



BRAIN-EATING AMOEBIA: A REVIEW OF *Naegleria fowleri*, PATHOGENESIS, MOLECULAR DETECTION AND TREATMENT

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Abstract

Naegleria fowleri which is known as “Brain-Eating Amoeba” is a thermophilic flagellated amoeba is the cause of a life threatening waterborne disease called Primary Amoebic Meningoencephalitis (PAM). PAM infects both humans and animals. Although, PAM is a rare disease but it is fatal. Recently, studies conducting in developing countries reported that the mortality rates of PAM reaches 95 – 99 %. The amoeba in its trophozoite phase enter the hosts body through the nose. During its journey the amoeba cross the cribriform plate and reaches the brain. Inside the brain, it causes a severe damage to the Central Nervous System (CNS) which leads to brain haemorrhage and death within 3 - 7 days in the cases of undiagnosed or maltreated infections. Despite the presences of many treatment programs, the survival rate of PAM stayed at 5 %. Normally, the misdiagnosis of PAM is due to its resemblances to bacterial meningitis. This present review aimed to focus on the type of meningitis that is caused by *Naegleria fowleri* and how to diagnose it and how to manage the disease.

Key words: *Naegleria fowleri*, Amebic Meningoencephalitis, Infection and Diagnosis.

1. Introduction

Naegleria fowleri (*N. fowleri*), a single-celled amoeba, causes a severe and uncommon disease referred to as Primary Amoebic Meningoencephalitis (PAM). It results in inflammations and destruction regarding the brain and its linings, and it is typically fatal (Owino, 2020). In South Australia, PAM is initially reported in the 1960s. Since that time, it was reported in various nations globally. Even though *N. fowleri* commonly occurs in environment, it just uncommonly results in disease. Since the year 2000, there were 4 verified conditions and single possible case reported in Queensland (Maciver *et al.*, 2020).

N. fowleri can be defined as a thermophilic, free living, pathogenic flagellate amoeba which belongs to class of Heterolobosea. In warm months, *N. fowleri* will

proliferate since it is capable of tolerating temperatures of about 45° Celsius and it is predominantly feeding on the bacteria that live in the warm natural freshwater's bodies (Hasniet *al.*, 2019). Also, it is referred to as amphibolic amoeba and there were 3 morphological states regarding the lifecycle of the species of the *Naegleria*: flagellate stage (10 mm – 16 mm), trophozoite (10 mm – 25 mm) and cyst stage (8 - 20 mm) (Jahangeer *et al.*, 2020b).

Based upon environmental states, *N. fowleri* might alter the phenotype, while the trophozoite has been representing reproductively active phase that showed within favorable conditions and taken into account as infective stage. In addition, it has only one nucleus and it uses binary fissions in order to multiply. For excellent growth of such stage, the suitable temperature is between (35 and 46 °C) (Bogitsh *et al.*, 2018). Trophozoites will be transformed into a temporary motile stage which is referred to as flagellate in the case when there is occurrence of nutritional deficiency in environment, yet water exists, and such stage is best thriving in temperatures between (27 and 37

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°C) (Siddiqui *et al.*, 2016). Within adverse or unfavorable conditions, the trophozoites originate the metabolically-dormant cyst stage with the ability for surviving in extremely low temperatures. Cyst and flagellate *N. fowleri* forms were non-feeding and non-reproductive phases, whereas just trophozoites might feed, reproduce, and becoming cystic and seen in SEM (Pana *et al.*, 2017).

As one of the free living protists, *N. fowleri* is majorly feeding on bacteria, Gram negative and Gram positive, also on yeast and algae. They are the only species which are causing a lethal infection of the brain referred to as PAM, whereas more than 40 *Naegleria* species were recognized. Even though PAM is uncommon, it is one of the fatal diseases affecting humans with rates of mortality between (95 and 97 %). Mortality happens within about 7 days, since it has been fulminant, necrotizing, lethal, and haemorrhagic meningoencephalitis (Żbikowska *et al.*, 2014). It significantly takes place in the immunologically-strong people, children and young adults being recently exposed to re-creational freshwater. PAM is considered as one of the waterborne diseases; thus, the majority of conditions were related to activities of swimming and diving in polluted spas and canals, less chlorinated pools, or throughout leisure sports like water skiing in the contaminated environmental water sources (Jahangeer *et al.*, 2020b).

In untreated fresh water, there is a natural occurrence of *N. fowleri* which is preferring temperatures in range of 25 - 40 Celsius. It has the ability for growing in stagnant, warm water bodies like hot springs and lakes. It occurs in untreated water which is piped for long distances over ground as well as in many more man made environments like spas, wading pools and the swimming pools which are badly maintained (Stahl and Olson, 2021).

