Successful Treatment of an Adolescent With *Naegleria fowleri* Primary Amebic Meningoencephalitis

W. Matthew Linam, MD, MS; Mubbasheer Ahmed, MD; Jennifer R. Cope, MD, MPH; Craig Chu, MD; Govinda S. Visvesvara, PhD; Alexandre J. da Silva, PhD; Yvonne Qvarnstrom, PhD; Jerril Green, MD

**abstract**

*Naegleria fowleri* is a thermophilic, free-living ameba that causes primary amebic meningoencephalitis. The infections are nearly always fatal. We present the third well-documented survivor of this infection in North America. The patient’s survival most likely resulted from a variety of factors: early identification and treatment, use of a combination of antimicrobial agents (including miltefosine), and management of elevated intracranial pressure based on the principles of traumatic brain injury.

The patient, a previously healthy 12-year-old girl, presented to the emergency department with a 2-day history of headache and a 1-day history of fever (39.4°C), along with nausea, vomiting, and somnolence. Results of her neurologic examination were normal. She reported swimming at an outdoor water park 7 days before the onset of symptoms. Her initial laboratory evaluation included a peripheral white blood cell count of 18.4 cells per μL (77% segmented, 13% banded neutrophils). Analysis of cerebrospinal fluid (CSF) revealed a white blood cell count of 3675 cells per μL (86% segmented neutrophils), a red blood cell count of 53 cells per μL, protein of 374 mg/dL, and glucose of 22 mg/dL. The Giemsa-Wright stain of the CSF revealed amebae consistent with *N fowleri*. The initial computed tomography scan of the patient’s brain was normal.

The patient was admitted to the PICU on July 19, 2013, and the following treatment was initiated: conventional amphotericin B 1.5 mg/kg per day intravenously in 2 divided doses, fluconazole 10 mg/kg per day, rifampin 10 mg/kg per day, and azithromycin 10 mg/kg per day.1,3 Dexamethasone was initiated concurrently. After 3 days, the daily dose of amphotericin B was decreased to 1 mg/kg.1 Approximately 36 hours after admission, the patient was started on miltefosine 50 mg every 8 hours. Consent was obtained from the family before administering miltefosine.

Almost 24 hours after admission, the patient developed a right-sided abducens nerve palsy. An external ventricular drain was placed while the patient was in the operating room, and her initial intracranial pressure (ICP)
was ∼50 mm Hg. Intrathecal amphotericin B was started at a dose of 1.5 mg daily for 2 days followed by a dose of 1 mg every other day for 8 days.1 On the third day of hospitalization, the patient’s ICP worsened. Management of her cerebral edema (goal ICP: <20 mm Hg) included drainage of CSF, hyperosmolar therapy with mannitol and 3% saline, moderate hyperventilation (goal PaCO2: 30–35 mm Hg), and induced hypothermia (32°C–34°C). The cerebral edema resolved after ∼2 weeks (Fig 1). The patient’s initial CSF specimen grew N fowleri on culture and was positive for N fowleri according to results of polymerase chain reaction. By day 3, her CSF specimen was negative for N fowleri. Serial CSF specimens revealed decreasing white blood cell counts and diminishing amounts of N fowleri DNA on polymerase chain reaction.

Magnetic resonance imaging (MRI) of the patient’s brain 2 weeks into her illness revealed blood in the frontal lobes and multiple areas of restricted diffusion, primarily in the cerebellum, right internal capsule, and corpus callosum (Fig 2). A repeat MRI of her brain 1 week later showed improvement. The patient completed 26 days of a planned 28-day course of antimicrobial agents (miltefosine, azithromycin, rifampin, and fluconazole); the regimen was stopped early due to nausea and vomiting. Upon transfer to the rehabilitation unit, the patient had left-sided weakness, dysarthria, and dysphagia. After 55 days of hospitalization, she was discharged from the hospital. At 6 months’ postinfection, the patient had normal levels of functioning and no residual deficits.

**DISCUSSION**

We report the third documented survivor of N fowleri PAM in North America. The patient’s survival was likely the result of a variety of factors: early diagnosis and treatment, use of a combination of antimicrobial agents (including miltefosine4), and management of elevated ICP based on the principles of traumatic brain injury. This report is the first of a patient with PAM successfully treated by using a regimen that included miltefosine. This report is also the first to document successful use of induced hypothermia (32°C–34°C) in the management of PAM.

