Primary amebic meningoencephalitis: a silent killer

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ABSTRACT

One week after swimming in a man-made lake, a 9-year-old boy presented to the emergency department with headache, vomiting and lethargy. He had neck pain upon flexion and was unable to stand or walk. Cerebrospinal fluid examination revealed trophozoite and diflagellate forms consistent with *Naegleria fowleri*, an ameba species known to cause primary amebic meningoencephalitis. Despite aggressive management with amphotericin B and rifampin, he died 2 days later. This case report describes the clinical presentation, diagnostic findings and management of this uncommon but lethal entity.

Key words: *Naegleria fowleri*; primary amebic meningoencephalitis; trophozoite; amphoterici B

RÉSUMÉ

Une semaine après avoir nagé dans un lac artificiel, un garçon de 9 ans se présente à l'urgence : il a des maux de tête, vomit et est léthargique. Il a une douleur au cou à la flexion et est incapable de se tenir debout ou de marcher. Une analyse du liquide céphalorachidien révèle la présence de formes de trophozoïtes et de diflagellés correspondant à *Naegleria fowleri*, une espèce d'amibe reconnue pour causer la méningoencéphalite amibienne primitive. En dépit d'un traitement agressif à l'amphpotéricine b et à la rifampine, il est mort deux jours plus tard. Le rapport de cas décrit les symptômes cliniques, les constatations diagnostiques et le traitement de cette entité rare mais mortelle.

Introduction

Primary amebic meningoencephalitis is caused by the small, pathogenic, free-living ameba *Naegleria fowleri*, *Acanthamoeba* species and *Balamuthia mandrillaris*. The first of these, *N. fowleri* produces a rare and sporadic acute central nervous system infection that culminates in the death of the host within 5 to 8 days.[1] Fowler and Carter first described the potential for free-living amebae to cause disease in 1965,[1] and shortly thereafter, Butt reported several cases in Florida, coining the term primary amebic meningoencephalitis (PAM).[2]

Of the 189 cases recorded in them medical literature, 91 occurred in the United States, although this is most likely a result of enhanced awareness and reporting. PAM presents in a manner very similar to acute bacterial meningitis but, because it is much less common than pyogenic meningitis, physicians may miss the diagnosis initially. Recent exposure to diving, swimming or splashing in warm fresh water should suggest the possibility of amebic meningoencephalitis, and prompt examination of the cerebrospinal fluid (CSF) for *N. fowleri*.[3]

Timely diagnosis requires a high index of suspicion in any individual presenting with subacute onset of meningitis-like symptoms after exposure to free-standing water or man-made lakes and pools.[3] We present a case of PAM masquerading as a subacute partially treated meningitis.

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Case report

A 9-year-old boy developed the gradual onset of fever and headache, beginning several days after swimming in a man-made lake. He was examined in a private emergency care facility, where physical evaluation, complete blood count, serum chemistry, blood urea nitrogen, creatinine and glucose were non-specific. Intramuscular ceftriaxone was given, and a nonsteroidal anti-inflammatory drug (NSAID) was prescribed for back and neck pain. Three to 4 days later, with an increasing headache and 1 day of vomiting, he presented to the emergency department. There was no history of prior headaches, trauma, toxins, known viral illnesses or exposure to infectious persons.

Physical examination revealed a lethargic young boy in moderate distress who was confused and irritable, with poor attention span. Vital signs were normal except for a heart rate of 119 beats/min and a respiratory rate of 22 breaths/min. Cranial nerves 2–12 were intact, pupils were equal at 4 mm bilaterally, and he had neither nystagmus nor papilledema. Examination of the head, eyes, ears, nose and throat was unremarkable, and no rashes or petechiae were seen; however, there was neck pain upon flexion and he exhibited both Kernig and Brudzinski signs. Of note, he was unable to stand or walk, and he was orientated only to person and place. During the examination he grew increasingly lethargic and irritable, requiring stimulation to remain alert. A tentative diagnosis of partially treated bacterial meningitis was made.

Blood, urine and CSF analyses were performed (Table 1), and CSF cultures were sent. Intravenous (IV) ceftriaxone (100 mg/kg) and vancomycin (15 mg/kg) were administered before transferring him to a tertiary pediatric referral centre. Additional CSF was sent with him for further analysis and diagnostic testing. CSF examination (Table 2) revealed trophozoite and diflagellate forms consistent with *N. fowleri*; therefore aggressive management of acute *Naegleria* meningitis was started with amphotericin B (1 mg/kg/d) and rifampin 100 mg/kg IV in divided doses. Despite this, the patient deteriorated, lost consciousness and pupillary reactions, and died on the 2nd day of hospitalization.

