CD Alert

National Centre for Disease Control,
Directorate General of Health Services, Government of India

October 2024

PRIMARY AMOEBIC MENINGOENCEPHALITIS

INTRODUCTION

Amoebic encephalitis is an acute, fulminant, and rapidly fatal disease of central nervous system caused primarily by infection with *Naegleria fowleri*. The disease typically occurs when people swim in bodies of warm freshwater (such as lakes and streams/rivers) where Naegleria fowleri is present. Certain other organisms such as Acanthamoeba, Balamuthia mandrillaris, Vermamoeba [hartmanella] vermiformis and Sappinia pedata also can lead to this life-threatening disease in humans. These amoebas are organisms usually found in water, wet soil, rotting vegetation, animals, and humans.

There are two types of amoebic encephalitis, namely Primary amoebic meningo-encephalitis (PAM) and granulomatous amoebic encephalitis (GAE). As the disease is infrequently occurring, its clinical diagnosis is often not considered. These diseases are difficult to diagnose and probably under reported. As with other infectious diseases endemic to the tropics, the incidence of amoebic meningoencephalitis may become more geographically widespread, or rise along with temperature trends.

HISTORICAL BACKGROUND

Naegleria fowleri is named after Malcolm Fowler, an Australian pathologist, who first isolated it from a patient with PAM around 1956. Bull coined the term “primary amebic meningoencephalitis” to distinguish it from the secondary meningoencephalitis caused by the intestinal ameba Entamoeba histolytica.

Approximately 400 confirmed cases have been reported globally as of July 2024. A total of 26 cases were from India. Three cases were reported from Kerala earlier apart from more than 10 cases reported in 2024. The PAM cases have been reported from a total of 39 countries including Australia, USA, UK, Thailand, Czechoslovakia, Mexico, Japan, China, Egypt, India, Pakistan, Nigeria, Namibia and Madagascar.

GLOBAL AND INDIAN SCENARIO

Approximately 400 confirmed cases have reported globally as of July 2024. A total of 26 cases were from India. Three cases were reported from Kerala earlier apart from more than 10 cases reported in 2024. The PAM cases have been reported from a total of 39 countries including Australia, United States, Great Britain, Czechoslovakia, Thailand and Mexico, Japan, China, Thailand, Egypt, India, Pakistan, Nigeria, Namibia and Madagascar.

EPIDEMIOLOGY

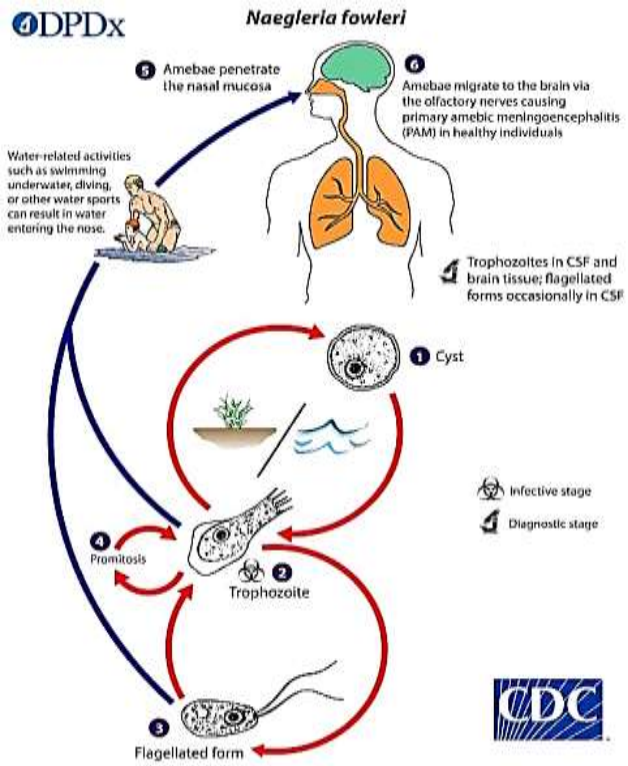
Several species of amphizoic amoebae including *Acanthamoeba* spp., *Balamuthiamandrillaris, Naegleria fowleri, Vermamoebavermiformis and Sappiniadiploidea*are pathogenic and opportunistic free-living and can cause infections of the central nervous system (CNS). *Acanthamoeba* and *Balamuthia*are cause chronic and fatal granulomatous amoebic encephalitis (GAE). *Naegleria fowleri* is more sensitive to the environment than acanthamoeba and it cannot survive in seawater. *N. fowleri* has also been found in inadequately chlorinated man-made recreational waters, as well as residential plumbing and water heaters.

