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Mini review: *Naegleria fowleri the fatal meningoencephalitis*

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***Abstract*— Primary amoebic meningoencephalitis (PAM) is a fatal parasitic disease caused by a free-living amoeba called *Naegleria fowleri* also called a brain-eating amoeba. The parasite can invade the central nervous system causing brain damage and death in a few days. PAM is characterized by a high fatal mortality rate of 98% and the estimated time for death is less than two weeks after symptoms onset making it the most deadly parasitic infection in the world. Treatment options for PAM are still the major obstacle since the drugs cannot pass the blood-brain barrier (BBB) to kill the parasite leading to a high mortality rate. This review came to focus on the new approach and updating regarding the new treatment options and recent case reports in addition to elucidating the diagnosis process.**

***Keywords*— Naegleria fowleri, Brain-eating amoeba, Primary amoebic meningoencephalitis (PAM).**

I. INTRODUCTION

Naegleria fowleri:

The parasite belongs to the free-living Amoeba family of Vahlkampfiidae, order Schizopyrenida, and class Heterolobosea (2, 3, 8). *Naegleria fowleri* has three stages which included the cyst, trophozoites, and flagellates, the reproductive stage is the trophozoit which can infect the human and can transform into the flagellate form when exposed to environmental factors like low food and hard environmental stress the trophozoit can be transformed to the cyst stage which approximately 6 microns in diameter. Cysts can bear temperatures up to 65 C^0(9). Parasite-like pear-shaped measuring 10-16 µm with two flagella thrive at 27-37 C^0 the shape has cytoplasmic inclusions, nucleolus, nucleus, mitochondria, and rough endoplasmic reticulum(4). According to internal transcribed spacers and 5.8rDNA analysis, the genus of this amoeba consists of 47 species and only three Naegleria species have been described as pathogenic including *Naegleria australiensis* and *Naegleria italic* infects lab animals while *Naegleria fowleri* causes fatal human disease (brain-eating amoeba) (5, 10). *Naegleria fowleri* is a free-living amoeba and its natural habitats involved rivers, hot springs, lakes, swimming pools, hospitals, untreated drinking water, fountains, and freshwater (1) and the parasite enters the human through the trophozoites form releasing many cytolytic enzymes destruct the host nerve cell those molecules included phosphorolytic, phospholipases, acid hydrolysis and neuraminidases enzymes(11). During the hostile condition, the parasite transforms too an inactive cyst (7-12 µm) to resist the environmental factor for survival and in winter the cyst can remain dormant at 4 C^0 and then reproduce its activity during the summer(12). *Naegleria fowleri* reproduced by binary fission and grow better in thermophilic conditions at 35-46 C^0. Furthermore, Gram-positive and Gram-negative bacteria, yeasts, and algae are the main nutrient source of the parasite (1).

Primary amoebic meningoencephalitis is a fatal primary rare, acute amoebic disease that results in death within days (3, 4). *Naegleria fowleri* is the causative agent of that fatal disease, the parasite enters through the nasal cavity penetrating the mucosa when exposed to contaminated water during nasal irritation, bathing, ablution, and swimming (13). *Naegleria fowleri* invades the central nervous system (figure 1) by attaching itself to the nasal epithelium and migrating to reach the porous cribriform via the olfactory neuroepithelial route and migrating along with the olfactory nerve causing what is called primary amoebic meningoencephalitis (PAM) which characterized by herniation and cerebral edema and finally brain death (figure 2), the disease was reported in 1965 by Fowler and Carter in Australia (4, 6, 14). According to the study data the estimated mortality rate of PAM is 95% (15), the incubation period ranges from 2-5 days and death is usually 3-7 days after the onset of symptoms (16).

The parasite has three stages during its life cycle the first stage is a dormant stage cycle, the second is the flagellate stage and the last is an active amoeboid stage, in this disease always the amoebic form is found in the brain biopsies and unfortunately, the disease is fatal despite of early and right diagnosis because the inability to achieve the inhibitory concentration of drug to the site of infection (13). Ubiquitous free-living amoeba can be found in the air, water, soil, swimming pools, hospital environment, and

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water pipes (17). In the United States of America, the estimated annual death caused by this parasite is 16 deaths (18). Furthermore, statistical data revealed that PAM has <0.5 of diagnosed encephalitis in the United States (19).

