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Characteristics and Clinical Manifestation of The Brain Eating Amoeba (Naegleria Fowleri) and Understanding The Pathogenicity-Overview

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ABSTRACT

The trophozoite stage of brain eating amoeba is having invasive nature. Their habitat is in water bodies. Primary amoebic meningoencephalitis (PAM) is a clinical condition caused by Naegleria fowleri. This pathogen causes serious disruption of the central nervous system (CNS). The route of the infection, the sign and symptoms of this disease are reviwed.

KEYWORDS: *trophozoite, Primary amoebic meningoencephalitis (PAM), Naegleria fowleri, infection, central nervous system (CNS)*

INTRODUCTION

Naegleria fowleri is an important ameboflagellate, commonly known as "the brain-eating amoeba". It causes a much acute, fulminant and sporadically fatal central nervous system (CNS) infection termed as primary amoebic meningoencephalitis (PAM). The infection occurs from inhalation of trophozoites. It enters the CNS, after the insufflation of infected water, by attaching itself to the olfactory nerve, then the migrating through the cribriform plate of the ethmoid bone along the fila olfactoria and also reach blood vessels, and then enters into the anterior cerebral fossae (Seidel et al.,2004). It feeds on nerve tissue and causes extensive inflammation, necrosis and hemorrhage paving to death. N. fowleri is a thermophilic amoeba that grows well in the tropical and subtropical climates. Raised temperature during hot summer months or the warm water from the power plants facilitates its growth. Infection occurs in healthy children and the young adults with a recent history of

exposure to warm fresh water (the polluted water in ponds, swimming pools and man-made lakes). The ameba has been also mainly detected in artificially heated industrial water sources, and in domestic water supplies. About 312 cases have been reported with a high case fatality rate of approximately 96%. The number of reported cases of PAM has increased worldwide in recent years. The aggrandized incidence may be due to greater awareness of the disease or due to the development of more rapid, highly sensitive and also specific diagnostic assays such as PCR (Jain et al.,2002).

Clinical Manifestations

N. fowleri invades mainly by migrating along the olfactory nerve across the cribriform plates. On reaching the CNS, it generates a rapidly progressive, hemorrhagic, and necrotizing meningoencephalitis. Onset of the symptoms occurs within one to nine days (median of five days) after exposure. Early symptoms encompass changes to taste or smell, however loss of the olfaction may not be readily noticed. Closely mimicking bacterial meningitis, the PAM presents with fevers, severe frontal headache, photophobia, the meningismus, nausea and vomiting. As disease rapidly progresses and cerebral edema ensues, confusion, visual hallucinations, focal or the generalized seizures, and the progression to coma are common(Brown et al.,1991).

