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REVIEW ARTICLE

Fungal and Parasitic CNS Infections

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Abstract Central nervous system fungal infections can be broadly divided into those that infect a healthy host such as *Cryptococcus*, *Coccidioides*, *Histoplasma, Blastomyces*, *Sporothrix* spp., and those that cause opportunistic infections in an immunocompromised host such as *Candida*, *Aspergillus*, Zygomycetes, *Trichosporon* spp. The clinical manifestations of central nervous system fungal infections commonly seen in children in clinical practice include a chronic meningitis or meningoencephalitis syndrome, brain abscess, rhino-cerebral syndrome and rarely, a fungal ventriculitis. Fungal central nervous system infections should be suspected in any child with subacute to chronic febrile encephalopathy or meningitis with or without raised intracranial pressure, seizures, orbital pain and/or sero-sanguinous nasal discharge. Diagnosis is corroborated by cerebrospinal fluid analysis, culture and PCR, special stains, serological tests and neuroimaging. Management of fungal central nervous system infections include specific antifungal therapy and supportive measures for associated problems, management of underlying predisposing condition and surgical intervention in cases with localized disease, abscess or presence of simultaneous foreign body such as intracranial shunts. In addition to the fungi, several parasitic infections can cause central nervous system infections in children. Of these, authors briefly discuss cerebral malaria, and amebic meningo-encephalitis.

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Fungal CNS Infections

Fungal central nervous system (CNS) infections can be broadly divided into those that infect a healthy host (*Cryptococcus*, *Coccidioides*, *Histoplasma, Blastomyces*, *Sporothrix* spp) and those that cause opportunistic infections in an immunocompromised host (*Candida*, *Aspergillus*, Zygomycetes, *Trichosporon* spp) [1]. Although fungal CNS infections in immune-competent host are rising, yet the majority of these infections occurs in children with underlying predisposing infections such as hematological malignancies, neutropenia, primary or acquired immunodeficiency syndrome, immunosuppressive drugs, malnutrition, prolonged potent antibiotic or corticosteroid therapy, prematurity and chronic systemic diseases such as diabetes and chronic renal failure [2, 3]. The true incidence of fungal CNS infections in children is unknown. The incidence of cryptococcal meningitis is estimated to be nearly one per one lakh population. *Candida, Zygomycetes* and *Aspergillus* are ubiquitous fungi and are reported from almost all geographical areas whereas *Coccidioides*, *Histoplasma* and *Blastomycosis* have rarely been reported outside of the US.

In majority of cases, the primary site of infection is the lungs and rarely the skin followed by hematogenous spread to the CNS. *Mucor* and *Aspergillus* may spread directly by contiguous spread from paranasal sinuses, ear or orbit or *via* blood vessels to the CNS. Direct inoculation during head injury or neurosurgical procedures and contiguous spread from osteomyelitis of skull or vertebrae are uncommon modes of infection in children. Once inside the nervous tissue, the pathological findings vary from meningitis and meningoencephalitis to micro-abscesses, focal necrosis, granulomatous

inflammation, large abscesses, angioinvasion and infarction [3]. The basic lesion is a combination of suppurative and granulomatous inflammation. Smaller fungi such as yeast spread *via* the cerebral microcirculation and cause micro-abscesses, while the hyphal forms and moulds cause focal lesions with angioinvasion resulting in infarction and hemorrhagic necrosis.

Clinical Features

CNS fungal infections do not have pathognomonic signs and symptoms. The clinical manifestations of CNS fungal infections commonly seen in children in clinical practice include a chronic meningitis or meningoencephalitis syndrome, brain abscess, rhino-cerebral syndrome and rarely, a fungal ventriculitis. Initial features are often non-specific consisting of general debility, failure to thrive, chronic fever, headache, vomiting, meningismus, subacute dementia, seizures or neurological deficits [4, 5]. The course is often severe and rapidly fulminant in immunocompromised children. Fungal CNS infections should be suspected in any child with subacute to chronic febrile encephalopathy or meningitis with or without raised intracranial pressure, seizures, orbital pain and/or serosanguinous nasal discharge [6]. Rarely, fungal spinal cord involvement may present as myelopathy, myeloradiculopathy, intramedullary granuloma or epidural abscess [2].