In the case where water is splashed or forced in nose, *N. fowleri* will enter through the nasal cavity and causes acute infection. It destructs the neurons as well as indicating which it is also referred to as “brain-eating amoeba”; such word is showing that toxins and enzymes of such organism were involved (usually) in

destructing (eating-up) the brain (Rajendran *et al.*, 2019). Also, PAM has been characterized through comparable symptoms and signs to the ones of bacterial or viral meningitis such as headaches, fever, vomiting, stiff neck, seizures, anorexia and lastly, mortality commonly happens between (3 and 7) days following the onset of such symptoms and signs. The virulence related to the strain as well as the inoculum's size have a role in specifying the time span between initially contacting the pathogenic *N. fowleri* and the onset of clinical symptoms and signs which might be varying from 2 – 3 days to up to 7 – 15 days (Bartrand *et al.*, 2014).

2. Diagnosis and Habitat of *N. fowleri*

Being a thermophilic protist, *N. fowleri*, especially inhabiting warm water such as hot springs in temperate zones and lakes in tropics. Yet, *N. fowleri* cysts or trophozoites were indicated on the basis of its natural environment in most-varied environment to 2 classes, which are, urban zones and natural habitat. The latter involve rivers, ponds, warm aquatic conditions, hot spring and freshwater lakes, whereas the former involve un-contaminated and contaminated sources of water, also to drink water distribution system via pipe wall biofilms (Ong *et al.*, 2017). There is greater number of *N. fowleri* in the sites with an increase in the temperature of water over 28 Celsius. Therefore, environmental monitoring through the use of fast and high-accuracy screening has been needed as one of the risk preventions to discriminate between the other *N. fowleri* and free living amoeba in samples of water. There were various approaches for identifying *N. fowleri* like molecular or immunological, other current approaches were visually included to detect *N. fowleri* (Morgan *et al.*, 2016).

Molecular-based approaches such as PCR were more specific, rapid and sensitive in comparison to the microscopic and culture approaches. Also, the direct detection and quantification of microorganisms in the samples of environment might be particularly done via qPCR, with no requirement for cultural isolations and this real time PCR based method of diagnostics can be useful and effective in the



case of being used in lab practices (Hernández-Rodríguez *et al.*, 2011).

3. *N. fowleri* Infection Pathophysiology

In human body, the acute infections can be identified in a case when water which contains *N. fowleri* has been inhaled (forcefully) to the upper nasal passages throughout swimming, bathing, or other re-creational actions. Firstly, the infection happens when the amoeba is attached to nasal mucosa, which is moving after that along the olfactory nerve as well as reaching olfactory bulbs in CNS. It is possible that the PAM risk is high between young adults and children which have further porous cribriform plates (Gompf and Garcia, 2019). Researches indicated that there is no possibility for initiating the infection when drinking water that is contaminated. However, another research specified that such amoeba might be just infecting an individual *via* olfactory route, not through oral route. There were specific events which might be considerable in the progression of the disease like the ability of trophozoites for being attached to nasal mucosa, a chemotactic response to nerve cell's elements, an increase in the rate of locomotion (French, 2010).

Forced, or splashed into the nasal cavity of humans, the contaminated water, might develop *N. fowleri* infection, which is initiated with the attachment of trophozoites to nasal mucosa, succeeded *via* locomotion of parasites along the cribriform plate and olfactory nerve, also chemo-tactic responses to the components of the nerve cells for lastly reaching CNS olfactory bulbs. Ultimately, severe inflammation is induced *via N. fowleri*, also neurons tissue necrosis and neurons destruction (Pook, 2020).

In *N. fowleri*, the pathogenic mechanisms involve the trophozoites adherence to mucin degradation and nasal mucosa. Then, trophozoites are enabled *via* food cups for ingesting the human tissues, while the secretion regarding acid hydrolases, naegleriapores, neuraminidases, proteases and phospholipases are contributing to demyelination and more lysis related to erythrocytes as well as the surrounding nerve cells. Also, trophozoites are showing mechanisms of evasion to the host's immune

response, like resistance to cytokines and removing membrane attack complex. The pathogenicity of *N. fowleri* and the overall intense host immune response, causes a considerable CNS and nerve damage, and lastly, the death of the cell (Betanzos *et al.*, 2019).