Table 1. Laboratory results for the patient who was ultimately diagnosed with primary amebic meningoencephalitis

Test	Result	Normal range
Na	137 mmol/L	136–145
K	3.6 mmol/L	3.5–5.1
Cl	95 mmol/L	98–107
CO_2	20 mmol/L	21–32
BUN	15 mg/dL	7–18
Creatinine	0.5 mg/dL	0.6–1.3
Glucose	184 mg/dL	74–106
Total bilirubin	2.7 mg/dL	<1.0
Alkaline phosphatase	184 U/L	50–136
WBC	22.9 K/μL	4.5–11.0
Hemoglobin	13.0 g/dL	12–16.0
Hematocrit	37.0%	37–47
Platelets	278 K/μL	150–400
Neutrophils	96%	50–70
Lymphocytes	1%	20–40
Band forms	1%	<0.25
Monocytes	2%	2–10

Na = sodium; K = potassium; Cl = chloride; CO_2 = oxygen; BUN = blood urea nitrogen; WBC = white blood cell count

Discussion

Epidemiology

*N. fowler*i is a thermophilic ameba that grows well in tropical and subtropical climates, tolerating temperatures up to 45°C. It is a ubiquitous inhabitant of warm fresh water and soil, but it does not multiply at temperatures below 40°C and does not survive in seawater.[4] Although rarely associated with clinical disease, exposure to this ameba is common, as exemplified by the widespread presence of anti-*N. fowleri* antibodies in the general population.[5] Elevated summer temperatures and warm water discharge from power plants facilitate the growth of *N. fowleri*.[6] Although the disease is typically associated with swimming or freshwater contact, it may also occur via inhalation of contaminated dust.[7–9]

Cases have been reported along the East coast of the

Table 2. Results of cerebrospinal fluid testing for study patient

Analysis	Result	Normal
Gross inspection	Hazy	Clear
Red blood cell count	380 cells/mm^3	0
WBC count	750 cells/mm^3	0–5
Neutrophils	83%	40–80
Lymphocytes	17%	15–45
Glucose	<10 mg/dL	40–70
Protein	>300 mg/dL	15–45
Gram stain	Many WBCs; ***no*** organism seen	0

WBC = white blood cell

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United States from Virginia to Florida, and in California. From 1962 to 2000, 18 cases of PAM were reported in central Florida,[10,11] and a 1977 survey found that 46% (12/26) of lakes in Florida were ameba infested.[11] Meningoencephalitis has been reported in the US (n = 91), Australia (n = 19) and Venezuela (n = 18), along with sporadic outbreaks globally. The US Centers for Disease Control and Prevention (CDC) reports 2–4 cases annually from collaborative surveillance reports of waterborne diseases.[12–14]

Incidence

PAM is a rare disease whose incidence is underestimated because of difficulty in making a definitive diagnosis. This is due in part to the fact that wet preparations of CSF are seldom examined under high magnification. Even under high magnification, amebae are sometimes not identified.

Males are affected 3 times more frequently than females,[15] probably reflecting a greater exposure risk rather than a true gender predisposition to infection. The probability of contracting *Naegleria*, once exposed to it, is estimated at 1 in 100 million exposures (Dr. Steve Tidwell, Texas Natural Resources and Conservation Commission Faculty, Austin, Tex.: personal communication, 1995 Aug 10). Once contracted, PAM is almost uniformly fatal, with only 10 survivors currently reported in the medical literature.[8,16–24] One French study[25] extrapolated the risk of contracting PAM after swimming once in water containing an ameba concentration of 10 per liter as being approximately 8.5×10^{-8}.

