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THE LETHAL JOURNEY OF BRAIN EATING AMOEBAE FROM NOSE TO NEURONS

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ABSTRACT

Naegleria fowleri, commonly known as the brain-eating amoeba, is a free-living, thermophilic protozoan, causes primary amoebic meningoencephalitis (PAM), which is a rare yet rapidly fatal infection of the central nervous system. *N.fowleri* is found in warm freshwater bodies, such as lakes, hot springs, poorly chlorinated pools, or tap water. *N.fowleri* enters the body through the nasal passages during activities such as swimming, diving, or nasal rinsing with contaminated water. This amoeba then crosses the cribriform plate and travels along the olfactory nerve to invade the central nervous system, causing rapidly progressive necrotizing meningoencephalitis. Early symptoms of *N.fowleri* infection mimic viral or bacterial meningitis, including fever, headache, nausea, and vomiting. These symptoms rapidly progress to confusion, seizures, photophobia, altered mental status, and coma. The disease is fatal in over 98% of cases with a median survival of just 5 days after symptom onset. PCR is the gold standard for definitive diagnosis. CSF findings resemble those of bacterial meningitis, showing elevated white blood cells, low to normal glucose, elevated protein, and increased opening pressure. Diagnosis is challenging due to nonspecific symptoms resembling viral or bacterial infections. Prompt recognition, accurate diagnosis, and aggressive combination therapy are crucial for improving outcomes, although fatality rate is very high. *N.fowleri* infection poses a serious public health concern due to lack of vaccines and effective treatment. The knowledge and scientific information on *N.fowleri* infection is still relatively limited to many clinicians, and received little attention; hence this comprehensive review of *N.fowleri* infection is undertaken to highlight its importance and further research.

Keywords: *Brain eating amoeba, Central nervous system, Naegleria fowleri, Primary amoebic meningoencephalitis.*

INTRODUCTION

In recent months, several cases of primary meningoencephaitis have been reported from Kerala, India, drawing global attention to this deadly infection. The culprit, *Naegleria fowleri* enters the body through the nose, travelling silently to the brain and destroying tissue with terrifying speed [1].

In humans, there are four main amoebas that can cause disease, namely *Naegleria fowleri*, *Acanthamoeba* species, *Sappinia pedata*, and *Balamuthia mandrillaris*. The amoebas have a propensity to cause central nervous system (CNS) infections. These free-living amebas can cause two distinct clinical syndromes, primary amoebic meningoencephalitis (PAM) and granulomatous amoebic encephalitis (GAE) [2].

Naegleria fowleri is a free-living amoeba primarily feeds on bacteria, but can become pathogenic in humans, causing an extremely rare, sudden, severe, and almost always fatal brain infection known as

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primary amoebic meningoencephalitis (PAM), also known as naegleriasis. The name primary amoebic meningoencephalitis (PAM) is given because the condition is a primary infection (first infection) of the brain and meninges, not a secondary complication of another disease [3].

Granulomatous amoebic encephalitis (GAE) is a rare, serious, and often fatal central nervous system (CNS) disease caused by free-living amoebae, *Acanthamoeba*, *Balamuthia mandrillaris*, and *Sappinia pedata*, often in immunocompromised individuals [2].

EPIDEMIOLOGY

Primary amoebic meningoencephalitis is relatively a rare disease and worldwide in distribution. *N fowleri* infections are more prevalent in healthy, immunocompetent young males during the summer when water temperatures are high and people engage in outdoor water activities. Most *N. fowleri* infections occur through recreational freshwater exposure, such as swimming or diving [4].

The first case of *Naegleria fowleri* was detected in Australia in the year 1965 by Malcolm Fowler and Carter and was named after Fowler. Infections caused by *N. fowleri* have been reported in 39 countries, with the United States, Australia, Pakistan, India, Mexico, and the Czech Republic reporting the highest number of cases, possibly due to their warm fresh water bodies and climates conducive to the pathogen's growth and replication [5].

The first documented case of primary amoebic meningoencephalitis (PAM) in India was reported in 1971 in two children by Pan and Ghosh in the Journal of the Indian Medical Association, with subsequent cases documented in various parts of the country. The first confirmed case in Kerala reported in March 2016 in the Alappuzha district [6].

According to India's National Center for Disease Control, Kerala, India, recorded two fatal cases of primary amoebic meningoencephalitis (PAM) in 2023. The Kerala state's health ministry has confirmed that since 2016 and up to the end of 2023, Kerala had reported eight confirmed cases, all of which were fatal. In 2024, Kerala reported 36 cases of primary amoebic meningoencephalitis (PAM), with 9 deaths, a significant spike from previous years and led to public health concerns [7].