Diagnosis

Cerebrospinal fluid (CSF) examination shows mononuclear pleocytosis (20–500 cells/mm^3), elevated proteins and reduced to normal glucose. Polymorphonuclear leukocytes are generally <50% and may predominate in meningitis caused by fungi such as *Aspergillus* and mucormycosis. Rarely, chronic neutrophilic meningitis or eosinophillic meningitis may be seen. In children with compromised immunity due to acquired immunodeficiency syndrome (AIDS) or high-dose corticosteroids, cell count in the CSF may be very low (<20 cells/mm^3) or normal, especially in cryptococcal meningitis. Very high protein concentrations (>1 g/dL) indicate a CSF subarachnoid block. A fungal brain abscess may present with normal lumbar CSF parameters or mildly elevated cells and proteins with normal glucose. Encapsulated yeasts are easily identified by India Ink stains under direct microscopic examination and yield is higher in children with AIDS infection. Identification of the organism by culture from CSF or biopsy samples remains the gold standard for diagnosis although cultures are frequently negative and have a lower turnaround time (3 d to 6 wk). Use of larger volumes of CSF (10–30 ml), centrifuged samples, cisternal CSF and repeated examinations may improve the yield of CSF. Methanamine silver stain helps in easy identification of the fungi from tissue samples even when cultures are negative for fungal growth. Blood cultures are generally negative during fungal meningitis, except for *Candida* in neonates and, *Cryptococcus* and *Histoplasma* in AIDS patients.

Serological tests are particularly helpful in cryptococcal infection and CSF-based polysaccharide antigen detections assays show 93–100% sensitivity and 93–98% specificity [7]. Lateral-flow immunoassay for detection of cryptococcal antigen has also been developed [8]. The polysaccharide antigen tests may be positive early in the infection and titers ≥1:8 are diagnostic of cryptococcal meningitis although any titer may be significant in the correct clinical and laboratory context [9]. When CSF cryptococcal antigen is positive in cases where cryptococcal meningitis was not being clinically considered (false positive), it should be repeated before a diagnosis is made. Repeated negative antigen titers over atleast 1 mo rule out the diagnosis of cryptococcal meningitis [9]. Complement fixing antibody titer of ≥1:32 from CSF is diagnostic of meningitis due to *Coccidioides* in >90% of cases. Other potentially useful serological tests include *Aspergillus* galactomannan index in CSF and serum (index value >0.5 in serum has >80% sensitivity and specificity), 1,3-beta-D-glucan test for disseminated candidiasis, CSF mannitol and lactic acid concentrations for identification of yeast and specific antibodies for *Histoplasma*, *Zygomycetes* and *Sporothrix*. Finally, fungal polymerase chain reaction (PCR) can be used to detect the organism as well as to monitor treatment response.

Neuroimaging may show non-specific features such as basal involvement, discrete mass lesions with or without contrast enhancement, associated abscess and areas of infarction. Fungal brain abscesses are T1-hypointense, T2-hyperintense with well-defined contrast-enhancement and high apparent diffusion coefficient. Proton magnetic resonance spectroscopy shows lipid, lactate, amino acids and trehalose. Specific neuroimaging findings include small intraventricular or intraparenchymal cryptococcomas (Fig. 1) and pseudocysts in *Cryptococcus*; opacification of paranasal sinuses, variable mucosal thickening, bony erosion in rhino-cerebral mucormycosis with intracranial vascular thrombosis and infarction, mycotic emboli, frontal lobe abscess (Fig. 2a & b) and involvement of cavernous sinus; multiple punctate enhancing nodules on contrast CT and T2-hypointense granuloma and micro-abscesses and ring enhancement on contrast administration, meningitis, vasculitis and infarction on MRI in *Candida* [10].

