

ORIGINAL ARTICLE

Primary amebic meningoencephalitis: A review of the clinical literature

WILLIAM HANNISCH, MT(ASCP)¹, and LUANNE F. HALLAGAN, MD, FACEP^{1,2*}

¹Yellowstone Park Medical Services, Yellowstone National Park, WY 82190, USA and ²Columbia Eastern Idaho Regional Medical Center, Idaho Falls, ID 83403, USA

Primary amebic meningoencephalitis (PAM) is a rapidly progressive and potentially fatal infection frequently contracted by swimming in bodies of warm fresh water. The etiological agent in most reported cases of PAM is the ameboflagellate *Naegleria fowleri*. Infection with this organism closely mimics and is often mistaken for a bacterial or a viral pyogenic meningitis. Recovery is rare and depends on rapid diagnosis and treatment. Physicians treating individuals who present with an acute pyogenic meningitis should consider the diagnosis of PAM, particularly if the patient has a recent history of swimming in warm fresh water. We review the recent literature for cases of PAM and discuss ecology of *N. fowleri* and the clinical presentation, diagnosis, and treatment of PAM.

Key words: amebic meningoencephalitis, *Naegleria fowleri*

Ecology of *Naegleria fowleri*

N. fowleri is an ameboflagellate from the family Vahlkampfiidae [1]. The organism exists in three forms in nature: an ameboid trophozoite, a biflagellate trophozoite, and a cyst form. The amebic form is the most common type isolated in clinical specimens, but all are considered infectious. The cyst form was detected in one patient suffering from primary amebic meningoencephalitis (PAM) [2]. Reproduction of the organism is through binary fission of the ameboid form.

The distribution of *N. fowleri* is circumpolar. Cases of PAM have been reported on all continents except Antarctica. The organism is found in warm, moist environments including soil and bodies of natural or man-made fresh water [3–6]. The organism feeds on bacteria and can be isolated in stagnant bodies of warm water as well as sewage-contaminated water. The cyst form of *N. fowleri* is tolerant to extremes of temperature and can be resistant to chlorine, having once been isolated from an indoor swimming pool. *Naegleria* species have also been isolated from the warm water effluent of power plants, sewage treatment plants, hot tubs [4,7,8], and natural hot springs near Yellowstone National Park (W. O'Dell, personal communication).

Two other species of *Naegleria* have been described: *N. australiensis* and *N. lovaniensis*. *N. australiensis* is pathogenic for mice but is antigenically and biochemically dif-

ferent from *N. fowleri* and have never been implicated in human infections [5]. One clinician reported isolating *N. lovaniensis* from the cerebral spinal fluid (CSF) of a child suffering from Arnold-Chiari syndrome; this species has not been reported in other cases of PAM [9]. The presence of any species of *Naegleria* in a given body of water will serve to indicate likely conditions for the presence of *N. fowleri*, the true human pathogen of the group.

Clinical disease

Infection by *N. fowleri* is acquired by swimming or bathing where the organism is found. Because the organism is distributed so widely in nature, any warm body of water may pose a threat. The organism gains entry through the nares and travels through the olfactory neuroepithelium. This mechanism usually makes submersion of the head a requirement for infection. Diving into water contaminated by *Naegleria* may increase the risk of infection by forcibly injecting the organism into the nasal passages [10]. Likewise, inhaling or swallowing water will also increase the likelihood of infection [1]. Curiously, in groups with identical exposures, only some individuals will become infected. *N. fowleri* almost always infects previously healthy subjects, unlike *Balamuthia mandrillaris* and several species of *Acanthamoeba*. These pathogenic "opportunistic" free-living amoebae cause granulomatous amebic encephalitis in immunosuppressed, debilitated, or malnourished individuals [11].

In North America, 10 recent cases of PAM have been

*Address for correspondence: PO Box 1442, Idaho Falls, ID 83403, USA.

reported, all fatal, including 2 in Arizona [10], 1 in Texas [12], 2 in North Carolina, and 5 in the Mexicali valley of Mexico [5]. The victims were all adolescents or young adults with the exception of one of the Arizona patients who was 8 months old at the time of death. The infant victim apparently acquired the infection during a full submersion baptism ceremony in a natural body of water [10].

Patients with PAM present with symptoms from 1 day to 2 weeks after becoming infected. The clinical disease is characterized by severe frontal lobe headache, stiff neck, photophobia, and spiking fevers. Seizures may also occur [1], and coma may soon follow. Death usually occurs 3 to 10 days after the onset of symptoms. Autopsy reveals severe tissue damage along the path of amebic invasion, with ulceration of the nasopharyngeal mucosa and necrosis of the olfactory nerves. Hemorrhagic necrosis will be concentrated in the region of the olfactory bulbs and at the base of the brain.