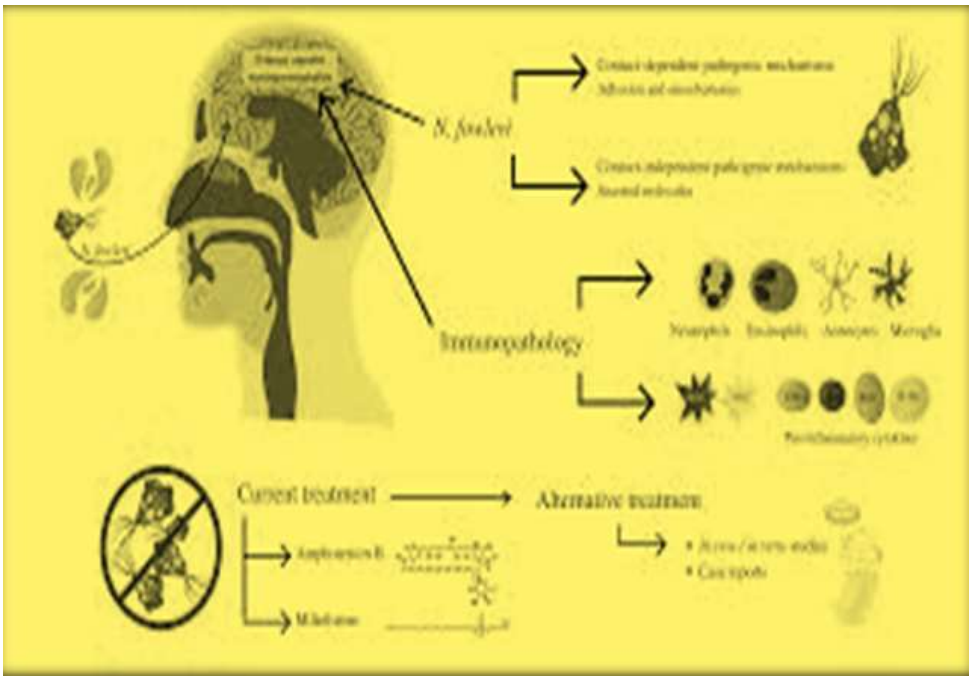

Figure: 1

Death occurs a median of 5 days from the symptoms onset. Upon autopsy, edema, hemorrhage and necrosis of the olfactory bulbs are observed. The Trophozoites are found on olfactory nerves, in the purulent exudate of the meninges and brain parenchyma, and within the perivascular spaces of the small to medium sized arterial vessels. Trophozoites may be found in other organs as well, encompassing the heart, lungs, and spleen.

Myocarditis has been delineated, as well as focal demyelination of the spinal cord without obvious amoebae; the cause of these findings remains quiet unknown. The predominance of pathology involves the brain as the point of primary invasion. The Cause of death is usually rakished to cerebral edema with brainstem herniation, systemic inflammatory response syndrome, or multiorgan system failure(Martinez ,1993) .

Unfortunately, less than 32% of cases from 1937 to 2013 were diagnosed premortem in the U.S., possibly due to late consideration of the diagnosis, difficulty and detecting the organism in the cerebrospinal fluid (CSF), or rapid death. As PAM cannot be distinguished from acute bacterial or the pyogenic meningoencephalitis by physical or CSF findings, solicitating a history of freshwater exposure is quiet critical to diagnosis, outcomes, and epidemiologic reporting (Poungvarin et al.,1993).

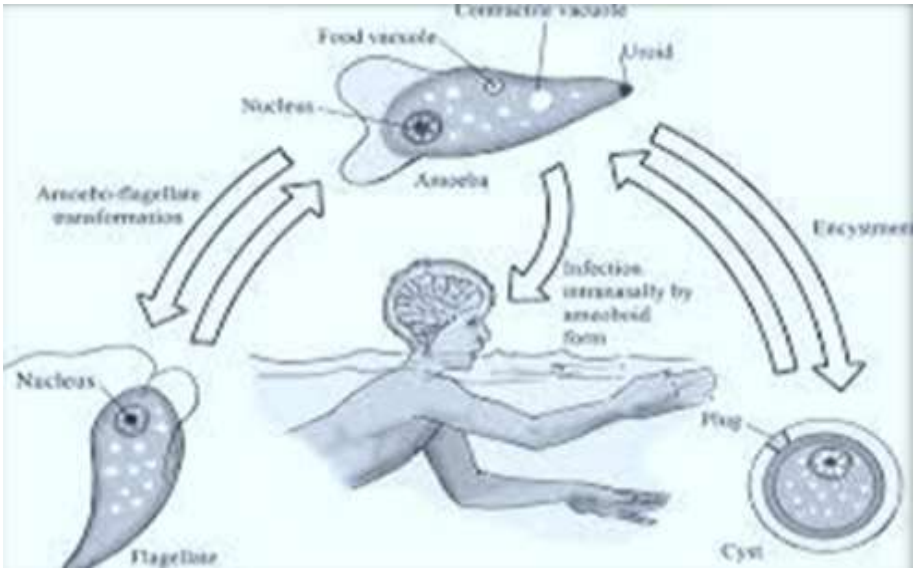

Figure: 2

Once a history of the freshwater exposure is elicited, CSF must be promptly examined via lumbar puncture. Opening pressure should always be measured and is usually much high.