Treatment

Management of fungal CNS infections include specific antifungal therapy (Table 1) and supportive measures for associated problems such as raised intracranial pressure, metabolic derangements, management of underlying predisposing condition and surgical intervention in cases with localized

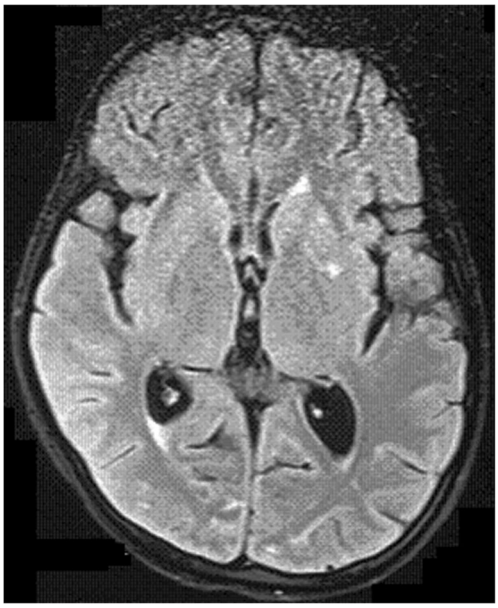

Fig. 1 Magnetic resonance imaging FLAIR-weighted axial sections showing small, discrete hyperintense lesion expanding the Virchow-robin space in the left basal ganglia consistent with CNS cryptococcoma

disease, abscess or presence of simultaneous foreign body such as intracranial shunts. Amphotericin-B is the most common and successful antifungal in majority of CNS infections although drug levels in the CSF are generally low or unmeasurable. Flucytosine has good CSF penetration and is commonly used as an adjunct to amphotericin or fluconazoele. Fluconazole also has good CNS penetration and is active against *Cryptococcus* and *Candida* although CSF sterilization is slower as compared to amphotericin-containing regimen. Voriconazole, a newer generation azole, has broader spectrum of activity against a variety of fungi including *Aspergillus, Fusarium, Scedosporium* and dematiaceous fungi and has shown favorable clinical experience making it the drug of choice against CNS aspergillosis and scedosporiosis. Capsofungin, an echinocandin, is a newer antifungal drug best used in combination with amphotericin-B for refractory invasive candidiasis and in combination with voriconazole for refractory CNS aspergillosis. Management of fungal brain abscess and fungal ventriculitis is not standardized and may require prolonged antifungal therapy. The Infectious Diseases Society of America has proposed clinical guidelines of the treatment of fungal CNS infections and should be looked into to guide the choice of appropriate antifungal therapy [11–13].

Outcome

Outcome is primarily determined by the causative fungus and the patient's underlying condition. Mortality is higher (10–50%) with angioinvasive fungi and lesser with *Candida* (10–20%) and *Cryptococcus* CNS infections.

Future Research

Role of cryptococcal vaccine and prophylactic azoles against histoplasmosis and coccidioidomycosis in HIV-infected patients is currently under investigation.

Parasitic CNS Infections (Excluding NCC)

Several parasitic infections can cause CNS infections in children such as *Plasmodium* spp. causing cerebral malaria, *Toxoplasmpsosa gondii* causing toxoplasmosis, free-living and parasitic ameba causing amoebic meningoencephalitis or brain abscess and African trypanosomes causing African sleeping sickness amongst the protozoans, and *Taenia solium* (pork tape worm) causing cysticercosis, Echinococcus species

