Use of the Novel Therapeutic Agent Miltefosine for the Treatment of Primary Amebic Meningoencephalitis: Report of 1 Fatal and 1 Surviving Case

Jennifer R. Cope,1 Dennis A. Conrad,2 Naiomi Cohen,3 Manuel Cotilla,3 Alexandre DaSilva,4 Jonathan Jackson,1 and Govinda S. Visvesvara1

1Centers for Disease Control and Prevention, Atlanta, Georgia; 2University of Texas Health Science Center, San Antonio; 3Miami Children’s Hospital, Florida; and 4US Food and Drug Administration, Laurel, Maryland

Primary amebic meningoencephalitis (PAM) is a fulminant central nervous system infection caused by the thermophilic free-living ameba Naegleria fowleri. Few survivals have been documented and adequate treatment is lacking. We report 2 PAM cases, 1 fatal and 1 surviving, treated with the novel antiparasitic agent miltefosine.

Keywords. primary amebic meningoencephalitis; Naegleria fowleri; miltefosine.

Primary amebic meningoencephalitis (PAM) is a fulminant central nervous system infection caused by the thermophilic free-living ameba Naegleria fowleri. The infection occurs when freshwater containing the ameba enters the nose, crosses the cribriform plate, and enters the brain. PAM is often clinically indistinguishable from bacterial meningitis, with early symptoms of headache, fever, nausea, and vomiting progressing rapidly to altered mental status, seizures, coma, and death [1]. Despite the availability of several antimicrobial agents that show in vitro activity against N. fowleri, use of these agents clinically, even when administered early in the course of illness, has resulted in few survivors. Amphotericin B has been the mainstay of PAM treatment, and all of the well-documented survivors have received it as part of their treatment regimen [2–5]. The antiparasitic agent miltefosine has shown some promise for the treatment of free-living ameba infections [6].

CASE REPORT 1

A 12-year-old boy presented to a local community hospital on 7 August 2013 with a 1-day history of headache, weakness, vomiting, fever (39.4°C), and altered mental status. The patient lived in a wooded area of central Florida where, on 5 August, he was riding on a kneeboard pulled by an all-terrain vehicle with friends in a 2- to 3-foot-deep ditch filled with stagnant rainwater. While participating in this activity, his head was, at times, completely submerged underwater. Lumbar puncture was performed with an opening pressure of 50 cm H2O (normal, 10–20 cm H2O). Cerebrospinal fluid (CSF) was noted to be cloudy with a white blood cell (WBC) count of 10 216 cells/µL, a red blood cell (RBC) count of 3500 cells/µL, protein level of 560 mg/dL, and glucose level of <20 mg/dL. Computed tomography (CT) of the head without contrast was normal. Broad antimicrobial coverage was started and included acyclovir, liposomal amphotericin B, fluconazole, rifampin, vancomycin, and ceftriaxone. The following day, the patient’s neurologic status deteriorated. In consultation with the Centers for Disease Control and Prevention (CDC), the treatment regimen was tailored to include deoxycholate amphotericin B intravenously, fluconazole, azithromycin, and rifampin. Miltefosine was added once it arrived, approximately 31 hours after his initial presentation. The diagnosis of PAM was confirmed with the identification of N. fowleri in the CSF by polymerase chain reaction (PCR) testing at CDC, at which time a lumbar drain was placed and intrathecal amphotericin B was added. A follow-up CT demonstrated cerebral edema, which was managed with hypertonic saline, mannitol, surgical decompression, and therapeutic hypothermia with no clinical improvement. Subsequent imaging showed brain herniation, and the patient was declared brain-dead on hospital day 16.