Most cases of PAM can be misdiagnosis since the infection is consistent with bacterial and viral meningitis, a reported case in China of 8- year- old male who was admitted to the hospital after 24 hours of fever, vomiting, and headache, and finally, the patient entered into a coma and brain death at the end metagenomics next generation sequencing technique was used to diagnose the causative agent which was *Naegleria fowleri* (20). A similar fatal case was confirmed by polymerase chain reaction for a Turkish 18- year- old male who complained of a headache after 2-3 days after returning from a hot spring (21). Many countries have reported PAM cases (figure 3). Recently in 2019, an interesting case has been reported in southern Brazil involving a four-year Angus cow infected with *Naegleria fowleri* and these results indicated the ability of the parasite to infect both humans and animals causing fatal meningoencephalitis (22).

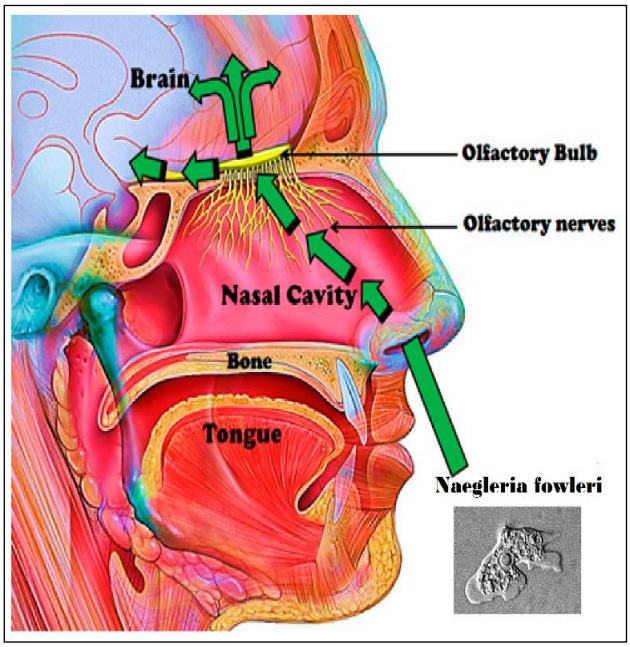

Figure 1: The entrance route of *Naegleria fowleri* after exposure to contaminated water. The parasite is attached to nasal epithelial and reaches the brain through the olfactory nerve (6, 7).

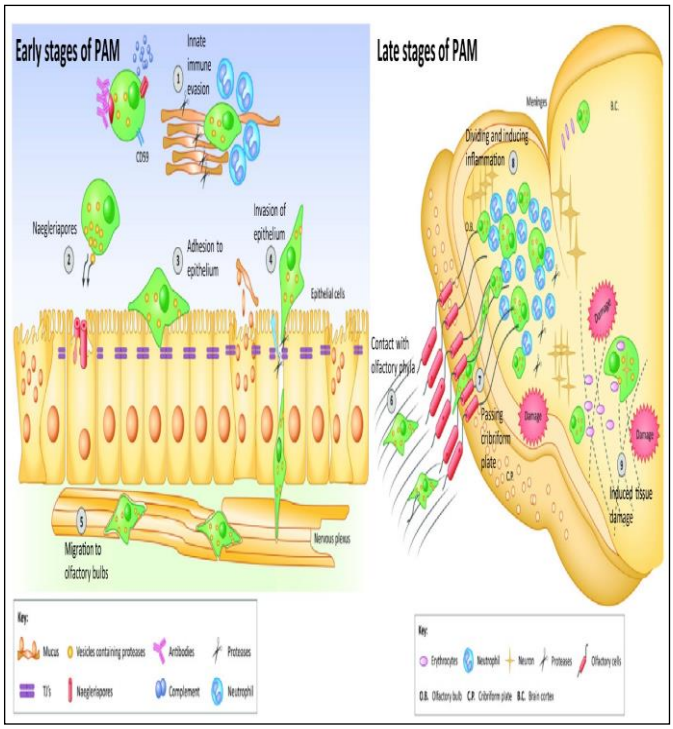

Figure 2: This figure elucidates the early and late stages of primary amoebic meningoencephalitis (PAM). The early stage shows the mechanism of entrance through migration of the parasite along with olfactory bulbs and the late stage represents the inflammation process in the brain cortex (3, 8).