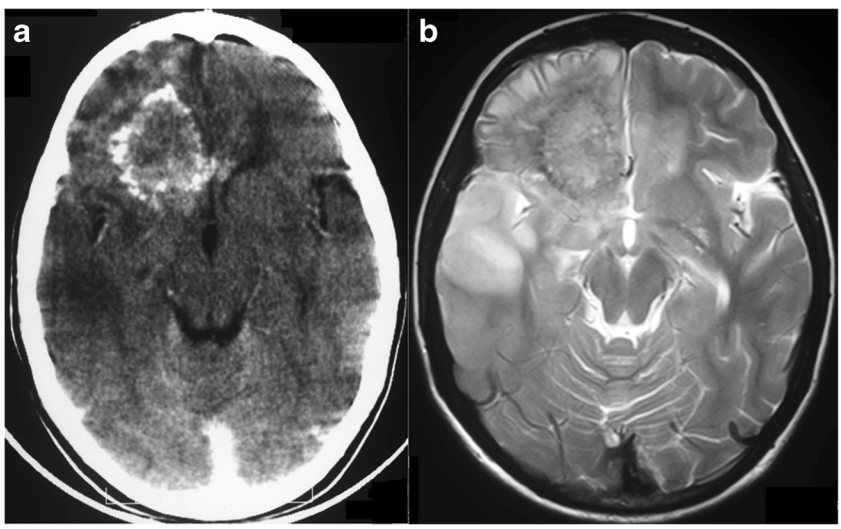

Fig. 2 **a** Contrast-enhanced computed tomography axial section of the brain showing a well-defined lesion in the right frontal lobe with surrounding edema and peripheral contrast enhancement (**b**) Magnetic resonance imaging T2-weighted axial section of the brain showing a well-defined circumscribed lesion in the right frontal lobe with hypointense rim, surrounding edema and gyral swelling

Table 1 Specific treatment recommendations for common pediatric fungal CNS infections

Fungal pathogen	Recommended antifungal therapy
Cryptococcus neoformans	First choice
	Amphotericin-B (0.7 to 1 mg/kg/d IV infusion) plus flucytosine (100 mg/kg/d PO in four divided doses) for 4 wk followed by maintenance with Fluconazole (6 mg/kg/d) PO for 6 mo to 1 y
	Second choice
	Liposomal amphotericin-B (3–5 mg/kg/d) *or* Lipid complex (5 mg/kg/d) plus flucytosine (100 mg/kg/d PO in four divided doses)
Candida	First choice
	Liposomal amphotericin-B (3–5 mg/kg/d) with or without Flucytosine (100 mg/kg/d PO in four divided doses) PO for 2–3 wk followed by fluconazole (6–12 mg/kg/d) PO for 4–6 wk. (based on clinical and radiological improvement)
	Second choice
	Fluconazole (6–12 mg/kg/d) or Voriconazole (6 mg/kg/d in two divided doses followed by 3 mg/kg/d) IV for patients unable to tolerate amphotericin-B
Aspergillosis	First choice
	Voriconazole (5–7 mg/kg IV every 12 h) for 6 mo to 1 y. Higher doses can be used in children and should ideally be guided by therapeutic drug monitoring, especially in refractory cases. Total duration of therapy is not clearly defined.
	Second choice
	Liposomal amphotericin B (3–5 mg/kg/d) IV, Lipid complex amphotericin (5 mg/kg/d) *or* combination therapy with voriconazole (6 mg/kg/d in two divided doses) and caspofungin (50 mg/m^2/d)
Mucormycosis	First choice
	Amphotericin B 1.5 mg/kg/d IV by continuous infusion *or* Liposomal amphotericin B (3–5 mg/kg/d) IV
	Second choice
	Posaconazole (200 mg PO four times a day or 400 mg PO twice a day) (Data for pediatric dosing not available)

causing hydatid disease, *Angiostrongylus*, *Gnathostoma* spp. causing eosinophilic meningitis and *Schistosoma* species causing schistosomiasis amongst the helminthes. Of these, authors briefly discuss cerebral malaria, and amebic meningo-encephalitis here. Neurocysticercosis has been discussed in a separate chapter.

Cerebral Malaria

Malaria is a major cause of mortality and morbidity in endemic countries. This important tropical infection is caused by five *Plasmodium* species (*vivax, ovale, malariae, falciparum* and *knowlesi*). Cerebral malaria is the clinical syndrome of unexplained coma in a patient with malarial parasitemia. In addition to signs of CNS dysfunction, patients, especially adults frequently have renal, hepatic and respiratory failures [14]. The condition is universally fatal without treatment and optimal care reduces the mortality to 15–25%. Even with treatment, one-third of pediatric survivors have neurological sequelae.