Kerala state of India experiencing a significant recent surge *Naegleria fowleri* infections, reported 80 confirmed cases and 21 deaths in 2025 as of September 29, 2025 with a cluster of cases across Kozhikode, Malappuram and Wayanad [8].

In previous years, cases in Kerala state of India tended to cluster around one lake or reservoir, making tracking and containment somewhat possible. But in 2025, infections are isolated, scattered across districts, not tied to the same water source, which makes it difficult to diagnose and treat. The reasons could be:

- Rising temperatures and monsoon impacts may worsen conditions in water bodies, creating ideal breeding conditions in stagnant water [9].
- Many small ponds, wells, or local bathing spots are not regularly disinfected.
- Limited public awareness about how to avoid brain eating amoeba exposure, particularly in rural and semi-urban areas [10].

Despite these challenges, Kerala's survival rate has improved due to early diagnosis, better laboratory facilities (like PCR testing), and the use of miltefosine (an amoebicidal drug), combined with better intensive care. Health authorities are actively educating people about brain eating amoeba in India and especially focusing on high-risk zones in the state. After the 2023 Nipah outbreak, Kerala implemented stricter protocols to investigate all encephalitis cases, leading to better detection of PAM [10,11].

Naegleria fowleri is typically found in warm fresh water bodies such as lakes, rivers, hot springs, warm water discharge from industrial or power plants, geothermal well water, and poorly maintained or minimally chlorinated swimming pools, water heaters, moist soil, and pipes connected to tap water, but cannot survive in sea water. *N. fowleri* is a thermophilic amoeba that thrives in temperatures up to 45°C [4,12].

Brain infections caused by *Naegleria fowleri* usually occur after someone goes swimming or diving in a lake, river, or other fresh water during summer months. Infections often happen when it's been hot for long periods, resulting in higher water temperatures, and lower water levels.

It is important to note that

- The infection can not spread from person to person
- It does not occur from drinking water, even if it contains the amoebae
- Most infections are linked to nasal exposure to water activities in untreated or poorly maintained water sources [1,4,12].

Factors contributing to the increased cases of primary amoebic meningoencephalitis are attributed to global warming, which warms freshwater habitats, climate change, environmental pollution, and poor sanitation, contributing to the spread of the *Naegleria fowleri*. Increased water activities in warm, unchlorinated water are a primary risk factor [10,11].

Primary amoebic meningoencephalitis (PAM) has been confirmed in Nepal, with reports of cases involving both children and elderly individuals. The first case in Nepal was reported by Shrestha G, et al, in 2015 and the patient died despite intensive multi-drug therapy [13]. Baral R and Vaidya B reported another

case of PAM in Nepal, in 2018 involving elderly immune-competent male without environmental exposure to freshwater, mimicking as herpes encephalitis [14].

ETIOLOGY

Naegleria fowleri, also known as the brain-eating amoeba, is an organism capable of behaving as both an amoeba and a flagellate, able temporarily to assume a flagellate form while being completely devoid of flagella in the amoeboid stage. *Acanthamoeba* never produce flagella and exists only in amoeboid stage [3,1].

N. fowleri exists in three forms, cyst, trophozoite (amoeboid), and biflagellate. While it does not form cysts in solid human tissue, where only the amoeboid trophozoite stage is present, the flagellate form has been discovered in CSF (Figure 1) [3,15,16].

Cyst stage

Under unfavorable environmental conditions (such as desiccation, low nutrients), trophozoites transform into cysts, which are spherical, and measure 7–15 µm in diameter. Factors triggering cyst formation include food scarcity, overcrowding, desiccation, waste accumulation, and cold temperatures. When conditions improve, the amoeba can emerge through the cyst [3,15,16].

Trophozoite stage

The trophozoite stage is the infective phase for humans, during which the organism can actively feed and replicate. The trophozoite attaches to olfactory epithelium, follows the axons of olfactory receptor neurons through the cribriform plate in the nasal cavity, and enters the brain and thrives by multiplying through binary fission. Pseudopods form in the direction of movement. In their free-living state, trophozoites feed on bacteria. In tissues, they appear to phagocytose RBCs and cause tissue damage [3,15,16].

Flagellated stage

The flagellated stage of *N. fowleri* is pear-shaped and biflagellate with two flagella. This stage can be inhaled into the nasal cavity, typically during activities such as swimming or diving. The flagellate form develops when trophozoites are exposed to a change in ionic strength in the fluid where it is (e.g., distilled water). The flagellated form does not exist in human tissue, but can be present in the cerebrospinal fluid. Once inside the nasal cavity, the flagellated form transforms into a trophozoite within a few hours [3,15,16].