Many researches proposed that the pathways of the signal transduction that are related to *N. fowleri* have been activated through the amoeba's attachments to the host cell which results in releasing and producing mucosal layer eroding proteases which are promoting the invasion and proliferation of such amoeba in CNS. There were a few factors causing such organism's adhesion involving the pore forming proteins (pores of *Naegleria*), the existence of carbohydrates residues in plasma membrane's outer surface (Marciano-Cabral and Cabral, 2007).

4. Symptoms and Signs

The involvement of neural tissue invasion and olfactory epithelium are signified via clinical symptoms like respiratory infection and changes in the sense of smell. Symptoms and signs reported *via* patients experiencing PAM don't involve any nasal inflammation symptom like bleeding, nasal pains, sneezing, persistent rhinorrhea and tenderness at nose bridge, prior to showing PAM signs like the meningitis. Besides, destruction and damage of olfactory bulb, adjacent areas and olfactory mucosa of the brain were observed mostly following postmortem findings, whereas comparable destructions in the region related to non-olfactory mucosa of nasal cavity isn't identified. A research specified that *N. fowleri* is favoring frontal lobe in comparison to the parietal lobe (Uversky *et al.*, 2020). Since the nasal rout is adopted *via N. fowleri* for entry, reporting that the *N. fowleri* possible has a close relation with the frontal lobe, which is due to the fact that there is anatomical proximity of olfactory bulb to frontal lobe; in nasal passage it has been terminal to olfactory neuroepithelium; therefore, traversing plate of cribriform to brain diagrammatically explained (Muller-Schwarze, 2006).



5. *N. fowleri* and host immune response

Nf-actin, carries out such food-cups formation, which is mediating the *N. fowleri*' phagocytic activity. After that, it is releasing various cytolytic molecules involving acid hydrolases, neuraminidases, phospholipolytic and phospholipases, enzymes, which in CNS, results in more nerves' destruction. Also, infections with *N. fowleri* are eliciting intense immune response, resulting in CNS destruction and infection-mediated destruction (Miller, 2017)

6. Primary Amoebic Meningoencephalitis in animals

PAM is caused by *N. fowleri* in humans and also in animals, while many un-prompted conditions of encephalitis or meningo encephalitis were indicated because of the free living amoeba in horses, carnivores, a few wild animals and ruminants. The lesions of PAM being developed in the cattle have close association with the ones indicated in humans. In addition, the severe olfactory bulb, adjacent cerebral lesions nerve neuritis, multifocal non suppurative lesions, and the demonstration of *N. fowleri* in olfactory nerve specified that pathogen entry routes in cattle have been olfactory nerves and nasal mucosa (Jahangeer *et al.*, 2020a).

7. Treatment

Since the infection of *N. fowleri* rarely occur in humans, there were no clinical test till now addressing the effectiveness of certain treatment regimen compared to others. The majority of medication efficacy information is on the basis of *invitro* studies or case reports. Possible, the most common medication to treat the infection of *N. fowleri* is amphotericin B, which was examined *invitro* and utilized in many case reports. In addition, other anti-infectives which were utilized in case reports involve miconazole, fluconazole, azithromycin, miltefosine and rifampin. Many other agents were examined *in vivo* and *in vitro*, such as rokitamycin, hygromycin, erythromycin, clarithromycin, zeocin and roxithromycin (National Academies of Sciences and Medicine, 2020).

8. Control

N. fowleri is killed by chlorine and it is the major approach for disinfecting reticulated water supplies as well as swimming pools. With regard to rural water supplies, the chlorine might have no ability for reaching areas in which amoeba might create colonies. In terms of such conditions, a process referred to as chloramination has more effectiveness in controlling *N. fowleri*. UV treatment systems and filtration might be efficient to control *N. fowleri* (Storey and Kaucner, 2009).

9. Prevention

It has been reported that such acute and lethal disease was related to water, as a PAM's causative agent is thermophilic amoeba that is proliferating in less-chlorinated waters in year's warm months. Thus, there is high importance in maintaining the water's chlorine levels, also the cases of PAM are related to using imperfectly chlorinated water for swimming, nasal rinsing and ablution practices. In addition, public awareness can be a major factor of such disease. There must be boards and awareness campaigns in colleges, schools, recreational places and mosques for increasing the awareness of individuals towards such brain eating amoeba (Martinez, 2019).

There might be some personal actions significant in decreasing the risks of PAM like using tap water or un-treated freshwater must be avoided, use of sterile, filtered and distilled water for flushing, rinsing or irrigating nasal passages, or making irrigation solutions, using water that is boiled previously. In addition, the irrigation device must be rinsed following every utilization with formerly filtered, boiled, sterile and distilled water. As stated *via* (WHO), free chlorine have residual concentrations of more than or equal 0.50 mg/L (Gompf and Garcia, 2019).

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