CASE REPORT 2

On 17 August 2013, an 8-year-old Hispanic boy presented to a Texas hospital with a 5-day history of fever, headache, chills, nausea, and vomiting progressing to photophobia and altered mental status. The patient’s mother had sought medical care at 3 clinics in Mexico prior to seeking care in the United States. The patient had been spending the summer with his mother, who lived in an informal settlement adjacent to the Rio Grande. This settlement had no potable public water supply or sanitary sewer system; water for consumption was purchased in Texas, whereas water used for bathing and cleaning was obtained by direct piping of surface water from the Rio Grande. The patient enjoyed “splashing in the shallows” at the edge of the river. CSF appeared cloudy with an RBC count of 1000 cells/µL, a WBC count of 2312 cells/µL with 92% neutrophils, and a protein level of 311 mg/dL. The glucose concentration could not be determined accurately. When the CSF Gram stain did not show any organisms, a Wright stain was performed, revealing amebic trophozoites.
With a Glasgow Coma Score of 3, the patient was intubated and mechanically ventilated. A right frontal external ventricular drainage (EVD) catheter was placed to monitor intracranial pressure and provide therapeutic drainage as warranted. At the time of placement, the intraventricular pressure exceeded 40 mm Hg (normal, 1–20 mm Hg). Treatment for PAM was promptly initiated and is summarized in Table 1. Miltefosine was requested from CDC and was administered 14 hours after the patient was admitted to the pediatric intensive care unit. At the conclusion of his treatment course, he could react with healthcare providers only by withdrawal from noxious stimuli. He was able to breathe spontaneously, but did not have a consistent gag or cough reflex, nor could he evidence any coordinated ability for self-care activities. After a 39-day hospital stay, the patient spent another 36 days on the pediatric rehabilitation service. He was discharged to home in the care of his family. Approximately 18 months following discharge, the patient has static encephalopathy with profound persistent mental disability and seizure disorder partially controlled with anticonvulsant therapy, is nonverbal, and cannot care for himself.

**DISCUSSION**

These 2 patients with PAM are notable in that they received the novel antiparasitic agent miltefosine as part of their treatment regimen. Miltefosine is an alkylphosphocholine compound that has predominantly been studied for the treatment of leishmaniasis [7]. Its antileishmanial and antiamebic mechanisms of action are unknown. The surviving patient reported here is the fifth case of well-documented survival in a PAM infection (Table 1). During the same summer in which these 2 PAM cases were diagnosed, a 12-year-old girl from Arkansas was diagnosed with PAM and survived, making a full neurologic recovery [5]. Her treatment regimen included all of the drugs given to the 2 patients reported here. Notable differences in her clinical course and treatment from the 2 patients reported here included being treated with Naegleria-specific drugs approximately 48 hours after symptom onset and undergoing aggressive management of elevated intracranial pressure, including therapeutic hypothermia. In contrast, the 8-year-old Texas male survivor reported here had symptoms for 5 days before a PAM diagnosis was made and specific PAM therapy was initiated. While his elevated intracranial pressure was managed both medically and surgically, therapeutic hypothermia was not used in his case. The Florida child presented here did present early in the course of illness. However, some aspects of his care differed slightly from the Arkansas survivor, including having a lumbar drain placed (vs EVD), receiving intrathecal amphotericin over 2 days after presentation to the hospital, and initially receiving liposomal amphotericin B (in vitro testing shows deoxycholate amphotericin B has lower minimum

---

**Table 1. Survivor Treatment and Outcomes in Primary Amebic Meningoencephalitis**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset to initiation of antiameba therapy, h</td>
<td>Unknown</td>
<td>&gt;72</td>
<td>9</td>
<td>48</td>
</tr>
<tr>
<td>Antiameba drug therapies</td>
<td>Amphotericin B (dose unknown) IV, IT, and via ventricular reservoir</td>
<td>Amphotericin B 1–1.5 mg/kg/d IV in 2 divided doses × 9 d; 1–1.5 mg IT daily × 10 d</td>
<td>Amphotericin B 0.25–1 mg/kg/d IV × 14 d</td>
<td>Amphotericin B 1–1.5 mg/kg/d IV in 2 divided doses × 26 d; 1–1.5 mg IT daily × 10 d</td>
</tr>
<tr>
<td>Rifampin 10 mg/kg/d PO in 3 divided doses × 9 d</td>
<td>Rifampin 10 mg/kg/d PO × 1 mo</td>
<td>Rifampin 10 mg/kg/d IV × 26 d</td>
<td>Rifampin 12 mg/kg/d PO × 19 d</td>
<td>Miconazole 350 mg/m² body surface area/d IV in 3 divided doses × 9 d 10 mg daily then 10 mg IT every other day × 8 d</td>
</tr>
<tr>
<td>Fluconazole 10 mg/kg/d IV (then PO) × 19 d</td>
<td>Fluconazole 10 mg/kg/day IV × 26 d</td>
<td>Fluconazole 10 mg/kg/day IV × 26 d</td>
<td>Fluconazole 12 mg/kg/d loading dose, then 9 mg/kg/d IV × 19 d</td>
<td></td>
</tr>
<tr>
<td>Azithromycin 10 mg/kg/d IV × 26 d</td>
<td>Azithromycin 10 mg/kg/d PO × 19 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miltefosine 150 mg PO in 3 divided doses × 26 d</td>
<td>Miltefosine 150 mg PO in 3 divided doses × 19 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunctive therapies</td>
<td>Dexamethasone</td>
<td>Dexamethasone</td>
<td>Dexamethasone</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Dexamethasone 0.6 mg/kg/d IV</td>
<td>Dexamethasone 0.6 mg/kg/d IV</td>
<td>Dexamethasone 0.6 mg/kg/d IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF drainage</td>
<td>CSF drainage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperosmolar therapy (mannitol and 3% saline)</td>
<td>Hyperosmolar therapy (mannitol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate hyperventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induced hypothermia (32°C–34°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Complete recovery</td>
<td>Complete recovery</td>
<td>Complete recovery</td>
<td>Complete recovery</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; IT, intrathecal; IV, intravenous; PO, per oral.
inhibitory concentrations for *N. fowleri*). However, it is unknown whether these small differences in care contributed to the varied outcomes of these 3 patients.

