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Brain Eating Amoeba: A Systemic Review

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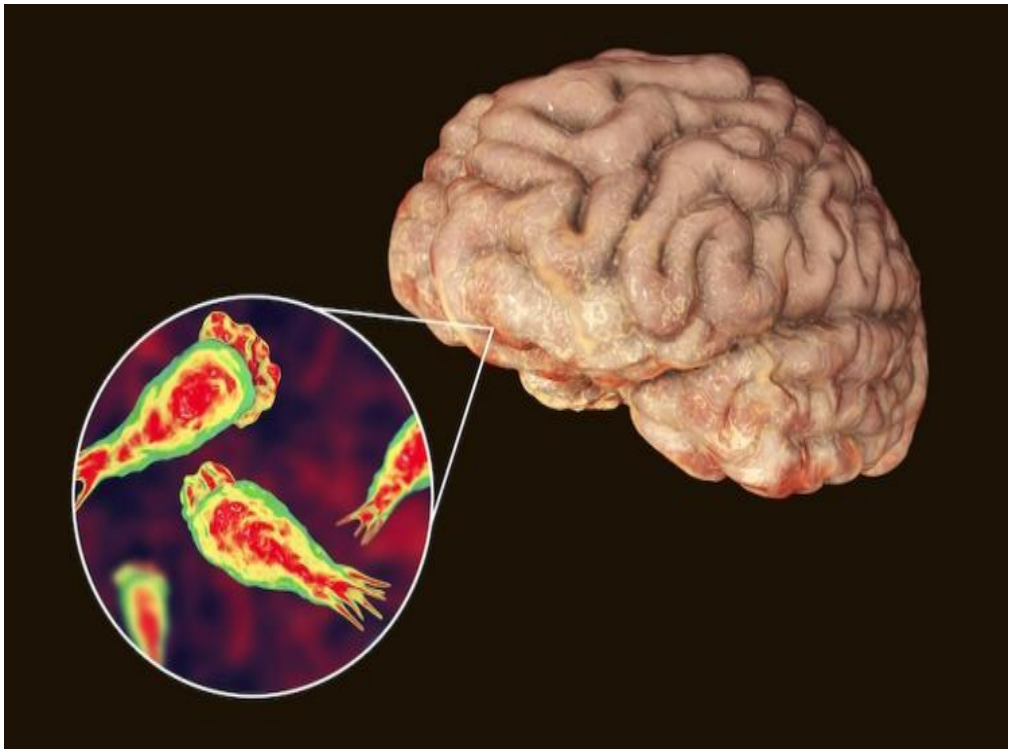
"The brain is conceded to be the master organ of the body, the regulator of life, and the source of human progress." –
Frederick Tilney

Abstract: ***Primary amoebic meningoencephalitis (PAM) is a rare but lethal infection of the brain caused by a eukaryote called Naegleria fowleri (N. fowleri). The aim of this review is to consolidate the recently published case reports of N. fowleri infection by describing its epidemiology and clinical features with the goal of ultimately disseminating this information to healthcare personnel. A 14-year-old boy from Payyoli is currently receiving treatment at a private hospital after the condition was quickly identified. Earlier, another 14-year-old boy died from the infection. A five-year-old girl from Malappuram died on May 21, and a 13-year-old girl from Kannur also succumbed to the condition on June 25. (New Delhi, UPDATED: Jul 10, 2024 12:34 IST)***

Keywords: Naegleria fowleri, primary amoebic meningoencephalitis, brain eating amoeba, immune response, prevention and treatment

1. Introduction

PAM, or primary amoebic meningoencephalitis, is a rare but severe infection caused by Naegleria fowleri, a free-living amoeba that thrives in warm freshwater environments such as lakes, ponds, and poorly maintained swimming pools. The amoeba enters the body through the nostrils, typically when individuals swim or dive in contaminated water. Once inside, it travels to the brain, causing severe damage.



Primary amoebic meningoencephalitis is a rare but severe infection caused by Naegleria fowleri, a free-living amoeba that thrives in warm freshwater environments. (Photo: Getty Images)

"The high affinity to the brain and the rapid damage thereafter earned Naegleria the name 'brain-eating amoeba,'" Dr Pillai explained. Initial symptoms often include fever, nausea, vomiting, headache, and neck stiffness.

