanosomiasis (sleeping sickness)

Epidemiology: Human African Trypanosomiasis (HAT) is endemic to sub-Saharan Africa (Smith *et al.,* 1998). But as the reporting is not standardized, it diminishes the actual number of cases reported. Widespread political unrest again adds to it. Two subspecies of *Trypanosoma brucei* cause human disease: *T. brucei gambiense* (West African or Gambian) and *T. brucei rhodesiense* (East African or Rhodesian, also known as sleeping sickness). The tsetse fly is the vector for both *Trypanosoma* spp. and is unique to Africa (Tilles, 2014). Only a few dozen cases of sleeping sickness in United States citizens have been reported over the past half-century, the majority occurring after travel through an endemic region (Hommel *et al.,* 2010).

Pathogenesis: A superficial chancre usually develops at the site of the tsetse fly bite (McGovern *et al.,* 2015). Larvae within the chancre migrate through blood and lymphatic vessels, maturing and reproducing during migration (Kristensson *et al.,* 2002). It is not clear how circulating parasites cross the BBB to produce disease though it has been proposed that it causes direct penetration of the capillary endothelium at the sites of the BBB as *Trypanosoma* can be visualized in direct association with the capillary endothelium (Elsheikha and Khan, 2010). The parasite can periodically modify surface glycoproteins to evade detection by the host immune system. Host immune response by monocytes, macrophages, and plasma cells often causes vascular permeability, resulting in adverse patient outcomes. Most often, vascular infiltration produces a meningoencephalitis, with prominent hemorrhage and edema (Walker and Zunt, 2005).

Clinical findings (Winn *et al.*, 2006; Berger, 1995): Duration of illness is months to years. Stage one of disease mainly shows hemolymphatic manifestations like spiking fever with afebrile periods, lymphadenopathy, transient edema of face and hands, pruritus and circinate rash etc. Stage two of disease is marked by the onset of neurological manifestations like irritability, personality changes, loss of concentration, somnolence, restlessness, indistinct speech, extra pyramidal signs, ataxia and parkinsonism symptoms (Ponte-Sucre, 2016). Although brain and meninges are involved, meningismus is uncommon. Death often results from coma or secondary infection caused by the severe neurological damage (e.g.,

aspiration during seizures) (Mhlanga *et al.,* 1997). Fatal arrhythmias produced by trypanosomal invasion of the heart are also a common cause of death (Walker and Zunt, 2005).

Diagnosis (Tilles, 2014**):** Definitive diagnosis is achieved by identifying trypanosomes in wet preparation of stained blood, centrifuged CSF or biopsied tissue (CDC, 2003). In addition, Buffy coat concentration method can also be used. A simple rapid card test, the card indirect agglutination trypanosomiasis test can be used for antigen detection. Serological techniques like ELISA, indirect haemagglution test and the card agglutination trypanosomiasis test are also available. If clinical suspicion for HAT is high, CSF should be examined using PCR assay and light microscopy (Lejon and Buscher, 2001). No specific CT findings have been reported. Brain MRI may demonstrate focal high signal abnormalities in the white matter, specifically with T2 sequences which may however disappear after treatment (Gill *et al.,* 2003).

Treatment (Tilles, 2014): Treatment should be started at earliest possible and require prolonged administration. Melarsoprol, a toxic trivalent arsenic derivative, is commonly used. Eflornithine is used for melarsoprol resistant infection (Walker and Zunt, 2005). Any individual treated for African trypanosomiasis should be monitored for 2 years after completion of therapy.

American Trypanosomiasis (Chagas Disease)

Epidemiology: *Trypanosoma cruzi* is endemic to most South and Central American countries. Infection is most often acquired from the bite of the reduviid bug but can also occur transplacentally, by ingestion of infected guinea pig or by blood transfusion or organ transplantation. With increasing urbanization and emigration, infection has spread beyond rural Latin America to the United States and other parts of the world. Transmission via transfusion occurs more often in urban areas, when migrants from highly endemic rural areas contribute infected blood to blood banks (Tilles, 2014; Walker and Zunt, 2005; Dias *et al.,* 2002).

Pathogenesis: While taking a blood meal from a potential host, the vector leaves fecal waste containing *T. cruzi* eggs on the skin or mucous membranes (Kirk and Schofield, 1987). Eggs are introduced into the human host through broken skin produced by itching around the site of the insect bite. Once inside the host, the larvae mature and divide via binary fission. These cells are shed into the bloodstream and travel to distant sites where they become intracellular organisms and mature into adults (Tilles, 2014; Hall and Joiner, 1993). Unlike African trypanosomes, *T. cruzi* do not replicate in the bloodstream, but divide only after infecting a new cell or after ingestion by an accidental host. Rupture of infected cells releases infectious parasites as well as potent inflammatory parasitic molecules that induce a strong host response (Hall and Joiner, 1993).