Between 1962 and 2013, a total of 132 cases of N fowleri PAM were reported to the Centers for Disease Control and Prevention (CDC).5,6 The number of infections reported each year (0–8 infections) remained stable, and the majority of these infections occurred in southern-tier states. Approximately 75% of infections are associated with swimming in warm freshwater lakes and rivers. The median age of infection is 11 years (range: 8 months–66 years). Recently, the epidemiology of N fowleri PAM has changed. Since 2010, two cases were reported in Minnesota6,7 and single cases were identified in Indiana and Kansas.6 These findings suggest that the geographic range of this thermophilic organism may be expanding. In addition, infections have been reported in patients exposed to nonsterile tap water that was used for sinus irrigation8 or ritual ablation.9

**FIGURE 1**

The relationship between mean arterial pressure (MAP), cerebral perfusion pressure (CPP), ICP, and core body temperature (Temp) during the management of a 12-year-old girl with N fowleri PAM. The graph illustrates our management strategy for maintaining CPP >60 mm Hg and ICP <20 mm Hg. With induction of hypothermia (7/22/13, 22:00), ICP was sustained at <20 mm Hg. Early attempts to rewarm the patient on 7/24/13 and 7/26/13 led to elevations of ICP. After 5 days of cooling, rewarming the patient was met with minimal elevation in ICP.
The time from exposure to *N. fowleri* to the onset of symptoms is ∼5 days (range: 1–7 days). The initial symptoms of PAM are indistinguishable from bacterial meningitis. Patients experience rapid deterioration, with death resulting from brain injury and edema occurring within ∼5 days (range: 1–12 days). In the 2 weeks before symptom onset, our patient swam in a number of locations. Epidemiologic investigation by the state health department suggested that a local water park was the likely source of infection. Water samples from only this site tested positive for *N. fowleri*, and our patient developed symptoms 7 days after this exposure. She presented to the hospital ∼30 hours after initial symptoms and was started on recommended therapy within 36 hours of symptom onset. By comparison, the median time from symptom onset to hospital presentation for patients with PAM is 2 days, and the median time from symptom onset to initiation of recommended therapy is 3 days (CDC, unpublished data). Because *N. fowleri* PAM is rare and not often considered as a diagnosis, premortem identification of the ameba is often delayed or not attempted, precluding the timely initiation of recommended therapy. Early identification and initiation of recommended therapy are critical for survival; however, this time frame is likely affected by multiple factors, including strain virulence, inoculum, and host immune response.

**FIGURE 2**
Noncontrast axial magnetic resonance images of the patient's brain with *N. fowleri* PAM. A, The axial fluid-attenuated inversion recovery image shows focal edema in the left frontal lobe (arrow). B, Axial susceptibility-weighted image shows hemorrhage within the left frontal edematous lesion (arrow). C, Axial fluid-attenuated inversion recovery image demonstrates multiple areas of edema in the cerebellum bilaterally (arrows). D, Axial diffusion-weighted image shows areas of restricted diffusion consistent with acute cerebellitis (arrows).
The only documented survivor in the United States received amphotericin and miconazole intravenously and intrathecally and rifampin intravenously.\textsuperscript{12} The survivor from Mexico received intravenous amphotericin, fluconazole and rifampin.\textsuperscript{3} Conventional amphotericin has a lower minimum inhibitory concentration compared with the liposomal formulation and is thus preferred even though the liposomal form has better CSF penetration.\textsuperscript{10}

Other medications such as fluconazole, voriconazole, and azithromycin have shown activity against \textit{N fowleri}.\textsuperscript{10–12} Studies suggest that azithromycin may have a synergistic effect when used in combination with amphotericin.\textsuperscript{13} Recently, the antiparasitic agent miltefosine has shown in vitro effectiveness against \textit{N fowleri} and other clinically important free-living amebae.\textsuperscript{11} Although miltefosine has recently been used to successfully treat patients with other free-living amebae infections,\textsuperscript{14,15} our patient is the first to be successfully treated with miltefosine for PAM. Miltefosine is available directly from the CDC for treatment of infections caused by free-living amebae in the United States.\textsuperscript{4}

Current neuroprotective management principles of brain injuries are based on maintaining adequate cerebral perfusion, tempering oxygen consumption, and limiting ICP.\textsuperscript{16} The data suggest that mild to moderate hypothermia (32°C–34°C) may have neuroprotective effects, including lowering ICP, reducing production of reactive oxygen and nitrogen species, reducing proinflammatory cytokine levels, and preventing neuronal apoptosis.\textsuperscript{16–18} Clinical studies evaluating the effects of mild to moderate hypothermia in patients with traumatic brain injury and bacterial meningitis have shown conflicting results.\textsuperscript{19–22}