As the infection progresses, patients may experience confusion, altered behaviour, seizures, and eventually coma and death.

History of Brain- Eating Amoeba

In 1899, Franz Schardinger first discovered and documented an amoeba he called Amoeba gruberi that could transform into a flagellate. The genus Naegleria was established by Alexis Alexeieff in 1912, who grouped the flagellate amoeba. He coined the term Naegleria after Kurt Nägler, who researched amoebae. It was not until 1965 that doctors Malcolm Fowler and Rodney F. Carter in Adelaide, Australia, reported the first four-human cases of amoebic meningoencephalitis. These cases involved four Australian children, one in 1961 and the rest in 1965, all of whom had succumbed to the illness. Their work on amebo-flagellates has provided an example of how a protozoan can effectively live both freely in the environment, and in a human host.

In 1966, Butt termed the infection resulting from N. fowleri primary amoebic meningoencephalitis (PAM) to distinguish this central nervous system (CNS) invasion from other secondary invasions made by other amoebae such as Entamoeba histolytica. A retrospective study determined the first documented case of PAM possibly occurred in Britain in 1909. In 1966, four cases were reported in the US. By 1968 the causative organism, previously thought to be a species of Acanthamoeba or Hartmannella, was identified as Naegleria. This same year, occurrence of sixteen cases over a period of three years (1962–1965) was reported in Ústí nad Labem, Czechoslovakia. In 1970, Carter named the species of amoeba N. fowleri, after Malcolm Fowler.

Society and Culture of Brain -Eating Amoeba

Naegleria fowleri is also known as the "brain-eating amoeba". The term has also been applied to Balamuthia mandrillaris, causing some confusion between the two; Balamuthia mandrillaris is unrelated to Naegleria fowleri, and causes a different disease called granulomatous amoebic encephalitis. Unlike naegleriasis, which is usually seen in people with normal immune function, granulomatous amoebic encephalitis is usually seen in people with poor immune function, such as those with HIV/ AIDS or leukemia.

Naegleriasis was the topic in Season 2 of the medical mystery drama House, M.D. in the two-part episode titled "Euphoria". It is also the topic of the episode "39 Differences" of season 6 of The Good Doctor.

People Fighting with Brain- Eating Amoeba: Challenges and new insights to open a road for the treatment of Naegleria fowleri infection

Naegleria fowleri, often called Brain-Eating Amoeba, is the deadliest free-living thermophilic pathogen affecting the human central nervous system. The epidemiological data states that its existence was rare but was first recognized in the United States in 1937. It generally grows in warm fresh waters during the months of July, August, and September in the United States but not in salt waters. However, several cases of this infection have been reported in Pakistan, and two of the documented cases of primary amoebic meningoencephalitis (PAM) were in people who had previously participated in recreational water activities. As a result, it can be concluded that N. fowleri is present in Karachi's residential water supply and that ablution is a major cause of infection. This is surprising because Karachi's water is often salty, and amoebas cannot thrive in salt water. This data shows that either the N. fowleri strain found in Pakistan is distinct from strains reported in the rest of the world or that it has evolved a resistance to saline surroundings.

N. Fowleri had a wide distribution range worldwide (around 15 countries) except Antarctica and was most prevalent in warmer nations. The pathogen even thrives and adapts to warmer or higher temperatures (50–65°C) and salinity around 1.4–2.0% NaCl and remains viable by feeding on bacteria, yeast, and algae. Though the number of cases with PAM remained stable (0–8) throughout the year, a recent breakout in South Korea is of great concern. On NaN Invalid Date, a recent breakdown of brain-eating amoeba was first reported in South Korea, according to the Korea Disease Control and Prevention Agency (KDCA). It was confirmed that the person in his 50s returned from Thailand after his 4 months stay. After admitting to the hospital the next day, he suffered from vomiting, nausea, neck stiffness, and slurred speech. On an Invalid Date, the man died due to an infection with N. fowleri, as suggested by the reports. Though it was reported earlier, the unavailability of effective treatment options makes it a great concern.