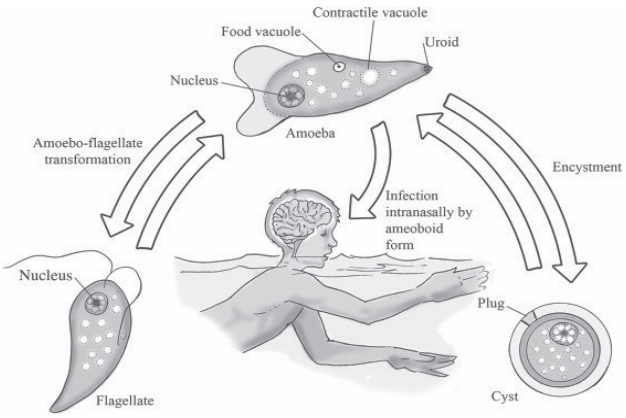

Figure 1: Life cycle of *Naegleria* fowleri [16]

PATHOGENICITY

Of the 47 species of *Naegleria*, only *N fowleri* causes primary amebic meningoencephalitis (PAM), which is a rare and almost always fatal CNS infection, leading to the death of patients within 3 to 7 days. The disease has an incubation period of 1 to 14 days and progresses rapidly, presenting with nonspecific signs and symptoms [3,18].

N fowleri infection occurs when contaminated freshwater enters the nasal passages, typically during swimming in freshwater bodies, using poorly chlorinated pools, or performing nasal rinses with nonsterile water [10,11,18].

Primary amoebic meningoencephalitis is a rapidly progressive and often fatal condition occurs upon accidental introduction of *N. fowleri* into the nose, after which the amoeba invades the central nervous system (CNS) through the cribriform plate and olfactory nerves. Invasion of the central nervous system results in cerebral edema, necrosis, brain herniation, and, in most cases, death (Figure 2) [19-21].

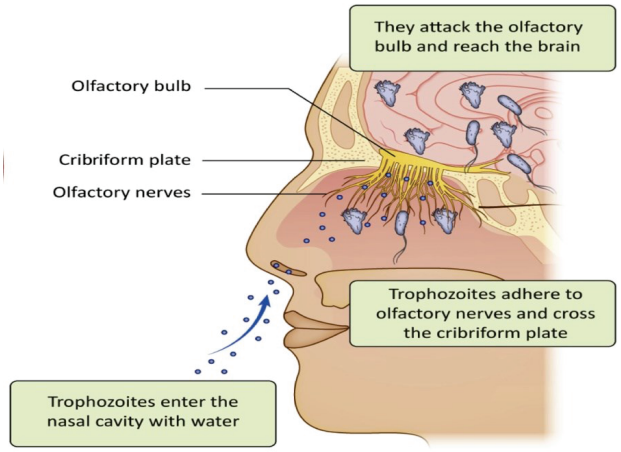

Figure 2: Transmission of *Naegleria fowleri* [18]

N fowleri triggers a strong innate immune response, and its virulence is influenced by multiple factors, including the protein Nfa1, nitric oxide production,

and pore-forming proteins. The Nfa1 protein is located in the amoeba's pseudopodia and involved in cell contact, movement, and cytotoxicity, playing a significant role in the amoeba's pathogenicity. The Nfa1 protein facilitates amebic attachment to target cells, while specialized feeding structures enable the amoeba to ingest bacteria and fungi in the environment and directly phagocytose brain cells. *Naegleria fowleri* trophozoites have been shown to destroy nerve cells, as well as other cell types, by trogocytosis (i.e. piecemeal ingestion) using a 'food-cup' structure on their surface [22] and by the release of cytolytic molecules. The organism further contributes to tissue destruction by secreting cytolytic molecules, including cysteine proteases, phospholipases, and phospholipolytic enzymes, which mediate extensive necrosis [23]. This intense immune response and aggressive virulence of *N fowleri* result in significant destruction of brain parenchymal tissue, leading to the rapid progression of PAM [24].

CLINICAL SYMPTOMS

Symptoms of primary meningoencephalitis appear within 1 to 14 days after exposure and progress rapidly. Because the early signs resemble other common illnesses, it can be difficult to identify the infection first. However, the condition worsens quickly and can become life threatening without prompt treatment. Common symptoms include sudden high fever, very painful or severe headache, nausea and vomiting, trembling or loss of balance, stiff neck and sensitivity to light, similar to meningitis, mental confusion, irritability or unusual behavior, seizures, coma in advanced stages. The fatality rate is higher than 97% even with treatment [7,12].