*Acanthamoeba*s also causes *Acanthamoeba* keratitis other than GAE. *V. vermiformis* has been isolated from natural freshwater reservoirs, tap water, swimming pools and hospital environments.

Mode of transmission:

Children and young adults who have recently been in contact with warm, fresh water which is infected with *N. fowleri* get the disease. Trophozoite is the infective stage of the pathogenic amoeba. The portal of entry by the

amoebae are through the olfactory mucosa (neuroepithelium) and the cribriform plate. The amoebae are phagocytosed by the sustentacular cells lining of the olfactory neuroepithelium while it enters the nasal passages. They then penetrate into the subarachnoid space and continue on to the brain parenchyma to cause the disease. The oral consumption of water contaminated with N. fowleri is not associated with symptomatic disease. Infection with ***Vermamoeba (Hartmanella) vermiformis*****:** amoebic species has been recently reported from the state Kerala in year 2024. First case of meningoencephalitis due to Hartmannella spp. was reported in Mexico in 1995. *Naegleria fowleri* cannot spread from person to person.



Mode of transmission of *N.fowleri* Source: CDC

Incubation Period:

The incubation period varies for different species ranging from 1-9 days for *Nagleria fowleri* to weeks for *Acanthamoeba spp.* The incubation period of PAM varies depending on the size of the inoculum, and on the virulence of the particular strain of infecting amoebae.

CLINICAL FEATURES

The clinical presentation of PAM is often similar to other bacterial meningitis presenting with fever, headache, nausea, and vomiting being the most common presenting signs and symptoms. Studies show a median incubation period of 5 days and a median time from onset of symptoms to death of five days. Cerebral edema develops quickly and is disproportionate to the clinical condition.

Clinicians should suspect PAM in patients of acute meningoencephalitis having history of exposure with negative results for bacteria and common viruses. Certain conditions like CNS involvement following fever, positive history of taking bath/swimming in stagnant waters, partially treated meningitis, anterior lobe affliction (hemorrhagic), disproportionate brain edema with RBCs in CSF. An increase in AES cases above baseline level might also hint towards PAM.

Initial symptoms include sudden onset of bifrontal or bitemporal headaches, high fever, rigidity of neck, followed by nausea, vomiting, irritability and restlessness. Alterations in taste and smell may occur initially because of involvement of the olfactory nerve. Photophobia may occur late in the clinical course, followed by neurological abnormalities, including lethargy, seizures, confusion, coma, diplopia or bizarre behavior leading to death within a week. Cranial nerve palsies (third, fourth, and sixth cranial nerves) may indicate brain edema and herniation. Cardiac rhythm abnormalities and myocardial necrosis have been found in some cases. The acute hemorrhagic necrotizing meningoencephalitis that follows invasion of the CNS generally results in death 7–10 days post infection.

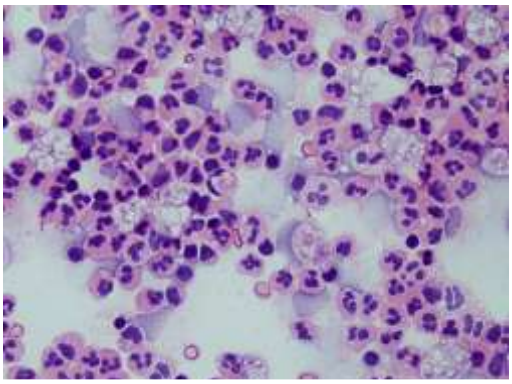
DIAGNOSIS

The laboratory diagnosis of PAM may be established by detection of mobile trophozoites of 10-25µm in size in fresh Cerebrospinal fluid wet mount of the suspected patient. CSF sample should be transported at room temperature and examined immediately after obtaining the sample. Trophozoites tend to lose motility upon freezing. Analysis of cerebrospinal fluid (CSF) usually reveals a high opening pressure, a predominantly neutrophilic pleocytosis, the presence of RBC, elevated protein concentration, and low glucose levels. Since the causative organisms are motile only for 30-40mins after sample collection and

may be missed on subsequent microscopy, guidelines can be issued to store the suspect CSF samples for few extra days so that any follow up request from clinician for re-examination can be accepted.

For confirmation and speciation of free-living amoeba, polymerase chain reaction (PCR) of CSF sample may be performed. *Naegleria fowleri* and other free-living amoebae (FLA) can be cultured on non-nutrient agar supplemented with other enteric bacteria like E. coli etc. A biopsy of brain tissue can also be stained and examined under a microscope or analyzed using PCR. Serology does not offer much useful information.

Environmental sample like water collected from implicated waterbodies may be utilized for environmental surveillance of FLA using all above modalities.