All 3 patients (the 2 reported here plus the Arkansas survivor) received miltefosine as part of their treatment regimen but with 3 very different outcomes: death, survival with poor neurologic outcome, and survival with full neurologic recovery. Therefore, although miltefosine is a promising anti-*Naegleria* agent, it is not a magic bullet, and its administration does not assure recovery. Since 2013, when miltefosine became available through CDC, 100% (2/2) of surviving US patients with PAM received miltefosine compared with 33% (3/9) of fatal US PAM cases (CDC unpublished data). Surviving PAM, including survival with few or no deficits, is likely multifactorial and includes early diagnosis and treatment, the use of combination drug therapy (including miltefosine), and aggressive management of elevated intracranial pressure based on the principles of traumatic brain injury [5].

Between 1962 and 2014, 133 cases of PAM were reported to CDC, with the majority occurring in southern-tier states in patients with recent exposure to warm freshwater lakes and rivers [1]. Although the number of infections reported annually has remained stable (0–8), recent changes in the epidemiology of PAM are concerning. For the first time in 2010, a PAM case was reported from the northern state of Minnesota followed by additional cases from Minnesota, Indiana, and Kansas in 2011 and 2012, raising concerns about an expanding geographic range of illness caused by this thermophilic, potentially climate-sensitive, pathogen [1]. In addition to exposure to recreational water, nasal exposure to tap water has now been associated with several PAM cases, including 2 patients who used tap water in a neti pot to irrigate their sinuses, 1 patient who used tap water to perform ritual ablution, and 1 patient who played on a backyard water slide supplied with tap water [8–10]. Given these changes, clinicians in all regions of the United States should consider the diagnosis of PAM in a patient with meningitis and recent nasal freshwater exposure.

Clinicians who suspect PAM in a patient under their care should contact the CDC Emergency Operations Center at (770) 488-7100 for 24/7 diagnostic assistance, specimen collection guidance, and treatment recommendations, including the use of miltefosine. Confirmatory PCR testing is available at CDC with a turnaround time of 2–4 hours. Miltefosine is available directly from CDC under an expanded-access investigational new drug protocol for treatment of free-living ameba infections in the United States [11]. With increased awareness of this deadly infection, prompt diagnosis, and initiation of combination drug therapy, and aggressive management of elevated intracranial pressure, more patients might survive PAM. Clinicians are encouraged to report all suspected PAM cases to CDC, as each case provides valuable information for improving understanding of pathogenesis and treatment, regardless of outcome.

**Notes**

**Acknowledgments.** The authors acknowledge Almea Matanock, MD, Jamae Morris, PhD, and the staff of Centers for Disease Control and Preventions (CDC’s) Drug Service and Emergency Operations Center for their roles in facilitating the rapid release of miltefosine from CDC for the treatment of these 2 patients.

**Disclaimer.** The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

**Potential conflicts of interest.** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**