Pathogenesis

Naegleria species typically cause PAM in children and healthy adults who have been swimming in polluted pond water or inadequately chlorinated swimming pools, as well as man-made or natural freshwater lakes. Organisms enter through the olfactory neuroepithelium at the level of the cribriform plate and invade the amyelinic submucosal nervous plexus.[7,26–28] Symptoms begin after a 3–7 day incubation period, and infections caused by *N. fowleri* tend to be fulminant, with rapid progression to death in most cases.[7,29] Pathological changes include acute hemorrhagic necrotizing meningoencephalitis with purulent exudates in the brain, brainstem and cerebellum.[7] Patients who develop *N. fowleri* meningoencephalitis may have an immunoglobulin IgA deficiency, which would imply weaker defenses at the mucus membrane level.[5]

Acanthamoeba and *Hartmanella* are similar organisms that cause a more subacute form of illness in immunocompromised, debilitated or malnourished individuals, including those undergoing suppressive therapy for organ transplant and HIV/AIDS patients.[30] These organisms enter the body through the respiratory tract or skin ulcerations, reaching the CNS by hematogenous spread,[31] causing a patchy, chronic granulomatous encephalitis with trophozoites and cysts in the lesions. The incubation period is unknown but is thought to be more than 10 days.[30,32]

Diagnosis

The onset of PAM is abrupt, with sore throat, headache, nausea, vomiting, abulia, malaise and fever.[33,34] Early findings may also include irritability, hallucinations, meningismus, cerebellar ataxia and cranial nerve palsies, although focal neurologic defects are usually absent.[35] Alterations in taste and smell may occur — probably due to involvement of the olfactory nerve.[36] Seizures progressing to coma are frequently followed by death within 4 to 6 days.[37]

In previously healthy persons, early PAM is often mistaken for a viral infection. Differential diagnosis includes acute bacterial meningitis, herpes simplex virus-1 encephalitis (HSV-1), and viral or fungal meningitis. With immunosuppressed patients, amebic meningitis might be confused with toxoplasmosis, cytomegalovirus infection, and other opportunistic pathogens. When primary amebic meningoencephalitis is suspected, infectious disease and neurosurgical consultations should be considered early in the evaluation process. The diagnosis is made by examination of CSF wet mounts for motile trophozoites that are 8–15 µm in size;[24,26] however, failure to visualize these ameba does not exclude PAM,[38,39] and the diagnosis is often missed when *Naegleria* organisms are mistaken for atypical mononucleocytes or lymphocytes in the CSF.

Therapy

Currently, the most effective therapy is Amphotericin B, which should be given intravenously and intrathecally in conjunction with miconazole, rifampin and doxycycline. Given the difficulty in diagnosis, early infection disease consultation and appropriate antimicrobial therapy should be considered for any individual with a history of stagnant warm water exposure, clinical signs of early meningoencephalitis, CSF findings consistent with meningitis, and a CSF gram stain showing no organisms.

Prognosis

Even if the diagnosis is made early and appropriate treatment is initiated, recovery is rare and the prognosis is grim. The disease's rapid progression leaves a very short time during which therapy might be effective, and the exceedingly high mortality rate suggest that, by the time patients present for medical care, most have reached a stage that is

unresponsive to currently available therapy.[15] Of interest, serologic studies in endemic areas show a high prevalence of protective antibodies, suggesting that subclinical disease and spontaneous recovery may occur with this infection.[39–42]

Prevention

It is difficult to prevent exposure to *N. fowleri*, which is a relatively ubiquitous organism. However, avoidance of swimming in lakes epidemiologically associated with this disease, blowing out the nose after swimming to remove any *N. fowleri* that may have been forcefully inhaled, and the use of nose plugs or holding the nose when jumping or diving into warm fresh water may reduce the risk of meningoencephalitis. Primary care physicians in endemic areas should caution their patients to be aware of symptoms after prolonged swimming in warm, freshwater lakes, and recommend the safety precautions suggested above. Public health authorities should advise closure of (or avoidance of submersion in) hot spring recreational sites where *N. fowleri* is present, and of waterways and rivers infected with this organism during times of high temperature [>30°C] and low water levels. Careful maintenance of swimming pool filters and adequate chlorination, to at least 1–2 ppm, are important preventive measures.[42]

Implications for the future

Development of a rapid enzyme-linked immunosorbent assay (ELISA) for CSF testing might expedite early detection of PAM infection and increase the effectiveness of antimicrobial treatment. State governments should share data, increase public awareness and educate health care providers about the importance of waterborne disease outbreaks by increasing mandatory surveillance and by reporting new outbreaks.

Conclusion

For any individual with CSF findings consistent with acute bacterial meningitis, a history of stagnant warm water exposure, and a gram stain of the CSF that is negative for any organism, PAM should be included in the differential diagnosis and early infection disease consultation, and appropriate directed antimicrobial management should be considered.

Competing interests: None declared.

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