Opinion

Summer time sadness: a tale of "brain-eating amoeba"

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Sunil K Joshi
Frank Reidy Research Center of Bioelectrics College of Health Sciences, Old Dominion University, USA

Correspondence: Sunil Joshi K, Laboratory Head, Cellular Immunology Lab, Frank Reidy Research Center of Bioelectrics, College of Health Sciences, Old Dominion University, 4211 Monarch Way, IRP-2, Suite # 300 Norfolk, VA 23508 USA, Tel +17576833214, Fax +17574511010, Email skjoshi@odu.edu

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Introduction

Every year during summer, warm fresh water reservoirs poses a reclusive threat to public health. This almost universally fatal disease (95-99% mortality) known as 'Primary Amebic Meningoencephalitis (PAM)' or 'Amebic Encephalitis' which is caused by a thermophile ameboflagellate, Naegleria fowleri aka 'Brain-eating amoeba'.[1–3] Due to low incidence rate, the dangers of this **'Summertime Sadness'** are underestimated and ignored. In past few years, number of cases worldwide has increased significantly due to global climate change, particularly 'El Nino' effect is playing major role. The Naegleria fowleri is a climate-sensitive which enters through nose either during swimming or performing 'neti' (nasal rinse) and ablution, a ritual cleansing that includes nasal passages.[2] This has been now confirmed that city water supply through household faucets also contain Naegleria fowleri and pose more significant health concerns. In cold water, this ameboflagellate remains in dormant form as a cyst which transform into infective flagellate form when water becomes warm. Once enter through nasal mucosa, the Naegleria fowleri migrates to the brain via the olfactory nerve and cause lethal neuro-inflammation and damage to the brain. Whether Naegleria can enter through the open wounds is not known. However, one cannot get infected with Naegleria from **swallowing** contaminated water.[3] Historically, the very first existence of brain-eating ameba was reported in Ireland, in 1909. Later, in 1965, two physicians named, R.F. Carter and M. Fowler from Australia, formally studied and identified the Naegleria fowleri as a causative agent of PAM.[1] In 1978, CDC created the national Free-living Ameba (FLA) Laboratory, which has become a national resource and global leader for providing diagnostic and clinical guidance as disease is rare. The CDC began formally tracking Naegleria fowleri infections since 1989.[2]

After entering through nose, Naegleria migrates along the olfactory nerve via disruption of the olfactory mucosa and penetration through the submucosal nervous plexus.[4] Finally organisms passage through the cribriform plate to frontal lobes of the brain. Once in the brain, the Naegleria destroy brain tissue and cause severe neuro-inflammation in the form of PAM.[4,5] Scientists suggest that once in brain, Naegleria organisms produce two proteases enzymes and toxins that dissolve proteins leading to brain hemorrhage and severe tissue necrosis. New research reveals that the brain damage is substantially caused by hyper immune response from the host rather by Naegleria itself.[4,5] This amplified immune response is mainly due to prior exposure to the antigens and larger size of these pathogens. This overwhelmed immune response, which is dominated by acute inflammatory cytokines, often causes the leakiness of the blood brain barrier (BBB) and severe damage to neuronal tissues.[6] The further irreversible brain damage is done by toxins and enzymes secreted by the pathogen.[4–6]

The PAM is a fulminant central nervous system infection and incubation period can range from 2-15days.[4] Initially infection start with mild symptoms such as headache, fever, nausea, or vomiting, which later becomes complicated very quickly. Death typically occurs within 5days of symptom onset. The pathogenesis of PAM is quite similar to bacterial meningitis and possibly misdiagnose most of the time and underreported. As in the case of bacterial meningitis, fulminant PAM manifests as high fever and severe headaches, nausea, vomiting, stiff neck, and confusion, lack of attention to people and surroundings, loss of balance followed by a rapid progression to seizures, hallucinations or coma. Since the incidence of PAM is rare, it is difficult to diagnose and >75% of diagnoses are usually confirmed after the death during autopsy. Diagnosis of PAM usually start by taking detailed history and observing cardinal signs of meningitis. Early symptomatic diagnosis of meningitis is performed by patient's physical evaluation and observing Kernig and Brudzinski signs.[5–7] The Kernig's signs represent the resistance or pain during extension of the patient's knees beyond 135degrees due to spasm of the hamstring muscles. While a positive Brudzinski's sign represent if passive flexion of the neck induce reflex flexion of the patient's hips and knees.[4–6] Currently there is no rapid diagnostic test is available and it takes longer than a week to identify. In the United States, only few laboratories can diagnose the disease using specific laboratory tests. These special labs are directed through national FLA lab of CDC. The diagnosis of PAM and identification of Naegleria can be performed by direct visualization of motile organisms in cerebrospinal fluid (CSF), biopsy, or tissue specimens. However, the available new tests can identify specific antigens (by indirect immunofluorescence/immunohistochemistry) and nucleic acid (by PCR) of Naegleria extracted from CSF or tissue specimens.[7,8]

The 'brain-eating ameba' related sickness is rare and often results into sudden and tragic death in almost every case. Since pathogenesis of Naegleria is relatively under studied, no specific treatment for PAM is available yet and line of treatment mainly limited to treating symptoms and apply empirical therapy.[7,8] Very few cases have been treated and survived. If medical help is available at early stage, there is possibility to treat PAM by available anti-parasitic drugs alone or in combination with antibiotics.[7,8] The drugs of choice must be

able to effectively cross the blood-brain barrier to target parasites residing deep in the brain tissue. Studies have shown the effectiveness of various drugs such as azole antifungals (e.g., Ketoconazole and Itraconazole); *Diamidines* (Pentamidine); Cotrimoxazole (a combination of two antibacterial medicines-a sulfonamide medicine called sulfamethoxazole, and trimethoprim). Also, the antifungal agent Amphotericin B is the drug of choice for PAM and is administered intravenously and intrathecally, usually in combination with anti-tuberculosis drug Rifampicin and antineoplastic/anti-leishmaniasis agent Miltefosine (alkylphosphocholine compound). Due to the severe side effects of these drugs, there is an urgency to develop new, cost-effective and safe drugs that can cross the blood-brain barrier. Modern computational tools and omics approaches may be used in high-throughput phenotypic screening, specifically for pathogenic N. Fowleri.[9,10]

Founding father and skilled scientist Benjamin Franklin shared the axiom, "An ounce of prevention is worth a pound of cure" implies in many situations in life including dealing with 'Summertime Sadness' incidences. The heartbreaking and devastating events due to exposure of Naegleria, particularly in young adults can be prevented very effectively by following the simple common sense precautions. The CDC has released a list of preventive steps that everyone should take when swimming in freshwater areas

http://www.cdc.gov/parasites/naegleria/prevention.html

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Conflict of interest

The author declares no conflict of interest.

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