Plasmodium falciparum causes almost all cases of severe disease including cerebral malaria; *P. vivax* and *P. knowlesi* are uncommon causes of cerebral malaria. *Plasmodium* life-cycle involves two hosts. During a blood-meal, an infected female *Anopheles* mosquito inoculates sporozoites into the human host. The sporozoites infect liver cells and mature into schizonts which rupture to release the merozoites. In *Plasmodium vivax* and *ovale,* a dormant stage (hypnozoites) may persist in the liver cells causing relapses. The merozoite subsequently infects the red blood cells and mature from ring trophozoites to schizonts which rupture to release the daughter merozoites and pyrogens into the blood stream. Some merozoites differentiate into sexual forms (gametocytes) and complete the life cycle in the *Anopheles* mosquito after a blood-meal [15]. The sequestration of parasitized red cells in the organ vasculature, excessive pro-inflammatory cytokine production [16], microvascular thrombosis [17], loss of endothelial barrier function [18] and endothelial dysregulation [19] are thought to cause the major complication of falciparum malaria [20]. Other potential contributors to raised intracranial pressure in children with cerebral malaria include cytotoxic edema, vascular congestion, hyperemia, acidosis, hyperthermia, seizures and hypoglycemia.

Clinical Features

In endemic areas, cerebral malaria commonly affects children between 6 mo and 5 y of age. Cerebral malaria is characterized by a non-specific prodrome of fever, anorexia, cough, restlessness, headache and vomiting lasting 1–3 d and rapidly progressing to seizures, meningismus, drowsiness and coma in untreated patients. Fever is generally acyclical in malaria and corresponds to the release of pyrogens at the time of schizont rupture. In endemic areas, any child presenting with fever and altered sensorium should be investigated and treated for cerebral malaria. A high index of suspicion is needed for subclinical seizures in the unconscious patients. Other systemic manifestations include severe anemia secondary to sequestration, accelerated splenic clearance and hemolysis; profound thrombocytopenia; hepatosplenomegaly; gastrointestinal bleeding; severe acidosis; hypoglycemia; shock and multiorgan dysfunction. The presence of distinctive retinopathy comprising of retinal whitening, blood-vessel color change and retinal hemorrhages helps differentiate cerebral malaria from other causes of encephalopathy especially in children [21]. The presence of retinal abnormalities is 95% sensitive and 90% specific in identifying children with sequestration of parasitized erythrocytes in brain vessels [22]. It is even said that children with clearly defined cerebral malaria and absence of retinopathy are more likely to have a non-malarial cause of coma [14].

Diagnosis

Diagnosis of cerebral malaria requires demonstration of asexual form of *P. falciparum* in thick and thin peripheral blood smears. Examination in cerebral malaria shows mildly elevated pressures, minimal cellular response, normal CSF-to-serum glucose ratio and mildly elevated proteins. CSF leukocytosis should raise the suspicion of concurrent or isolated bacterial meningitis. Bedside rapid diagnostic tests based on antigen detection such as *P. falciparum* histidine rich protein 2 and lactate dehydrogenase are helpful for early confirmation. Advanced investigations such as m-RNA or DNA-based PCRs may be helpful in species identification but take time and are not routinely available [23]. Neuroimaging commonly reveals diffuse cerebral and cerebellar edema, cortical or subcortical infarcts in watershed zone, diffusion restriction in cortex and deep gray matter, white-matter signal changes and rarely bilateral thalamic necrosis.

Treatment

Cerebral malaria is a neurological emergency. The mainstays of therapy are optimal supportive care, timely antimalarials drugs and early detection and treatment of complications such as hypoglycemia, shock, anemia, clinical and subclinical seizures, and organ dysfunction syndromes. Specific parenteral antimalarial treatment is the only intervention that unequivocally affects the outcome of cerebral malaria [15]. Currently, the two classes of antimalarials are the cornerstone of therapy: parenteral cinchona alkaloids (quinine or quinidine) and artemisinin derivatives (artesunate and artemether) [24]. Cinchona alkaloids act only on later stages of the parasite and are associated with more side-effects; hence less commonly used as compared to artemisinin derivatives [25]. Artesunate (2.4 mg/kg intravenous first dose, repeated at 12 and 24 h, followed by 2.4 mg/kg once daily) is preferred over artemether (3.2 mg/kg followed by 1.6 mg/kg/d for 5 d or till oral acceptance) as it can be administered both intravenously and intramuscularly. Once the patient has received atleast 24 h of parenteral therapy and is able to tolerate oral medications, oral artemisinin drugs are combined with longer-acting drugs such as mefloquine, amodiaquine or lumifantrine. Primaquine should be given to all patients to prevent relapse. The role of adjuvant therapy in reducing mortality and neurological sequelae is not clearly established.