The triad of the raised CSF white blood cells, negative Gram stain, and history of freshwater exposure should raise suspicion of the PAM. Either neutrophils or lymphocytes may predominate. The CSF Gram stain, for the preliminary diagnosis is usually negative because it does not stain the large, round nucleolus that precisely distinguishes *N.fowleri* from inflammatory cells and macrophages. Wright or the Giemsa stain, however, is routinely performed for the CSF , the WBC differential and has been very useful as a rapid detection method within hours in the most recent cases of early diagnosis and successful treatment. Wright and Giemsa stains quite readily distinguish the pale blue cytoplasm and small pink nuclei of *Naegleria* from the surrounding inflammatory cells (Carter,1969).

Trophozoites may also be visually observed during the manual hematocytometry for the WBC differential, although automated hematocytometry may misidentify amoebae as the inflammatory cells; in 1969, few researchers noted over 100 motile amoebae per μL by hematocytometry in a case report of amoebic meningoencephalitis (Loschiavo et al.,1993) .

Figure: 3

Treatment or Management

Due to the rarity of the disease and the lack of clinical trials, the definitive treatment for GAE is not clear at this time. A combination of drugs is availed. The Centers for Disease Control and Prevention recommend combination treatment with the pentamidine, sulfadiazine, the flucytosine, and either fluconazole or the itraconazole. Multiple other regimens are also

recommended. The Chronic Acanthamoeba meningitis was successfully treated in 2 children with a combination of the oral trimethoprim/sulfamethoxazole, rifampin, and the ketocona--zole. Resection of brain lesions may help as well (Cope et al., 2018).

Similarly, the optimal treatment of the PAM is unknown; reports range from 9 to 32 days. For the treatment of PAM amphotericin B, both intravenously and also by the intrathecal route is recommended, but considering the fulminant course of the disease and also the high mortality rates, a combination of drugs is generally availed. Reports include the use of amphotericin in addition to rifampin, fluconazole, miltefosine, and the azithromycin. Posaconazole has also been shown to be effective in mouse models of the disease. It may replace fluconazole as the azole of choice, although further studies and assessment are warranted to confirm this choice (Maciver et al.,2020).

Only one case of GAE due to *Sappinia* has been reported and assessed in humans (attributed to *S diploidea*). The patient was a previously healthy male farmer who mainly engaged in handling livestock. The disease manifested as headache, nausea, vomiting, blurry vision, and loss of consciousness following a sinus infection. The Histopathology of a single 2 cm focal lesion in the posterior left temporal lobe demonstrated the trophozoites (40 to 60 microns in diameter) with two nuclei. The infection was likely acquired by the inhalation. He was treated with a combination of flucytosine (2.75 g, 4 times a day for 25 weeks), the itraconazole (200 mg/day), intravenous pentamidine isethionate (300 mg/day for 6 weeks), and the azithromycin (250 mg/day for 31 weeks). The treatment resulted in the complete recovery (Graciaa et al.,2018).

The Effective treatment options are limited, but several therapeutic strategies have shown promise. The most commonly availed drugs include amphotericin B, rifampicin, and triazoles, which have been part of the treatment regimens for the few reported survivors of PAM .Additionally, miltefosine has been successfully availed in treating an adolescent patient, highlighting its potential as a viable treatment option .The Recent research has identified new compounds with the significant anti-Naegleria activity. For instance, the 4-aminomethylphenoxy-benzoxaborole AN3057 has keenly demonstrated nanomolar potency against *N. fowleri* and has shown a 28% relapse-free cure rate in the experimental mouse models. Furthermore, natural compounds such as andrographolide, the forskolin, and borneol,

when synthesised into nanoconjugates (AND-AgNPs, the BOR-AgNPs, and FOR-AgNPs), have exhibited biopotent antiamoebic and the cysticidal activities *in vitro*, with minimal cytotoxicity to human cells. Another promising candidate is the Nitroxoline, which has shown low micromolar activity against both trophozoite and cyst stages of the *N. fowleri*, along with a favourable selectivity index, making it a strong and robust candidate for alternative PAM treatment. Despite these advancements, the challenges remains in finding drugs that can effectively cross the blood-brain barrier and also exhibit minimal side effects (Matanock et al.,2018).