Clinical findings (Winn *et al.,* 2006; Tilles, 2014): Children are most commonly affected than adults. In the acute form of the disease, an inflamed and oedematous chagoma may develop at the site of bug bite, commonly face area. When the conjunctiva is the portal of entry, painless oedema of the perioccular tissue developes called as classic Romana's sign. Fever, malaise, anorexia, generalized lymphadenopathy, oedema of face and lower extremities and hepatosplenomegaly of varying degrees of severity may be observed. Progression from an acute generalized febrile illness to a symptomatic (chronic) infection occurs in less than 5% of infected people (Prata, 2001). The most common CNS manifestation of chronic infection is meningoencephalitis (Walker and Zunt, 2005). Meningoencephalitis progressing through confusion, apathy, stupor coma and death may occur. In the chronic form, cardiomyopathy is the leading cause of the death. Megaoesophagus and megacolon are the other complications.

Diagnosis (Tilles, 2014): Parasites can be detected in the blood so multiple thick and thin smears should be prepared and in addition Buffy coat concentration method can also be used (CDC, 2003). Molecular diagnostics like PCR are used in reference laboratories and xenodiagnosis where reduviid bug is endemic. Immunoassays are used to detect antigens in urine and sera of patients and are useful for early diagnosis. Serlogical tests include complement fixation, indirect fluorescent antibody and indirect haemagglutination test and ELISA. It can also be diagnosed on the basis of histology. Imaging findings are variable and depend primarily upon the patient's immune status. The most common abnormality encountered is one or more ring-enhancing lesions involving both gray and white matter (Di Lorenzo *et al.,* 1996).

Treatment: Only acute Chagas' disease can be eradicated by treatment. Treatment of chronic infection is symptomatic. When clinical suspicion is high, treatment of acute infection should be initiated early, even if preliminary testing is negative (Urbina, 2001). Nifurtimox(Lampit) and Benznidazole (Radamil) reduce severity of the acute disease. Other drugs like allopurinol, flucanazole, itraconazole and ketoconazole have been used in treatment in limited number of patients. Drug therapy has little effect in reducing the progression of chronic chagas disease and surgery may sometimes help (Tilles, 2014).

Primary Amoebic Encephalitis (PAM)
Naegleria

Epidemiology: *Naegleria fowleri* is a free-living amoeba encountered in soil, fresh water, and hot springs. It is found in swimming pools, lakes, and rivers, which are commonly used during the summer months, when the parasite preferentially multiplies (Chimelli, 2011). It has a worldwide distribution, occurring as individual cases or small outbreaks. Although the majority of case reports are from the USA, Australia, and Central America this may reflect recognition of the disease (Chimelli, 2011). Most infections occur in children and young adults who play or dive in bodies of stagnant freshwater during warm summer months (Gyori, 2002).

Pathogenesis: The amebae may enter the nasal cavity by inhalation or aspiration of water, dust or aerosols containing the trophozoites or cysts, following that, it penetrates the nasal mucosa, probably through phagocytosis of the olfactory epithelium cells and migrates via olfactory nerves to brain (Tilles, 2014). *N.fowleri* uses the brain vasculature to reach the meninges surrounding the frontal lobes, in which they multiply and destroy CNS tissue (Morton, 1997). Adhesion plays a crucial role in the amoeba's ability to quickly access its infection target. This is due in part to the amoeba's possession of a surface protein that is similar to the human integrin-like receptor that provides exceptional bonding to fibronectin, one of many extracellular matrix glycoproteins that make up the structure of the matrix of the host's cells. Efficient locomotion

and a relatively direct access to the site of infection minimize opportunities for a strong immune response to be launched by the host prior to the parasite reaching the sensitive brain tissue.

Clinical Findings: PAM caused by *N. Fowleri* is an acute, suppurative infection of the brain and meninges and it is rapidly fatal in humans. The period between organism contact and onset of symptoms such as fever, headache and rhinitis varies from a few days to 2 weeks. Early symptoms include vague upper respiratory tract distress, headache, lethargy and occasionally olfactory problems. Progressive symptoms include pyrexia, vomiting and stiffness of neck (Tilles, 2014). Mental confusion and coma occur usually 3-5 days prior to death (Tilles, 2014). Later, photophobia and cranial nerve palsies that may indicate brain edema and herniation can be observed. Intracranial pressure is usually raised to 600 mm H2O or higher. Increased intracranial pressure and herniation are usually the cause of death (Trabelsi *et al.,* 2012).

Diagnosis: A high index of suspicion is often critical for early diagnosis. CSF examination will show low glucose and high protein concentration with leukocyte count from several hundreds to >20,000/ $mm^{3.}$ A confirmed diagnosis is made by the identification of the amoebae in the CSF or in the biopsy specimen (Tilles, 2014). Trichrome and Giemsa staining of CSF may also be useful. Most cases are diagnosed at autopsy. Confirmation findings must include culture and / or staining with monoclonal reagents in direct fluorescent antibody procedures. Neuro-imaging is usually normal initially, but severe edema may be present, localized to the posterior fossa and brain stem (Ferrante , 1991; Tilles, 2014).