Stages of CYST

To endure harsh environmental conditions, trophozoites transform into microbial cysts, spherical, single-layered structures about 7–15 μm in diameter, enclosing a single cell nucleus. Acting as a resilient capsule, the cyst enables the amoeba to withstand adverse circumstances. Factors triggering cyst formation include food scarcity, overcrowding, desiccation, waste accumulation, and cold temperatures. When conditions improve, the amoeba can emerge through the pore or ostiole at the center of the cyst. N. Fowleri has been observed to encyst at temperatures below 10 °C (50 °F).

Trophozoite stage

The trophozoite stage is the infective phase for humans, during which the organism can actively feed and replicate. The trophozoite attaches to the olfactory epithelium, follows the axons of olfactory receptor neurons through the cribriform plate in the nasal cavity, and enters the brain. This reproductive stage of the protozoan organism transforms around 25 °C (77 °F), and thrives best at approximately 42 °C (108 °F), multiplying through binary fission.

Trophozoites are characterized by a nucleus surrounded by a flexible membrane. They move via pseudopodia, extending parts of their cell membrane (pseudopods) and filling them with protoplasm to facilitate locomotion. Pseudopods form in the direction of movement. In their free-living state, trophozoites feed on bacteria. In tissues, they appear to phagocytize (enclose and digest) red blood cells and cause tissue damage either through the release of cytolytic substances or by direct cell-to-cell contact using cytolytic membrane proteins.

As trophozoites, Naegleria fowleri may develop approximately 1 to 12 structures on their membrane known as amoebastomes (amorphous cytostomes), also referred to as "suckers" or "food cups," which they use for feeding in a manner similar to trogocytosis.

Flagellate stage

The flagellate stage of Naegleria 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 it is in, such as being placed in distilled water. The flagellate 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.

Previous Review on the Brain Eating Amoeba by the Experts

Understanding the mechanisms underlying the early immune failure and the triggers for the ensuing fulminant inflammation may point to advances in clinical care as there are still no proven clinical treatments for PAM. The rapidity of PAM and the rarity of surviving individuals make it extremely difficult to decipher these immunological pathways and retroactively comprehend the human immune response. Fortunately, animal models of PAM show striking similarities to human infections and provide an effective method for describing how the immune system views and reacts to N. fowleri. Although many of the pathogenic pathways used by N. fowleri have been identified through *in vitro* investigations, a lack of mechanistic in vivo studies on the immune response to N. fowleri has left many fundamental concerns unexplained. Various research studies showed a comprehensive exploration of the immune responses and defense mechanisms against Naegleria fowleri infection, the causative agent of PAM.

The findings underscore the significance of both humoral and cellular immune responses in protecting against N. fowleri. Intranasal administration of N. fowleri lysates, in combination with cholera toxin, proves effective in inducing robust immune reactions, as evidenced by increased antibody titers and altered migration molecules in immune compartments. Notably, the involvement of the Signal Transducer and Activator of Transcription 6 (STAT6)-induced T helper type 2 (Th2) response is highlighted, where Th2-deficient mice exhibit reduced protection. Furthermore, the researchers delve into the intriguing role of neutrophil extracellular traps (NETs) in responding to N. fowleri, showcasing their potential to counteract the amoeba's evasion tactics. Neutrophils release NETs to capture and neutralize pathogens, but N. fowleri was observed to evade killing by NETs unless opsonized (bound to antibodies). Identification of immunogenic antigens offers promising avenues for vaccine development, with specific antigens conferring substantial protection against infection. Altogether, the research investigations provide valuable insights into the complexities of N. fowleri immunity, offering a foundation for future strategies in preventing and managing PAM.