Prevention

Primary prevention strategies include insecticide-impregnated bed nets, chemoprophylaxis with sulfadoxine-pyrimethamine in special vulnerable population groups in high transmission areas and development of anti-malaria vaccine.

Future Research

Further studies are needed in the role of adjuvant therapy, efficacy of vaccines against malaria, and effective malaria control measures in malaria endemic areas with high transmission rates.

Free-Living and Parasitic Amebic Infections

CNS infection with free-living and parasitic amebae is rarely seen in children but is potentially life-threatening. Free-living amebae are aerobic, single-celled protozoan that are ubiquitously found in fresh water lakes, sediments, thermal springs, swimming pools, air conditioning vents and domestic water supplies [26]. Amebic meningo-encephalitis refers to an infection of the brain parenchyma and meninges caused by these organisms. Four genera are associated with human disease: *Naegleria (only N. fowleri), Acanthamoeba (several species), Balamuthia (only B. mandrillaris), Sappinia (only S. pedata).* Primary amebic meningoencephalitis (PAM) is caused by *Naegleria fowleri* in previously healthy children and young adults following exposure to fresh water during the summer months with high ambient temperatures. Granulomatous amebic encephalitis (GAE) is caused by *Acanthamoeba* spp. and *Balamuthia mandrillaris* that may occur round the year.

Rarely, amebic encephalitis may be caused by the genus *Sappinia*. Amongst the parasitic forms, *Entamoeba histolytica* is a common feco-orally transmitted parasite of the human gut and may rarely cause a brain abscess in conjunction with hepatic and/or lung abscess.

The pathogenesis of PAM involves brain invasion by *Naegleria fowleri* ("brain-eating amoeba") *via* olfactory nerves within 72 h post-inoculation and development of fulminant hemorrhagic meningoencephalitis with fibrinopurulent leptomeningitis [27]. *Acanthamoeba* may reach the brain by hematogenous spread from cutaneous or pulmonary lesion, or invasion *via* the olfactory nerves. It leads to necrotizing granuloma formation in the parenchyma with multinucleated giant cells, amebic cysts and trophozoites, and a severe, fibrinoid, necrotizing angitis in the brain [27]. The source and mode of infection of *Balamuthia* and *Sappinia* are less characterized, with possible hematogenous spread to the brain. *E. histolytica* brain lesions commonly affect the basal ganglia followed by frontal and occipital lobes and are associated with polymorphonuclear response, amebic trophozoites, focal hemorrhage and/or necrosis.

Clinical Features

PAM resembles fulminant acute bacterial meningoencephalitis. Children present with sudden-onset rhinitis, change in taste or smell 2–5 d after swimming, fever, severe headache, vomiting, irritability, seizures and raised intracranial pressure with progression to coma and death within 7–10 d [28]. GAE resembles chronic meningitis and presents as a subacute to chronic altered sensorium, low grade fever, seizures, focal CNS deficits, cranial nerve palsies and meningismus. A single case of *S. pedata* encephalitis described in literature presented with acute-onset raised intracranial pressure with nausea, vomiting, headache, photophobia and diplopia following a sinus infection leading rapidly to coma [29]. PAM should be considered in all children with acute bacterial or viral meningoencephalitis like presentation, especially if there has been exposure to fresh-water. GAE should be differentiated from all other chronic CNS infections such as tuberculosis, toxoplasmosis, neurocysticercosis, bacterial leptomeningitis, fungal infections and brain tumors [27, 30]. *E. histolytica* should be suspected in patients with abdominal pain, dyspnea, pleural effusion and weight loss besides the neurological symptoms and history of recent travel to an endemic area. Although amebic liver abscesses are quite common in Indian children, amebic brain abscess due to *E. histolytica* is a rare CNS manifestation.

