Opinion

Insights into the Pathogenicity of the Emerging *Naegleria fowleri*: Emphasis on Contact-Dependent Virulence Mechanisms

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Opinion

What is *Naegleria fowleri*?

Naegleria fowleri, also known as the brain-eating amoeba, infects the brain of humans and animals through the nose, crossing the blood-brain barrier (BBB) and causing primary amoebic meningoencephalitis (PAM) [1-3]. This infection is acute and highly fatal, often leading to death within about two weeks [4]. While reports of deaths or infections are relatively rare (fewer than 10 cases per year according to PubMed), almost all infected individuals die. In the United States, 167 cases of PAM were reported between 1962 and 2024, with only four survivors [5].

Impact of increasing water temperature on infection of emerging *N. fowleri*

N. fowleri inhabits swimming pools, lakes, and tap water. While chlorination of these habitats and filtration of tap water (although not completely effective in removing *N. fowleri*) can minimize infection, the fact that it causes acute infection means that *N. fowleri* infection is often only diagnosed after the patient's death through autopsy or biopsy. This suggests that the actual number of cases is likely much higher than the fewer than 10 reported cases annually. A 2023 report from Taiwan indicated that *N. fowleri* was detected in one out of 56 specimens examined from an indoor surfing center in Taiwan [6]. Furthermore, rising water temperatures in swimming pools, lakes, and other water bodies create a more favorable environment for *N. fowleri* to thrive and survive. *N. fowleri* can feed on or interact with certain bacteria, enabling its survival and molecular and cellular biological changes. Therefore, rising water temperatures suggest that *N. fowleri* infections may become more frequent in the future. Especially given the increasing popularity of water-based recreational activities and the difficulty of disinfecting vast bodies of water, the risk of infection is likely to increase.

Contact-dependent pathogenicity related with extracellular lectin and glycoproteins

To prevent *N. fowleri* infection, Centers for Disease Control and Prevention (CDC) advises that “Personal actions such as swimming precautions and sinus rinsing to reduce the risk of *N. fowleri* infection should focus on preventing water from going up the nose”. Due to the rapid progression and severe consequences of PAM, there is a critical need to develop immunological factors or therapeutic drugs that can increase protective effects in humans and other hosts. Understanding the pathophysiology of *N. fowleri* is essential in addressing this challenge [7]. *N. fowleri* can interact with bacteria and survive by preying on them. It interacts with a significantly smaller number of bacteria compared to other free-living amoebas like *Acanthamoeba*. However, bacteria that come into contact with the extracellular membrane of *N. fowleri* can enter the cytoplasm and survive briefly before being destroyed. Therefore, because *N. fowleri* lives freely in the environment, a

comprehensive evaluation of its interactions with bacteria and its inherent toxicity is necessary to find ways to inhibit its pathogenicity and prevent infection. Meanwhile, *N. fowleri* can survive in three forms: trophozoite, flagellate, and cyst, depending on environmental conditions or within an infected host. The fact that its form changes depending on favorable or unfavorable conditions makes understanding the pathogenicity of *N. fowleri* quite challenging. Looking at the process by which *N. fowleri* causes pathogenicity, *N. fowleri* binds to host cells when destroying target cells. *N. fowleri* uses proteases it secretes to destroy target cells, proliferate, and invade the central nervous system (CNS) [8,9]. It can also form amoeboid structures such as amoebastomes, allowing for physical contact with host cells [10,11]. Factors that facilitate this amoebial attachment include pore-forming proteins, carbohydrate residues present on the outer surface of the cell membrane, and terminal L-fucose and D-glucose present in glycoconjugates [8,12]. The lectins present on the outermost surface of *N. fowleri* bind to sugar residues of glycoproteins present on bacteria and target cells, and conversely, the glycoproteins of *N. fowleri* bind to lectins present on target cells, initiating a contact-dependent pathogenic mechanism. In our previous research, mannose sugar was identified as playing the most significant role in the pathogenicity of *N. fowleri* [13]. However, despite varying several reaction conditions in our host-*N. fowleri* studies, it had difficulty to achieve 100% killing of *N. fowleri*. This suggests the need for molecular biological analysis of the functions of other second or third candidate monosaccharides.

Challenges of transcriptomics for differential RNAs related with lectins and glycoproteins

Next-generation sequencing (NGS), for example, RNA-based sequencing (e.g., transcriptomics), has been used to analyze genes expressed differently in the life cycle of parasites using messenger RNA [14-17]. RNA sequencing analysis showed that 146 genes in cysts of *N. fowleri* indicated 2-fold upregulation, and 163 genes were downregulated [18]. In addition to the life history of the parasites mentioned above, the differences between pathogenic and non-pathogenic protozoa have recently been analyzed using transcriptomics (Herman et al., 2021). Differentially expressed analysis was performed for pathogenicity transcriptomic data using the programs Cuffdiff [19] and Trinity [20]. Therefore, it can be implied that applying transcriptomics in *Naegleria* itself has great significance. By transcriptomics, the results of this study may clarify the contact-dependent pathogenicity of *N. fowleri* and will be helpful in understanding the pathogenicity of *N. fowleri* due to contact-dependence other than monosaccharide/lectin.

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