Section: Medicine

Original Article

ISSN (0): 2347-3398; ISSN (P): 2277-7253

Naegleria Fowleri "The Brain -Eating Amoeba": A Review

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Abstract

Naegleria fowleri is a free-living amoeba (FLA) that is commonly known as the "brain-eating amoeba." This parasite can invade the central nervous system (CNS), causing an acute and fulminating infection known as primary amoebic meningoencephalitis (PAM). Even though PAM is characterized by low morbidity, it has shown a mortality rate of 98%, usually causing death in less than two weeks after the initial exposure. This review summarizes the most recent information about N. fowleri, its pathogenic molecular mechanisms, and the neuropathological processes implicated. Additionally, this review includes the main therapeutic strategies including the possible use of immunomodulatory agents to decrease neurological damage.

Keywords: Brain eating amoeba; CNS; Neuroinflammation and Neurodegeneration.

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Received: 31 March 2024 **Revised: 05 June 2024** **Accepted: 22 June 2024** **Published: 14 August 2024**

Introduction

Naegleria genus belongs to the free-living flagellate amoebae, which is ubiquitous in the environment.[1] They have been found in various water resources (rivers, lakes and hot springs) and soil environments all around the world. Naegleria genus is classified in the Vahlkampfiidae.[2] family consisting of 47 species. There are three morphological forms to its life cycle: feeding trophozoite stage, transitional flagellate stage and dormant cyst stage. Naegleria fowleri is the only pathogen species of the genus Naegleria that is commonly known as brain-eating amoebae.

It can cause a rare and devastating infection of the brain called primary amoebic meningoencephalitis (PAM), an acute fatal disease the central nervous system (CNS) after being in exposure to contaminated recreational, domestic or environmental water sources.[3]

This disease is rare and infections with N. fowleri occur mainly during the summer while it is almost fatal and its case fatality rate is greater than 97%. The first case of PAM was reported in 1965 in four patients from South Australia.The initial symptoms might include.[4] headache, fever, nausea or vomiting, and in progressive conditions, the N. fowleri infection destroys the brain tissue causing brain swelling and eventually death. If patients with PAM are not given specific therapy after initial symptoms, it can lead to death 3–7 days after exposure. Unfortunately, symptoms of PAM are clinically similar to bacterial meningitis, which lowers the chance of accurate diagnosis of PAM.[1]

Three morphological stages have been detected in Naegleria fowleri life cycle depending on the environmental conditions.[4]

Life cycle of Naegleria fowleri is as follows

Trophozoite stage: Considered as the active, infective, feeding, reproductive stage (10–to 25 mm) with one nucleus that multiplies by mitosis in optimum environmental conditions.

Flagellate stage: Pear - shaped, mobile, non-reproductive and non-feeding stages of 10 – 16 mm.

Cyst stage: Non-reproductive and non-feeding stages of about 8 - 20 mm.

EPIDEMIOLOGY

Primary amoebic meningoencephalitis(PAM) was recorded for the first time in Florida, USA in 1962 followed by South Australia where the disease,[5] was first recorded in 1965 by Malcom Fowler and Carter, the reason of the name Naegleria fowleri was given to the disease. In 1966, Butt gave the name Primary Amoebic Meningoencephalitis (PAM) to the disease. Recently, in Asia the number of recorded PAM cases has been increased.[6] In the recent studies, it was recorded that only four patients have been survived from 16 cases of PAM in India. Most of them were using ponds and groundwater for swimming and bathing, the occurrence of Naegleria fowleri has been confirmed in all water sources of India,[2] has been Australia; Europe; Pakistan; North America; Iraq; China and Iran.

Clinical Manifestations of PAM

PAM is a hemorrhagic-necrotizing meningoencephalitis caused by N. fowleri and is seen mainly in immunocompetent children and young adults. PAM's clinical manifestations usually appear from 5-to-7 days after the initial exposure but may develop after only 24 h. Patients with present headaches, fever, nausea, fatigue, and

vomiting. During later stages, patients may have other signs and symptoms such as anorexia, irritation, nuchal rigidity, Kernig's sign, Brudzinski's signs, lethargy, photophobia, confusion, seizures, and possible coma. People infected with N. fowleri usually die 1–2 weeks after the initial exposure. For an accurate diagnosis, it is essential to consider both CNS symptoms and a history of contact with contaminated water.[3]

Clinical symptoms

When polluted water with Naegleria fowleri is forcing into human nasal passage by diving, skiing swimming and other activities, PAM begins in approximately 5 - 7 days, and may even begins in 24 hrs.[4] It is important to get "12 week" past history of the patient to know if there is any fresh water contact "such as hot springs and swimming pools. Naegleria fowleri symptoms begins first with a bifrontal headach, a rigid nuch, fever, nausea, restlessness, irritability and vomiting. The neurological changes such as lethargy, seizures, confusion, coma, diplopia or bizarre behaviour, leading to death within a week. Brain edema may cause a cranial nerve palsies in the third, fourth, and sixth cranial nerves, myocardial necrosis and abnormalities of the Cardiac rhythm have been occur.[5]