Laboratory findings will include several hundred to more than 20 000 white blood cells/ μL in the CSF, with polymorphonuclear cells dominating the differential. The CSF protein will be elevated and the glucose decreased. The Gram stain and initial bacterial cultures will be negative, as will antigen testing assays for the common bacterial pathogens.

Diagnosis

Unfortunately, the majority of cases of PAM are not detected until autopsy [1,3,5,10]. The clinician must maintain a high index of suspicion for the rapid diagnosis of PAM as it may be clinically indistinguishable from other types of bacterial or viral meningoencephalitis. A classical appearing pyogenic meningitis accompanied by a recent history of swimming in a body of warm fresh water should alert the clinician to the possibility of amebic meningoencephalitis. The physician should request the laboratory to perform a simple wet mount examination on a sample of the patient's unrefrigerated CSF, using either bright light or phase microscopy. This examination is not normally included in a routine CSF workup, but in the case of infection with *N. fowleri*, this simple test could be lifesaving.

The trained eye will be able to detect ameboid trophozoites, approximately 10–20 μm in size with blunt fingerlike pseudopodia. The movement may be directional and rapid. If *Naegleria* is suspected, a small drop of sedimented CSF should be mixed with 1 mL of sterile water in a sterile tube and incubated for 2 to 3 hours at 37°C. The tube should be examined periodically after incubation for the presence of a pear-shaped organism swimming freely and possessing a pair of flagella at its small end. This experiment is known as enflagellation and will help to confirm the diagnosis.

The organism can be visualized in stained preparations, using Wright, Giemsa, or Trichrome stains, with the Tri-

chrome being the preferred method [6]. Ameboid trophozoites will resemble mononuclear cells but will be larger, with a central nucleus and a large karyosome that will stain red with trichrome. Vacuoles may be present and may contain human red blood cells [3].

N. fowleri can be cultured on 1.5% nonnutrient agar that has been seeded with a live or killed enteric bacteria, such as *Escherichia coli* or *Enterobacter*. The ameba will phagocytize the bacteria, leaving clear plaques on the media. The plaques can be removed with a sterile microbiological loop and examined under the microscope for ameboid trophozoites. Most clinical laboratories are not equipped to perform such a procedure. It is also time consuming and not practical as a diagnostic tool. It can be used as a confirmatory test for *N. fowleri*. Serologic tests have not proved useful in the diagnosis of PAM; the disease progresses so rapidly that the patient is unable to mount an adequate immune response [13]. *Naegleria* can be identified to the species level using indirect fluorescent-antibody procedures with monoclonal or polyclonal antibodies [13,14].

Treatment

There have been seven documented recoveries from PAM described in the literature. All recoveries have occurred using amphotericin B, either alone or in combination with rifampin. *N. fowleri* is susceptible to amphotericin B in vitro, but no controlled studies have been done on treatment of the PAM because of the rarity of infectious cases. The doses of amphotericin B used to treat PAM in recovered patients ranged from 0.75 to 1.5 mg/kg/d for a duration of 10 days [10]. One of these patients was diagnosed when the organism was detected in the drainage of a brain abscess. This particular patient was treated for 6 weeks with amphotericin B, rifampin, and chloramphenicol. Complete recovery was reported in all seven cases. Conventional dosage with intravenously administered amphotericin B may involve regimens with test doses followed by rapid escalation of 0.25 maximum 1.5 mg/kg/d. Infusion-related reactions are common and of an anaphylactoid nature; these are usually treated with meperidine, ibuprofen, and/or hydrocortisone [15]. Intrathecal amphotericin, used in cases of fungal meningitis, has not been reported in cases of treatment for PAM.

Conclusion

PAM is a severe, progressive disease with a rapid onset and a high associated mortality. The disease is contracted by swimming or becoming submerged in warm water containing the agent of the disease, the ameboflagellate *N. fowleri*. The victims of this disease are usually young and previously healthy. The disease is considered relatively rare but is almost certainly underdiagnosed. PAM can be diagnosed eas-

ily by simple microscopy, but a high level of suspicion on the part of the physician is required and must be communicated to the clinical laboratory. Rapid diagnosis and treatment with amphotericin B can result in a positive clinical outcome. More aggressive diagnosis and reporting of the disease may assist in clarifying risk factors and improving therapeutic interventions and possible strategies for prevention of this disease [1].

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