Diagnosis

The Clinical symptoms and signs of infection with *N. fowleri* usually present within 2 to 8 days of infectivity, though some have been reported and assessed within 24 h .Despite the absence of specific signs and symptoms indicating the *N. fowleri* infection, the most common symptoms include severe headache, fever, chills, the positive Brudzinski sign, positive Kernig sign, the photophobia, confusion, seizures, and possible coma (Dzikowiec et al.,2017). In addition, cardiac rhythm abnormalities and the myocardial necrosis have been observed in some cases. Perhaps most importantly, elevates in intracranial pressure and cerebral spinal fluid (CSF) pressure have been directly allied with death. CSF pressures of 600 mm H_2O have been observed in patients with *N. fowleri* infection. The CSF analysis has shown various abnormalities in colour, ranging from gray in the early stages of the infections to red in late stage disease, due to a significant increase in red blood cell. Additional elevates are seen in polymorph nuclear cell concentrations (as high as 26,000 mm^3), as well as the presence of the trophozoites in the CSF (using trichrome or Giemsa stain) .The Magnetic resonance imaging (MRI) of the brain often shows abnormalities in various regions of the brain, encompasssing the midbrain and subarachnoid space(Visvesvara et al.,2007).

Young boys are most at the risk for Naegleria fowleri infections. While the reasons are unclear, young boys might participate in more water activities like diving and playing in the sediment at the bottom of lakes and rivers, mainly from these water bodies. In the U.S., most infections have come from freshwater lakes, rivers, and hot springs located in southern-tier states. Recently people have become infected in the northern states following periods of very warm temperatures (Damhorst et al.,2022). The amoeba can be found in:

- **Terrains like -** Bodies of warm freshwater, like lakes and rivers

- Geothermal (naturally hot) water, like the hot springs
- Warm water discharge from industrial plants
- The Tap water
- Other recreational water that is not treated, such as some splash pads, surf parks, or by other recreational venues.

There are varying dynamics of disease (Dr. S. Sreeremya, 2024a). Placebo is an effective way of treatment (S. Sreeremya, 2022). The advancement in pharmacology (Dr. S. Sreeremya, 2024b) and biotechnology paved the way to understand in detail about the drugs and diseases (Dr. S. Sreeremya,2024c).

Symptoms

Symptoms of PAM usually start about 5 days after infection. The Symptoms can be mild at first, but worsen very quickly. In its early stages, symptoms may encompass:

- headache
- fever
- nausea
- vomiting

Later symptoms may include:

- stiff neck
- confusion
- the lack of attention to people and surroundings
- the loss of balance
- seizures
- hallucinations

After symptoms begin, the disease can move quickly and can cause death within about 5 days (Pugh et al.,2016). People should seek medical care immediately whenever they have a very sudden fever, headache, stiff neck, and vomiting - particularly if they have been in the warm fresh water within the previous 2 week s(Visvesvara,2010).

CONCLUSION

The unique and common symptooms of brain eating amoeba are *N. fowleri* infection, the most common symptoms include severe headache, fever, chills, the positive Brudzinski sign (Brudzinski's sign is a clinical test and physical examination procedure where the involuntary flexion (benting) of the hips and knees occurs when a patient's neck is passively stiff. This sign is a key indicator of meningeal irritation, most commonly caused by meningitis), positive Kernig sign, the photophobia, confusion, seizures. So each conditions of the brain-eating amoeba is discussed.

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