Cytocentrifuged CSF Smear Stained with Giemsa showing *Naegleria fowleri*

MANAGEMENT

Medical management

There are no definitive studies highlighting the treatment efficacy as the disease is rare and the diagnosis is difficult. Based on the experience of patients who survived, it is suggested that aggressive treatment with multidrug regime is often necessary as the mortality rate is high in this disease.

Initial treatment should be to control the cerebral edema with measures like dexamethasone, CSF drainage by ventricular drain, hyperosmolar therapy with mannitol and 3% saline. Antibiotics which includes antifungals and antiparasitic should be initiated early and continued for 2-4 weeks.

Surgical decompression

In patients who continue to have signs of raised intracranial pressure despite medical therapy, decompressive craniectomy may be helpful.

List of medications their dosage and duration as suggested by CDC are listed in the following table:

Drug	Dose	Route	Maximum Dose	Duration	Comments
Amphotericin B*	1.5 mg/kg/day in 2 divided doses, THEN	IV	1.5 mg/kg/day	3 days	
	1 mg/kg/day once daily	IV		11 days	14-day course
Amphotericin B	1.5 mg once daily, THEN	Intrathecal	1.5 mg/day	2 days	

Drug	Dose	Route	Maximum Dose	Duration	Comments
	1 mg/day every other day	Intrathecal		8 days	10-day course
Azithromycin	10 mg/kg/day once daily	IV/PO	500 mg/day	28 days	
Fluconazole	10 mg/kg/day once daily	IV/PO	600 mg/day	28 days	
Rifampin	10 mg/kg/day once daily	IV/PO	600 mg/day	28 days	
Miltefosine**	Weight<45 kg 50 mg BID Weight>45kg 50 mg TID	PO	2.5 mg/kg/day	28 days	50 mg tablets
Dexamethasone	0.6 mg/kg/day in 4 divided doses	IV	0.6 mg/kg/day	4 days	

*Conventional amphotericin (AMB) is preferred over liposomal amphotericin B
**Dose adjustment may be needed in renal disease

PREVENTION AND CONTROL

Risk Communication: High index of suspicion should be made by clinicians who are treating patients with suspected case symptoms. Once a history of freshwater exposure is elicited, CSF must be promptly examined via lumbar puncture. Since free living amoebae (FLA) *are* vulnerable to chlorine in water (one part per million), the growth of amoebas can be managed by proper chlorination of frequently used swimming pools, especially in the summer. However, the effectiveness of chlorine can be diminished by sunlight and the presence of organic materials in swimming pools. Nonetheless, it's not feasible to chlorinate natural water sources like lakes, ponds, and streams, where FLA might thrive.

Community awareness:

- Seek medical attention immediately if someone suddenly starts vomiting or develops a headache, fever, or stiff neck after swimming or playing in warm fresh water
- Avoid water activities during warmer months when temperatures rise and water levels go down. *Naegleria fowleri* amoebas thrive in these conditions.
- Divers to hold nose shut or use a nose clip when jump or dive into the water.
- Always keep head above water in hot springs and other naturally hot (geothermal) water.
- Avoid digging in, or stirring up, sediment in shallow, warm fresh water. *Naegleria fowleri* amoebas are more likely to live in sediment at bottom of lakes, ponds, & rivers.
- In areas at high risk, local public health officials should consider checking recreational water for FLA and should post warnings, especially during the warm summer season.

KEY MESSAGES

- Amoebic encephalitis is an acute, fulminant, and rapidly fatal disease of central nervous system caused primarily by infection with Naegleria fowleri. The disease typically occurs when people swim in bodies of warm freshwater (such as lakes and streams/rivers) where Naegleria fowleri is present.
- There are two types of amoebic encephalitis, namely Primary amoebic meningo-encephalitis (PAM) and granulomatous amoebic encephalitis (GAE). Secondary meningoencephalitis caused by the intestinal amoeba Entamoeba histolytica.
- Children & young adults who have recently been in contact with warm, fresh water infected with N. fowleri get the disease.
- The incubation period varies for different species ranging from 1-9 days for Nagleria fowleri to weeks for Acanthamoeba spp.
- The clinical presentation of PAM is often similar to other bacterial meningitis presenting with fever, headache, nausea, and vomiting being the most common presenting signs and symptoms.
- The laboratory diagnosis of PAM may be established by detection of mobile trophozoites of 10-25µm in size in fresh Cerebrospinal fluid wet mount of the suspected patient.
- Aggressive treatment with multidrug regime is often necessary as the mortality rate is high in this disease.
- High index of suspicion should be made by clinicians who are treating patients with suspected case symptoms and Community awareness in endemic areas can play an important role in reducing the morbidity and mortality of population.