Treatment: In treating PAM, the drug of choice is the antifungal polyene antibiotic amphotericin B (AMB). In fact, *Naegleria* are highly sensitive to this drug, with a minimal amoebicidal concentration of 0.026 to 0.078 mg/mL (Duma *et al.,* 1971). This treatment must be started early in order to be effective. Adjunct hyperbaric therapy has been used, with limited success. Miconazole, rifampin, and sulfisoxazole may also be effective (Seidel *et al.,* 1982).

Granulomatous Amoebic Encephalitis (GAM)

Epidemiology: Several species of *Acanthamoeba* and *Balamuthia mandrillaris* are ubiquitous within the environment in both soil and water and are the most frequent free-living amoebae that cause this pattern of disease, especially in immunocompromised, chronically ill or otherwise debilitated patients (Tilles, 2014). The main risk factors are HIV infection, lymphoma, malnutrition, cirrhosis, and diabetes. These patients usually have no relevant history of involving fresh water exposure. There have been fewer cases of *Acanthamoeba* CNS infection than of *Naegleria* infection. More than half of these are reported in USA (Tilles, 2014; John, 2010). Both are present throughout the world in soil and sometimes in freshwater. Although both organisms are capable of living in water, they are not encountered as frequently as *Naegleria* spp. and stagnated water is not a requirement (Healy, 2002). *A. histolytica* has been isolated from water fountains and contact lens and is a common cause of self-limited and mild keratitis (McCulley *et al.,* 2000).

Pathogenesis: The ways of entry include the lower respiratory tract and skin lesions followed by hematogenous spread. *Acanthamoeba* enter into the CNS most likely occurs through the BBB, particularly, through the endothelial lining of cerebral capillaries (Martinez, 1985; Bruschi and Pinto, 2013). In few cases, pathogens that reach CSF enter by the choroid plexus. Lesions are also observed in the basal ganglia, midbrain, brain stem and cerebral hemispheres with characteristic lesions in the CNS parenchyma resulting in chronic granulomatous encephalitis. Haematogenous spread can also occur to other body parts. The microscopic findings of the post-mortem biopsies reveal amoebae trophozoites and cysts, predominantly in the perivascular spaces in the parenchyma (Khan, 2006).

Clinical findings: The clinical course tends to be subacute or chronic and is usually associated with trauma or underlying diseases and not as a result of swimming. GAM may present with symptoms of confusion, dizziness, drowsiness, nausea, vomiting, headache, lethargy, stiff neck, seizures and sometimes hemiparesis (Tilles, 2014). Dissemination to other tissues like liver, kidneys, trachea and adrenals can occur in immunocompromised patients. Some patients, especially with AIDS, can develop erythematous nodules, chronic ulcerative skin lesions or abscess (Tilles, 2014). Until 1997, all human cases of *B. mandrillaris* infection had been diagnosed at autopsy (Healy, 2002). Encephalitis develops more slowly with *B. mandrillaris* infection and often takes months until clinical symptoms develop. Immunosuppressed hosts are more likely to develop a virulent hematogenous or cutaneous infection or granulomatous meningitis (Martinez and Visvesvara, 1997).

Diagnosis: Definitive diagnosis can be obtained by demonstration of trophozoites or cysts of *A. histolytica* on stained smears of biopsy specimens or corneal scrapings (CDC, 2003; John, 2010). Direct IFA tests can be useful. Differentiation between *B. mandrillaris* and *A. histolytica* infection requires immunofluorescence studies (CDC, 2003). Examination of contact lenses from patients with keratitis can reveal *A. histolytica*. Contrast-enhanced head CT of patients with *B. mandrillaris* CNS infection usually demonstrates ring-enhancing lesions. MRI shows diffusion-restriction within the abscess cavity and prominent edema on T2 that can resolve after treatment. Calcifications are seen in patients with chronic infection (Healy, 2002).

Treatment: There is no satisfactory treatment for GAE, partly because most of the cases are diagnosed after death. Few cases have been found to be sensitive to ketokonazole, pentamididne, hydroxyl--stilbamidine, paromomycin etc (Tilles, 2014). In children, successful treatment has included trimetho-primsulfamethoxazole, rifampin, and ketoconazole (Singhal *et al.,* 2001). Eye and skin infections are treatable, but if the CNS is infected, death usually occurs within weeks to months (Martinez and Visvesvara, 1997).

Conclusion

Although parasitic infections of the CNS seem to be infections of resource-limited and developing countries, with the increasing amount of international travel, all travelers to endemic regions are potentially at risk, with such infections becoming increasingly prevalent throughout the world. As unappealing as parasitic infections are, it's worth noting that most of the time, these infections go unnoticed. As close as we may be with these organisms, though, invasion of CNS is too close for comfort and must always be taken seriously. CNS

parasitic infections can be life-threatening, but are often preventable and treatable; however, clinical outcomes largely depend on early diagnosis and treatment. Basic familiarity with common pathogens can make diagnosis more efficient. For the clinician confronted with a patient with suspected parasitic infection, additional assistance with diagnostic evaluation and therapy can be obtained at the following websites www.cdp. cdc.gov/dpdx/ and www.who.int/inffs/en/index.html.

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