Despite the apparent protective potential of antibody responses, developing vaccines or immunotherapeutic strategies still needs a better understanding of the relevant antibody isotypes and Fc receptors that confer protective immunity. In addition, identifying specific antigens for recognition is crucial in developing immuno therapeutic strategies. Although it is simple to assess antibody titers, in-depth mechanistic *in vivo* studies are necessary to address the functions of other lymphocytes, including gamma/delta T cells, natural killer (NK) cells, NKT cells, or even possibly CD8+ T cells. This will necessitate rectifying a historical underfunding of basic research on the host response to N. fowleri and other free-living amoebic viruses. Still, it will trigger revolutionary improvements in the clinical options for preventing and treating a fatal disease. Proteomic studies have identified various proteins in Naegleria fowleri, including those involved in metabolic pathways, cell structure, and virulence. These analyses have provided a snapshot of the molecular machinery that enables the amoeba to survive and interact with its environment, contributing to potential therapeutic strategies and preventive measures against infections caused by this amoeba.

Early Symptoms of Brain- Eating Amoeba

Headache

This is caused by the amoeba entering the brain through the nasal passages. It is an early sign of inflammation and pressure build-up in the brain.

Fever

This is your body's response to the infection. While it can be mild, it is usually persistent.

Nausea and Vomiting

It happens due to increased pressure within the body. It is also your body's reaction to the infection.

Stiff Neck

Due to meningitis which is an inflammation of the membranes covering the brain and spinal cord, you might have a stiff neck. This leads to discomfort and reduced neck mobility.

Altered Mental State

You might also have confusion, hallucinations, and changes in personality or behaviour. This is also an indication that the amoeba is affecting brain function.

Seizures

This usually happens because there's a disruption of normal brain activity.

Sensitivity to Light

Also known as Photophobia, this happens when there's pain or discomfort in your eyes when exposed to light. This is linked to meningitis and brain inflammation.

Ways to Prevent Amoebic Meningoencephalitis

- Don't swim, wade or do water sports in warm freshwater locations, especially still waters.
- Don't use tap water for a neti pot or any other device that cleans your nasal passages.
- You can use filters to remove germs from water.
- You can also use chlorine bleach liquid or tablets to disinfect your water for cleaning your nose and sinuses.

Diagnostic Challenges

The disease presents diagnostic challenges to medical professionals as early symptoms can be mild. 16% of cases presented with early flu-like symptoms only. Symptoms may also appear similar to a viral or bacterial meningitis which may delay correct diagnosis and treatment. Most cases have been diagnosed post-mortem following a biopsy of patient brain tissue. It takes one to twelve days, median five, for symptoms to appear after nasal exposure to N. fowleri flagellates. Symptoms may include headache, fever, nausea, vomiting, loss of appetite, altered mental state, coma, drooping eyelid, blurred vision, and loss of the sense of taste. Later symptoms may include stiff neck, confusion,

lack of attention, loss of balance, seizures, and hallucinations. Once symptoms begin to appear, the patient usually dies within two weeks. N. fowleri is not contagious; an infected person cannot transmit the infection.

Primary amoebic meningoencephalitis is classified as a rare disease in the United States as it affects fewer than 200,000 people. From 2013 to 2022, 29 infections were reported in the US, which compares with about 4,000 annual deaths by drowning. It is so rare that individual cases are often reported internationally, with 381 cases reported globally. The true number of cases is likely to be higher than those reported due to problems relating to diagnosis, access to diagnostic testing and a lack of surveillance.

Animals may be infected by Naegleria fowleri. This is rarely observed, although it may occur and be overlooked. Experimentally, mice, guinea pigs, and sheep have been infected, and there have been reports of South American tapirs and cattle contracting PAM.

Development and immunological evaluation of an mRNA-based vaccine targeting Naegleria fowleri for the treatment of primary amoebic meningoencephalitis