Pathogenesis of PAM

More than 90% of infections by N. fowleri occur when people submerge, dive, or splash in warm water bodies, allowing the amoeba's trophozoites to enter the body through the nasal cavity.[6] Even though the infection usually originates through the practice of recreational aquatic activities, it can also occur through ablution practices performed by religious groups and hygiene devices like neti-pots. Additionally, it has been suggested that the amoeba can "dry-infect" through cyst- laden dust, causing infection after transforming into their trophozoite form. Although the latter mechanism accounts for only about 6.5% of PAM cases, it is

extremely concerning, as little can be done to prevent the inhalation of dust. Once the amoeba is inside the nasal cavity,[7] it attaches itself to the nasal mucosa, penetrates it, and migrates along the olfactory nerves through the cribriform plate until it reaches the olfactory bulb. It then enters the brain through olfactory nerve bundles, where it multiplies and causes cerebral edema, herniation, and eventually death.N. fowleri causes severe damage to the CNS because of the amoeba's pathogenicity and the intense immune response it unleashes. There is limited information on N. fowleri's virulence factors, but in vivo, in vitro models have been developed to understand the molecular mechanisms associated with the pathogenesis of PAM. Thus far, two pathogenic mechanisms have been recognized in N. fowleri:

- Contact-dependent mechanisms related to adhesion and phagocytic food- cups
- Contact-independent mechanisms involving cytolytic molecules secreted by the amoeba.[7]

Diagnosis

During the initial stages of the infection, contrast-enhanced computerized tomography (CT) scan and magnetic resonance (MR) usually reveal cerebral edema, cortical sulcal effacement, and cisternal obliteration around the midbrain and the subarachnoid space.

PAM can be officially diagnosed by obtaining cerebrospinal fluid (CSF) through a lumbar puncture, which will reveal many polymorphonuclear leukocytes and N. fowleri trophozoites. CSF stained with Giemsa-Wright or trichrome, but not Gram, will reveal the presence of the amoeba and allow a morphological analysis of the parasite. N. fowleri can be cultivated by transferring a few drops of CSF into a non-nutrient or low-nutrient agar plate seeded with living or heat-killed bacteria. The most recommended medium for N. fowleri is Nelson's growth medium Additionally, supplementing Nelson's growth medium with 1% peptone has shown to improve the amoeba's growth.[8] To transform the trophozoites into flagellates, one must combine one drop of the amoebae culture or sedimented CSF with one mL of distilled water during 1-to-2 h. This flagellation process can help distinguish

N. fowleri from other pathogenic amoebae.[9] Even though solid non-nutrient agar is the standard method for growing N. fowleri, it has limitations, such as bacterial contamination and a lower yield of cysts Further confirmation of the amoeba's presence may be done through microscopy, immunofluorescence assay (IF), enzyme-linked immunosorbent assay (ELISA), or flow cytometry (FC).

Furthermore, a reverse transcription polymerase chain reaction (RTPCR) is recommended to determine the amoeba's genus and species. Additionally, intracranial and CSF pressure usually increases to 600 mm H2O or higher, a symptom that has been directly associated with the patient's death. CSF's color may vary from greyish to yellowish-white during the early stages of the infection, but as the disease progresses, it may turn red as a consequence of the large number of red blood cells (RBCs), which have been reported as high as 24,600/mm3. Furthermore, white blood cells (WBCs) count ranges from 300 cells/mm3 to 26,000 mm3, protein concentration may vary from 100 mg/100 mL to 1000 mg/100 mL, while glucose may present values equal or lower to 10 mg/100 Ml.[8]

Treatment

Systemic amphotericin B with or without miconazole, sulfisoxazole and rifampinis were the best treatments of PAM because Naegleria fowleri is very sensitive for that medication in vitro.[10] A serious acute reaction after the infusion was detected including headache, nausea, chills, dyspnoea, tachypnoea and fever.[11] Fluconazole was effective treatment in reducing the dysfunction of the infected organs by increasing neutrophils numbers and due to its ability in penetration the blood-brain barrier.[12] For experimental PAM in mice, Azithromycin was a good treatment, Phenothiazine compounds had the ability to inhibit Naegleria fowleri in vitro because it can accumulate in the CNS. Fluconazole, Amphotericin B and oral Rifampicin were recorded as the best medications for PAM infected patient during the early diagnosis.[13] Also the effect of antibacterial agents such as Neomycin, Roxithromycin, Clarithromycin, Rokitamycin, Zeocin,

Hygromycin and Erythromycin all were tested in both in vitro and in vivo showing Naegleria fowleri inhabitation, Chlorpromazine was recorded as a rapid and strong treatment for Naegleria fowleri trophozoites more than Fluconazole and Amphotericin.[14]

Prevention and Control

Naegleria fowleri can be controlled in swimming pools during hot months by using Chlorinated water to prevent reproduction, furthermore in the recreational water areas where the infection chance of PAM is high, people should not immerse their heads in non-chlorinated water. Also purified water should be used in nasal cleans in process.[15]

Conclusion

Naegleria fowleri is a dangerous parasite that is responsible for primary amoebic meningoencephalitis with a death rate approximately 95 % in human. It is a wide
spread in the countries where summer months are very hot. The parasite cause the disease when human is in contact with polluted water. The infection begins with the entrance of the infective stage "Trophozoites" to the nasal passage, reaches the brain, causing the infection to the central nervous system and finally death in 3 – 7 days. It is important to make further studied about this parasite and how to protect the immune system by controlling, diagnosing and treating this pathogen.

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How to cite this article: M Angad, Naegleria fowleri "The Brain -Eating Amoeba": A Review. Asian J. Med. Res. 2024;13(2): 4-6.

DOI: dx.doi.org/10.47009/ajmr.2024.13.2.2

Source of Support: Nil, **Conflict of Interest:** None declared.