One of the scariest things about brain eating amoeba symptoms is their rapid progression. So, if you ask, what is brain eating amoeba infection like, it starts like a bad flu but quickly escalates into fatal brain swelling. The symptoms often begin 1 to 9 days after exposure, and once they set in, death usually follows within a week if untreated [18,20].

PAM starts like a bad flu but quickly escalates into fatal brain swelling. The symptoms often begin one to nine days after exposure, and once they set in, death usually follows within a week if untreated. Recognizing brain eating amoeba symptoms early can be lifesaving. The infection progresses rapidly, so time is crucial [18,20].

Early symptoms (within 1–9 days) such as fever, headache, lethargy, nausea, and vomiting, may resemble bacterial meningitis. As the disease progresses, later symptoms with more severe manifestations develop, including confusion, neck stiffness, photophobia, seizures, and cranial nerve abnormalities. In most cases, PAM progresses rapidly, leading to coma and death within a matter of days (Table 1) [18,20].

Table 1: Clinical symptoms of primary amoebic meningoencephalitis [18, 20]

Stages	Symptoms	Clinical indications
Early	Fever, severe headache, nausea, vomiting	Looks like common viral illness
Mid	Stiff neck, confusion, seizures	Indicates brain involvement
Late	Coma, respiratory failure, death	Rapid deterioration

N fowleri infection leads to several clinical complications such as severe cerebral edema, hemorrhagic necrosis, and increased intracranial pressure, which can result in brain herniation and death within days of symptom onset. Other complications include seizures, cranial nerve dysfunction, hydrocephalus, and coma. Due to its aggressive nature, PAM has a 98% mortality rate, even with treatment. Survivors may experience neurological deficits, although recovery is rare. Early diagnosis and prompt initiation of therapy are critical in preventing fatal outcomes and minimizing long-term complications [18, 20].

A detailed patient history and thorough physical examination is important because the disease is difficult to diagnose clinically, as its early symptoms are often nonspecific and can resemble flu-like illnesses, bacterial meningitis, or viral meningoencephalitis. Given its severity, high fatality rate, and limited treatment options, obtaining an accurate epidemiological history is crucial. Clinician awareness is necessary for prompt diagnosis and the immediate initiation of available therapies [24].

RISK FACTORS

Risk factors for primary amoebic meningoencephalitis include [10-12]

- Freshwater exposure in warm climates, particularly through swimming, diving, or water sports in untreated fresh water, such as lakes, rivers, and warm pools
- Stirring up sediment at the bottom of shallow warm water bodies, where amoeba often lives
- Hot climates and summer seasons when water temperatures rise and water levels drop
- Poorly maintained swimming pools or tanks with inadequate chlorination
- Using contaminated tap water for nasal irrigation
- Immunocompromised individuals
- Children and teenagers or young adults who spend more time in water parks, splash pads or swimming pools due to their higher participation in water-related activities.

DIAGNOSIS

A high index of suspicion is essential for diagnosis, as mortality reaches 98%, with a median time from symptom onset to death of 5 days. In many cases, death occurs before a diagnosis is made, and the disease is confirmed postmortem if an autopsy is performed [4].

The CSF is cloudy to purulent, with prominent leucocytosis (predominantly neutrophils), elevated proteins, and low glucose level, resembling pyogenic meningitis. Failure to find bacteria should raise the possibility of primary amoebic meningencephalitis [10].

Wet mount preparation of CSF is examined under microscope for demonstration of motile amoeboid trophozoites. Cysts are never seen in CSF or brain. Microscopic examination of the cerebrospinal fluid (CSF) or brain tissue for trophozoites can be done by Wright or Giemsa or trichrome stains. Amoebae have small, pink nuclei with sky blue cytoplasm. Amoebae can also be demonstrated in CSF or brain tissue by direct or indirect immunofluorescence. A brain biopsy, if feasible, can provide definitive evidence of PAM. Histopathological examination typically reveals hemorrhagic meningitis, with the base of the brain and olfactory bulbs being the most severely affected areas. Numerous trophozoites are often observed within the necrotic meninges [4,26].

Non-nutrient agar (1.5%) spread with a lawn of washed *Escherichia coli* or *Enterobacter aerogenes* is used for culture. The CSF sample is inoculated on this medium and incubated at 37°C for overnight. The amoebae grow on moist agar surface and use the bacteria as food and thus produce plaques as they clear the bacteria. The trophozoites are visible microscopically at the edge of the plaque [10].