More than 95% of patients fall victim to primary amoebic meningoencephalitis (PAM), a fatal disease attacking the central nervous system. Naegleria fowleri, a brain-eating microorganism, is PAM's most well-known pathogenic ameboflagellate. Despite the use of antibiotics, the fatality rate continues to rise as no clinical trials have been conducted against this disease. To address this, we mined the UniProt database for pathogenic proteins and selected assumed epitopes to create an mRNA-based vaccine. We identified thirty B-cell and T-cell epitopes for the vaccine candidate. These epitopes, secretion boosters, subcellular trafficking structures, and linkers were used to construct the vaccine candidate. Through predictive modeling and confirmation via the Ramachandran plot (with a quality factor of 92.22), we assessed secondary and 3D structures. The adjuvant RpfE was incorporated to enhance the vaccine construct's immunogenicity (GRAVY index: 0.394, instability index: 38.99, antigenicity: 0.8). The theoretical model of immunological simulations indicated favorable responses from both innate and adaptive immune cells, with memory cells expected to remain active for up to 350 days post-vaccination, while the antigen was eliminated from the body within 24 h. Notably, strong interactions were observed between the vaccine construct and TLR-4 (− 11.9 kcal/mol) and TLR-3 (− 18.2 kcal/mol).

Management and Treatment

On the basis of the laboratory evidence and case reports, heroic doses of amphotericin B have been the traditional mainstay of PAM treatment since the first reported survivor in the United States in 1982.

Treatment has often also used combination therapy with multiple other antimicrobials in addition to amphotericin, such
as fluconazole, miconazole, rifampicin and azithromycin. They have shown limited success only when administered early in the course of an infection.

While the use of rifampicin has been common, including in all four North American cases of survival, its continued use has been questioned.[5] It only has variable activity in vitro and it has strong effects on the therapeutic levels of other antimicrobials used by inducing cytochrome p450 pathways.[5] Fluconazole is commonly used as it has been shown to have synergistic effects against naegleria when used with amphotericin in vitro.[5]

As of 2015, there was no data on how well miltefosine is able to reach the central nervous system. As of 2015 the U.S. CDC offered miltefosine to doctors for the treatment of free-living amoebas including naegleria.[4]

Nevertheless in 2013–2016, three successfully treated cases in the United States utilized the medication miltefosine. [4] In one of the cases, a 12-year-old female, was given miltefosine and targeted temperature management to manage cerebral edema that is secondary to the infection. She survived with no neurological damage. The targeted temperature management commingled with early diagnosis and the miltefosine medication has been attributed with her survival. On the other hand, the other survivor, an 8-year-old male, was diagnosed several days after symptoms appeared and was not treated with targeted temperature management; however, he was administered the miltefosine. He suffered what is likely permanent neurological damage. In 2016, a 16-year-old boy also survived PAM. He was treated with the same protocols of the 12-year-old girl in 2013. He recovered making a near complete neurological recovery; however, he has stated that learning has been more difficult for him since contracting the disease.

In 2018, a 10-year-old girl in the Spanish city of Toledo became the first person to have PAM in Spain, and was successfully treated using intravenous and intrathecal amphotericin B.

A 2023 study has showed that the treatment (with usage of benzoxaboroles) of infected mice significantly prolonged survival and showed a 28% cure rate without relapse.

2. Prognosis

Since its first description in the 1960s, only seven people worldwide have been reported to have survived PAM out of 450 cases diagnosed, implying a fatality rate of about 98.5%. The survivors include four in the United States, one in Mexico and one in Spain. One of the US survivors had brain damage that is likely permanent, but there are two documented surviving cases in the United States who made a full recovery with no neurological damage; they were both treated with the same protocols.

There is also a fourth survivor in the United States. However, he had a different strain.

3. Conclusion

Brain-Eating Amoeba (Naegleria fowleri):

The brain-eating amoeba, scientifically known as Naegleria fowleri, is a rare but deadly microorganism found in warm freshwater bodies such as lakes, rivers, and hot springs. It

infects people when contaminated water enters the nose, typically during activities like swimming or diving. Once inside the nasal passages, it can travel to the brain, causing a severe and almost always fatal brain infection called primary amoebic meningoencephalitis (PAM).

Although infections are extremely rare, the disease progresses rapidly and is difficult to treat, with a high mortality rate. Preventive measures- such as avoiding water-related activities in warm freshwater during hot weather, using nose clips, and avoiding the use of untreated tap water in nasal rinsing- are crucial.

In summary, while Naegleria fowleri poses a very low risk to the general population, its potential for fatal outcomes highlights the importance of awareness, early diagnosis, and preventive action.

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