Diagnosis

PAM should be considered in any patient presenting with meningoencephalitis and absence of bacteria from a purulent CSF. Elevated pressures, purulent appearance with neutrophilic predominance, low glucose, elevated proteins, and presence of red blood cells is commonly seen in CSF from patients with PAM. Direct light microscopic examination of a fresh, wet-mount of the CSF to identify motile trophozoites is important in all suspected cases. *N. fowleri* can be cultured from CSF and brain biopsies. Serological diagnosis is non-specific for *Naegleria.* Molecular diagnosis by PCR, real-time PCR, monoclonal antibodies and DNA probes can also be used if available. CE-CT commonly shows obliteration of cisterns around the mid-brain and the sub-arachnoid space due to extensive exudates with diffuse meningeal enhancement. MRI features may be nonspecific and vary from normal in early disease to diffuse brain edema, basilar meningeal enhancement, hydrocephalus or infarctions [31].

CSF in GAE shows normal to low glucose levels, mild to severely elevated proteins and lymphocytic pleocytosis. Unlike Naegleria, *Acanthamoeba* and *Balamuthia* are generally not found in the CSF and are primarily diagnosed by tissue identification or culture from brain biopsy specimens. Specific antisera are required for morphological differentiation between *Acanthamoeba* and *Balamuthia.* Molecular diagnosis by multiplex real-time PCR is available and helps in early diagnosis and differentiation of free-living amebae [32]. Neuroimaging in GAE shows two types of patterns with variable necrotizing angitis and hemorrhages: (a) multifocal pattern: ring-enhancing lesions with perilesional edema seen randomly at the cortico-medullary junction and (b) Pseudotumour pattern: Large solitary mass-like lesion. A single reported case of *Sappinia pedata* has presented with tumor-like mass lesion without an abscess-wall [29].

The diagnosis of *Entamoeba histolytica* brain abscess is classically made by the identification of trophozoites in the periphery of the abscess. Elevated titers of serum antibodies may corroborate the diagnosis; neuroimaging features may remain non-specific.

Treatment

PAM is a fulminant CNS infection with >95% mortality and no standardized treatment regimens or guidelines [33]. A combination of amphotericin B and rifampin is the most commonly tried regimen but duration of therapy is largely unknown [34]. Triple therapy has also been tried by combining the above two drugs with either miltefosine, ketoconazole, fluconazole, miconazole or sulfisoxazole [35]. The optimal treatment of GAE is unknown. In general, diamidines such as propamidine, pentamidine and dibromopropamidine have been found to be active against *Acanthamoeba* and *Balamuthia*. Multiple microbial agents have been tried in individual cases but there is no consistent benefit with any single form of therapy [34]. Metronidazole remains the mainstay of therapy for invasive amebiasis along with aspiration and

drainage of the brain abscess. In the single reported case of Sappinia, the patient was successfully treated with surgical excision and a combination of azithromycin, pentamidine, itraconazole and flucytosine [29, 32].

Prevention

The risk of acute meningoencephalitis may be reduced by certain practices such as careful maintenance of swimming pools and adequate chlorination (1–2 ppm), blowing the nose after swimming or using nose-plugs and avoidance of swimming in water bodies and hot springs epidemiologically associated with the disease. Infection with *Acanthamoeba* may be prevented by proper care of contact lenses, periodic inspection of water supplies and ventilation units.

Future Research

Research may be directed towards evaluation of role of azithromycin in humans for PAM, enhancement of early diagnosis with universal availability of rapid ELISA-based assay for CSF testing and identification of more potent drug delivery systems to the brain.

Contributions PS: Planned and drafted the manuscript and final review for important critical content; AGS: Drafted and reviewed the manuscript. PS will act as guarantor for the paper.

Compliance with Ethical Standards

Conflict of Interest None.

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