\textit{N fowleri} initially causes direct damage to surrounding neuronal and other cells through direct cell-to-cell interaction as well as the release of a number of cytotoxic proteins.\textsuperscript{2} In addition, cytotoxic proteins released by \textit{N fowleri} and debris from lysed neuronal and other cells generate a cascade of proinflammatory cytokines, resulting in hyperinflammation and further injury.\textsuperscript{23} It is possible that the beneficial effects of hypothermia seen in patients with traumatic brain injury and bacterial meningitis may also attenuate the inflammatory response that occurs in patients with \textit{N fowleri} PAM. Cytokine levels were not measured in our patient, and it is thus unclear whether the use of hypothermia affected the host inflammatory response. Although \textit{N fowleri} is a thermophilic organism, it is also unclear whether the degree of hypothermia used in our patient resulted in reduced pathogenicity of the ameba.

The changing epidemiology of \textit{N fowleri} necessitates its inclusion in the differential of patients with meningoencephalitis, particularly those who report a recent history of swimming in warm fresh water (regardless of geographic location) or use of nonsterile water for nasal irrigation or ritual ablution. Because early diagnosis and therapy are critical, laboratory technicians must be able to quickly identify amebae on CSF specimens. Prompt initiation of a regimen including conventional amphotericin, fluconazole, azithromycin, and rifampin is recommended (Table 1). Miltefosine should be added to this regimen as soon as possible. If there are signs of increased ICP, we recommend placement of an external ventricular drain and administration of intrathecal amphotericin. Elevated ICP should be managed aggressively, maintaining an ICP <20 mm Hg. Because dexamethasone was used in all 3 documented survivors and has shown benefit in central nervous system insults due to infectious etiologies,\textsuperscript{1–3,24} it should be administered concurrently with the antimicrobial agents. The treating physicians should also consider lowering the patient’s core body temperature (32°C–34°C) because this action may have beneficial effects beyond lowering ICP. Additional data are needed to determine the adequate length of therapy and to determine the effects of hypothermia in the management of PAM. Ongoing surveillance and continued reporting of PAM cases are needed to continue to learn the best way to manage these infections.

### Table 1

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
<th>Maximum Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B\textsuperscript{4,11}</td>
<td>1.5 mg/kg per d in 2 divided doses, then</td>
<td>Intravenous</td>
<td>1.5 mg/kg per d</td>
<td>3 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 mg/kg per d once daily</td>
<td>Intravenous</td>
<td>1 mg/kg per d</td>
<td>11 d</td>
<td>14-d course</td>
</tr>
<tr>
<td>Amphotericin B\textsuperscript{4,11}</td>
<td>1.5 mg once daily, then</td>
<td>Intrathecal</td>
<td>1.5 mg/d</td>
<td>2 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 mg/d every other day</td>
<td>Intrathecal</td>
<td>1 mg/d</td>
<td>8 d</td>
<td>10-d course</td>
</tr>
<tr>
<td>Azithromycin\textsuperscript{12}</td>
<td>10 mg/kg per d once daily</td>
<td>Intravenous/oral</td>
<td>500 mg/d</td>
<td>28 d</td>
<td></td>
</tr>
<tr>
<td>Fluconazole\textsuperscript{3}</td>
<td>10 mg/kg per d once daily</td>
<td>Intravenous/oral</td>
<td>600 mg/d</td>
<td>28 d</td>
<td></td>
</tr>
<tr>
<td>Rifampin\textsuperscript{1,3}</td>
<td>10 mg/kg per d once daily</td>
<td>Intravenous/oral</td>
<td>600 mg/d</td>
<td>28 d</td>
<td></td>
</tr>
<tr>
<td>Miltefosine\textsuperscript{13}</td>
<td>Weight &lt;45 kg: 50 mg BID</td>
<td>Oral</td>
<td>2.5 mg/kg per d</td>
<td>28 d</td>
<td>50-mg tablets</td>
</tr>
<tr>
<td></td>
<td>Weight &gt;45 kg: 50 mg TID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone\textsuperscript{3,24}</td>
<td>0.6 mg/kg/d in 4 divided doses</td>
<td>Intravenous</td>
<td>0.6 mg/kg per d</td>
<td>4 d</td>
<td></td>
</tr>
</tbody>
</table>

All medications should be started in combination as soon as the diagnosis is suspected. Intrathecal amphotericin B should be initiated if the patient develops signs or symptoms of increased ICP, and miltefosine should be started once available. BID, twice daily; TID, thrice daily.

\textsuperscript{a} Conventional amphotericin preferred.
ACKNOWLEDGMENTS

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REFERENCES


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