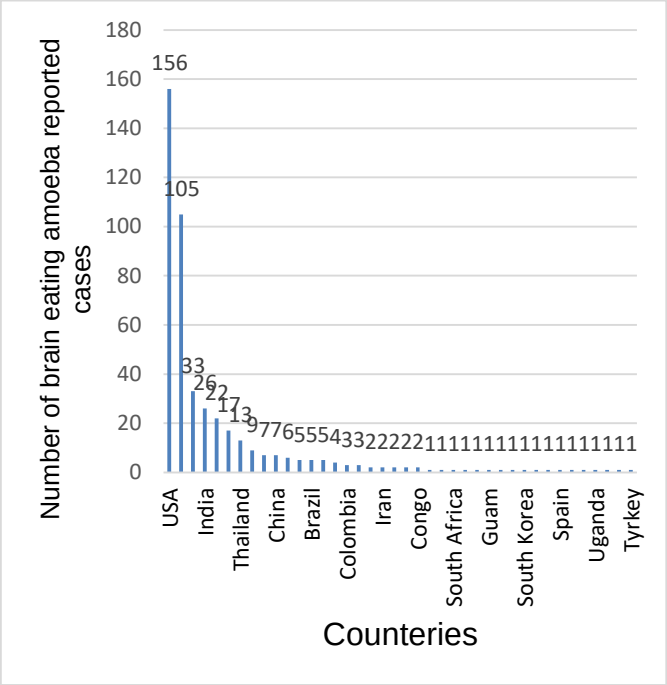

Figure 3: Worldwide reported cases of brain-eating amoeba until 2022 (1-5).

DIAGNOSIS:

Diagnosis of the PAM can be relay on multiple methods including magnetic resonance (MR) and computerized tomography (CT) which reveal necrotic areas, aneurysms, and stenosis (23). *Naegleria fowleri* can be found in cerebrospinal fluid with many polymorph nuclear leukocytes. CSF stained with Giemsa-Wright stain to show the trophozoites while Gram-stain has no benefit revealing the parasite (4, 24). Nelson's growth medium with fetal calf serum can be used to culture *Naegleria fowleri* (4). The polymerase chain reaction was recently used for early diagnosis of the disease along with immunofluorescence assay (IF), flow cytometry, and enzyme-linked immunosorbent assay (ELISA) (23). Clinical symptoms also can be relayed to diagnose the infection which included chill, fever, severe headache, seizures, photophobia, cardiac abnormalities, myocardial necrosis, and comma (6).

TREATMENT CHALLENGING:

Since the infection with *Naegleria fowleri* characterized by a high mortality rate and all information documented are came from reported cases so there is not much information regarding treatment options and needs to be updated through more studies and clinical trials (2). According to the studies, Amphotericin B (AmB) is an anti-fungal used to kill the parasite by inducing the apoptosis process (25). AmB can be administrated alone or with other drugs like Fluconazole (FCZ), Rifampin (RIF), and Azithromycin (AZM) during the early stage of infection and showed some efficacy in eliminating the parasite (6, 23). However, the biggest obstacle to treatment, is that most drugs need to be administered in high concentration to pass the blood-brain barrier (BBB) and reach the minimum inhibitory concentration (MIC) to kill the amoeba (26). Breast cancer and Leishmania drug Miltefosine (MLT) have been used on a 12-year-old girl along with RIF, AZM, AmB, and dexamethasone in addition to the physical treatment included hypothermic state to reduce brain inflammation process interestingly, the girl survived the infection (27, 28).

CONCLUSION:

Naegleria fowleri is a free-living parasite causing a fatal neurologic disease with a high mortality rate and patients die after less than two weeks from brain herniation and elevated intracranial pressure (29). Rivers, swimming pools, freshwater, hospitals, and untreated drinking water consider the source of infection. Meningoencephalitis in *Naegleria fowleri* mimics bacterial and viral meningitis including neck stiffness, vomiting, high fever, and headache, and needs to be differentiated for an accurate diagnosis. Furthermore, a molecular Cerebral spinal fluid (CSF) test panel for most pathogens should include all treatment options has a low chance of killing the amoeba and in most cases of recovery, the patient will permanently suffer from dormant neurological damage. Urgent studies need to be conducted to reveal another treatment efficiency that might improve the outcome of treatment. Swimming pools need to be extremely under the control of health authorities.

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