Flagellation tests detect *Naegleria fowleri* by exposing amoebae to a hypotonic (distilled water) medium, which triggers the transformation of *Naegleria* from trophozoites into pear-shaped, biflagellated forms within 48 hours. These trophozoites typically measure between 10-25 µm and exhibit limacine/eruptive amoeboid movement. A positive test shows these distinctive flagellated cells, confirming the presence of *Naegleria*. However, due to potential false negatives and the need for specific identification, flagellation tests are often followed by more definitive tests like ELISA, PCR, and restriction fragment length polymorphism (RFLP) to confirm *N. fowleri* [27].

Molecular techniques are more sensitive than culture or microscopy methods [27]. Polymerase chain reaction (PCR) testing can detect *N fowleri* DNA directly from CSF and is now considered the gold standard for PAM diagnosis. PCR offers a quicker alternative to traditional screening tests, such as the flagellation test (which yields insufficient data), RFLP (which is expensive), and ELISA (which provides a late diagnosis), making it excellent for analyzing clinical specimens. However, ELISA is performed postmortem, while RFLP can detect only specific *Naegleria* species [28].

DNA probe-based methods were designed in the 1990s to detect *N. fowleri* in various CSF samples. Loop-mediated isothermal amplification (LAMP) technique can be used for amplifying specific DNA regions [29]. Next-generation sequencing has recently gained attention as a promising diagnostic tool for free-living amoebae, including *N fowleri* [30].

TREATMENT

Treatment of primary amoebic meningoencephalitis is challenging because it is extremely rare and often diagnosed late, after symptoms have rapidly progressed. Amphotericin B is the primary drug of choice for PAM, exhibiting amoebicidal activity at low concentrations [31]. Azoles such as fluconazole and voriconazole, penetrate the CNS effectively and are commonly used as adjunctive therapy with amphotericin B. Azithromycin has demonstrated *in vitro* and *in vivo* activity against *N fowleri* [26,32,33].

An antiparasitic drug Miltefosine has been used. Miltefosine, originally developed as an antineoplastic agent for breast cancer, has shown promise in treating *N fowleri* infections. Dexamethasone and therapeutic hypothermia may be used to reduce inflammation. Therapeutic hypothermia reduces the body's temperature to a hypothermic state to prevent further brain injury resulting from hyper inflammation and increased intracranial pressure. Experimental treatment combinations under close medical supervision can be carried out [26,32].

PAM is a rare but rapidly progressing disease with a poor prognosis, even when treatment is given. *N fowleri* infection is associated with a mortality rate exceeding 98%, with a median time of just five days from symptom onset to death [32,34].

PREVENTION

Here are some practical steps to stay safe and reduce the risk of brain eating amoeba infection, though no method is absolutely foolproof given how aggressive this amoeba is.[19,35,36]

- Avoid letting water enter your nose during swimming or bathing in ponds, lakes, natural water bodies or unchlorinated pools.
- Use nose clips, especially for children or frequent swimmers.
- Use safe water (boiled or filtered water) for any nasal hygiene and nasal rinsing
- Avoid stagnant, warm water after heavy rains or heat waves.
- Ensure proper maintenance of swimming pools with chlorination
- Keep swimming pools clean, proper chlorination

kills *Naegleria fowleri*.

CONCLUSION

The word "brain eating amoeba" sounds like something from science-fiction, but it's a grim reality. Primary amoebic meningoencephalitis is a rare but deadly disease with worldwide occurrence. *Naegleria fowleri* is a free-living ameba, a kind of one-celled organism that thrives in warm freshwater lakes, rivers, and hot springs. The recent outbreak of primary meningoencephalitis in Kerala, India, highlighted the need for greater public awareness about this rare but deadly infection. Improved clinician awareness, resulting in earlier diagnosis and treatment, may contribute to increased survival among PAM patients. Clinicians must maintain a high index of suspicion and be aware of epidemiological risk factors and potential exposures, as failure to recognize PAM can result in delayed diagnosis and rapid fatality.

There is a strong need to address research gaps, for example, in understanding *N.fowleri* transmission and disease mechanism. The pathogenesis of PAM and the role of host immunity to N. fowleri are poorly understood. Strategies for combating infection are limited because disease progression is rapid and *N.fowleri* has developed strategies to evade the immune system. More in-depth research on the genetics and pathogenic proteins of *N.fowleri* is essential to understand antigens, which could lead to the development of an effective vaccine.

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