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

Jennifer R. Cope, MD, MPH,
Centers for Disease Control and Prevention, Atlanta, GA, USA

Dennis A. Conrad, MD,
University of Texas Health Science Center, San Antonio, TX, USA

Naiomi Cohen, MD,
Miami Children's Hospital, Miami, FL, USA

Manuel Cotilla, MD,
Miami Children's Hospital, Miami, FL, USA

Alexandre DaSilva, PhD,
U.S. Food and Drug Administration, Laurel, MD, and Centers for Disease Control and Prevention, Atlanta, GA, USA

Jonathan Jackson, and
Centers for Disease Control and Prevention, Atlanta, GA, USA

Govinda Visvesvara, PhD
Centers for Disease Control and Prevention, Atlanta, GA, USA

Abstract

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 two PAM cases, one fatal and one 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

Corresponding author: Jennifer R. Cope, MD, MPH, 1600 Clifton Rd NE, MS C-09, Atlanta, GA 30329, 404-718-4878, jcope@cdc.gov. Alternate corresponding author: Dennis Conrad, conradd@uthscsa.edu.

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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 *Naegleria 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 male presented to a local community hospital on August 7, 2013 with a one-day history of headaches, weakness, vomiting, fevers (39.4 °C), and altered mental status. The patient lived in a wooded area of central Florida where, on August 5, he was riding on a kneeboard pulled by an all-terrain vehicle with friends in a 2–3 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 H_2O (normal 10–20 cm H_2O). Cerebrospinal fluid was noted to be cloudy with a white blood cell (WBC) count of 10,216 cells/μL, a red blood cell (RBC) count of 3,500 cells/μL, protein 560 mg/dL, and glucose <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 *Naegleria 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 August 17, 2013, an 8-year-old Hispanic male presented to a Texas hospital with a five 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 three 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 a RBC count of 1,000 cells/μL, a WBC count of 2,312 cells/μL with 92% neutrophils, and protein 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 in order 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 PICU. 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 eighteen months following discharge, the patient has static encephalopathy with profound persistent mental disability, seizure disorder partially controlled with anticonvulsant therapy, is non-verbal and cannot care for himself.

Discussion

These two PAM patients 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 two PAM cases were diagnosed, a 12-year old adolescent female from Arkansas, USA was diagnosed with PAM and survived, making a full neurologic recovery [5]. Her treatment regimen included all of the drugs given to the two patients reported here. Notable differences in her clinical course and treatment from the two 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 five 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 two days after presentation to the hospital, and initially receiving liposomal amphotericin B (*in vitro* testing shows deoxycholate amphotericin B has lower MICs for *Naegleria fowleri*). However, it us unknown whether these small differences in care contributed to the varied outcomes of these three patients.

All three patients (the two reported here plus the Arkansas survivor) received miltefosine as part of their treatment regimen but with three very different outcomes: death, survival with poor neurologic outcome, and survival with full neurologic recovery. Therefore, while

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 U.S. PAM cases received miltefosine compared with 33% (3/9) of fatal U.S. PAM cases (CDC unpublished data). Surviving PAM, including survival with few or no deficits is likely multifactorial and includes early diagnosis and treatment, using 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]. While 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 two patients who used tap water in a neti pot to irrigate their sinuses, one patient who used tap water to perform ritual ablution, and one 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 (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 (IND) 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.

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Table 1

PAM Survivor Treatment and Outcomes

	Australian Survivor (1971) [2]	**U.S. Survivor (1978) [3]**	**Mexican Survivor (2003) [4]**	**U.S. Female Survivor (2013) [5]**	**U.S. Male Survivor (2013) [current case]**
Symptom onset to initiation of anti-ameba therapy (hours)	Unknown	>72	9	48	>120
Anti-ameba drug therapies	Amphotericin B (dose unknown) IV, IT, and via ventricular reservoir	Amphotericin B 1–1.5 mg/kg/day IV in 2 divided doses × 9 days; 1–1.5 mg IT daily × 10 days	Amphotericin B 0.25–1 mg/kg/day IV × 14 days	Amphotericin B 1–1.5 mg/kg/day IV in 2 divided doses × 26 days; 1–1.5 mg IT daily × 10 days	Amphotericin B 1 mg/kg/day IV × 19 days; 0.1 mg IT × 5 days
		Rifampin 10 mg/kg/day PO in 3 divided doses × 9 days	Rifampin 10 mg/kg/day PO × 1 month	Rifampin 10 mg/kg/day IV × 26 days	Rifampin 12 mg/kg/day PO × 19 days
		Miconazole 350 mg/m^2 body surface area/day IV in 3 divided doses × 9 days 10 mg daily then 10 mg IT every other day × 8 days	Fluconazole 10 mg/kg/day IV (then PO) × 1 month	Fluconazole 10 mg/kg/day IV × 26 days	Fluconazole 12 mg/kg/day loading dose, then 9 mg/kg/day IV × 19 days
				Azithromycin 10 mg/kg/day IV × 26 days	Azithromycin 10 mg/kg/day PO × 19 days
				Miltefosine 150 mg PO in 3 divided doses × 26 days	Miltefosine 150 mg PO in 3 divided doses × 19 days
Adjunctive therapies		Dexamethasone	Dexamethasone 0.6 mg/kg/day IV	Dexamethasone 0.6 mg/kg/day IV	Dexamethasone 0.6 mg/kg/day IV
				CSF drainage	CSF drainage
				Hyperosmolar therapy (mannitol and 3% saline)	Hyperosmolar therapy (mannitol)
				Moderate hyperventilation	
				Induced hypothermia (32–34°C)	
Outcome	Complete recovery	Complete recovery	Complete recovery	Complete recovery	Significant neurologic deficits

IV=intravenous; IT=intrathecal; PO=per oral