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

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Abstract

Naegleria fowleri is a thermophilic free-living amoeba that causes primary amoebic meningoencephalitis. Infections are nearly always fatal. We present the third well-documented survivor of this infection in North America. Survival most likely resulted from a combination of early identification and treatment, use of a combination of antimicrobials including miltefosine and management of elevated intracranial pressure based on traumatic brain injury principles.

Keywords

Naegleria fowleri; Primary Amebic Meningoencephalitis; miltefosine; hypothermia

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W. Matthew Linam: Dr. Linam provided medical care for the patient, drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Jennifer R. Cope: Dr. Cope advised the medical care of the patient, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Govinda S. Visvesvara, Alexandre J. da Silva, and Yvonne Qvarnstrom: Drs. Visvesvara, da Silva, and Qvarnstrom performed diagnostic studies and interpretation of results, critically reviewed the manuscript, and approved the final manuscript as submitted.

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Naegleria fowleri is a thermophilic free-living amoeba found in warm freshwater. Infection is rare and occurs when water containing the amoeba enters the nose and subsequently invades the brain. Infection with *N. fowleri* causes primary amoebic meningoencephalitis (PAM), resulting in destruction of brain tissue and cerebral edema. There have been two well-documented survivors in North America: one in California in 1978¹⁻² and one in Mexico in 2003.³ We present the third documented survivor of PAM in North America.

Case

The patient, a previously healthy 12-year-old female, presented to the emergency department with a two-day history of headache and a one-day history of fever (39.4°C), along with nausea, vomiting and somnolence. She had a normal neurologic exam. She reported swimming at an outdoor water park seven days prior to symptom onset. Initial laboratory evaluation included peripheral white blood cell count of 18.4 cells/ μ L (77% segmented, 13% banded neutrophils). Cerebrospinal fluid (CSF) revealed a white blood cell count of 3675 cells/ μ L (86% segmented neutrophils), red blood cell count of 53 cells/ μ L, protein of 374 mg/dL and glucose of 22 mg/dL. The Giemsa-Wright stain of the CSF revealed amoebae consistent with *N. fowleri*. The initial computed tomography scan of her brain was normal.

She was admitted to the pediatric intensive care unit on July 19, 2013 and started on the following: conventional amphotericin B 1.5mg/kg/day intravenously in two divided doses, fluconazole 10mg/kg/day, rifampin 10mg/kg/day and azithromycin 10mg/kg/day.^{1, 3} Dexamethasone was initiated concurrently. After three days, the amphotericin B was decreased to 1mg/kg/day.¹ Approximately 36 hours after admission, she was started on miltefosine 50mg every eight hours. Consent was obtained from the family prior to administering miltefosine.

Almost 24 hours after admission, she developed a right-sided abducens nerve palsy. An extraventricular drain (EVD) was placed in the operating room, and initial intracranial pressure (ICP) was approximately 50 mmHg. Intrathecal amphotericin B was started at a dose of 1.5mg daily for two days followed by a dose of 1mg every other day for eight days.¹ On the third day of hospitalization, she developed worsening intracranial pressure. Management of her cerebral edema (goal ICP below 20 mmHg) included: drainage of CSF, hyperosmolar therapy with mannitol and 3% saline, moderate hyperventilation (goal pCO₂ of 30–35 mmHg), and induced hypothermia (32–34°C). Cerebral edema resolved after approximately two weeks. (Figure 1)

Her initial CSF specimen grew *N. fowleri* on culture and was positive for *N. fowleri* by polymerase chain reaction (PCR). By day three, her CSF specimen was culture negative for *N. fowleri*. Serial CSF specimens showed decreasing white blood cells and decreasing amounts of *N. fowleri* DNA on PCR.

A magnetic resonance image (MRI) of her brain two 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 (Figure 2). A repeat MRI of her brain one week later showed improvement. She completed 26 days of a planned 28-day course of antimicrobials

(miltefosine, azithromycin, rifampin and fluconazole), which were 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 home. At six months post infection, her level of functioning was normal and without residual deficits.

Discussion

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

Between 1962 and 2013, 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) remains stable.^{5–6} The majority of these infections occurred in southern-tier states. Roughly 75% of infections are associated with swimming in warm freshwater lakes and rivers.^{5–6} The median age of infection is 11 years (range 8 months to 66 years).^{5–6} Recently the epidemiology of *N. fowleri* PAM has changed. Since 2010, two cases were reported in Minnesota^{6–7} as well as single cases identified in Indiana and Kansas.⁶ This suggests 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 ablution.⁹

The time from exposure to *N. fowleri* to the onset of symptoms is approximately 5 days (range 1 to 7 days).⁵ The initial symptoms of PAM are indistinguishable from bacterial meningitis. Patients experience rapid deterioration with death resulting from brain injury and edema occurring within about 5 days (range 1 to 12 days).⁵ In the two weeks prior to 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*. Our patient developed symptoms seven days after this exposure. She presented to the hospital approximately 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 two days, and the median time from symptom onset to initiation of recommended therapy is three days (CDC unpublished data). Because *N. fowleri* PAM is rare and not often considered as a diagnosis, pre-mortem identification of the ameba is often delayed or not attempted, precluding the timely initiation of recommended therapy. Early identification and initiation of recommended therapy seems critical for survival; however, this timeframe is likely impacted by multiple factors including strain virulence, inoculum and host immune response.

The only documented survivor in the United States received amphotericin and miconazole intravenously and intrathecally and intravenous rifampin.^{1–2} The survivor from Mexico

received intravenous amphotericin, fluconazole and rifampin.³ Conventional amphotericin has a lower minimum inhibitory concentration compared to the liposomal formulation and is thus preferred even though the liposomal form has better CSF penetration.¹⁰ Other medications such as fluconazole, voriconazole and azithromycin have shown activity against *N. fowleri*.^{10–12} Studies suggest that azithromycin may have a synergistic effect when used in combination with amphotericin.¹³ Recently, miltefosine, an antiparasitic agent, has shown *in vitro* effectiveness against *N. fowleri* and other clinically important free-living amebae.¹¹ Although in recent years miltefosine has been used to successfully treat patients with other free-living amebae infections^{14–15}, our patient is the first to be successfully treated with miltefosine for PAM. Miltefosine is available directly from CDC for treatment of infections caused by free-living amebae in the United States.⁴

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

N. fowleri initially causes direct damage to surrounding neuronal and other cells through direct cell-to-cell interaction as well as release of a number of cytotoxic proteins.² In addition, cytotoxic proteins released by *N. fowleri* and debris from lysed neuronal and other cells generate a cascade of proinflammatory cytokines resulting in hyperinflammation and further injury.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 *N. fowleri* PAM. Cytokine levels were not measured in our patient, so it is unclear whether the use of hypothermia impacted the host inflammatory response. Although *N. fowleri* is a thermophilic organism, it is unclear whether the degree of hypothermia used in our patient resulted in reduced pathogenicity of the ameba.

The changing epidemiology of *N. fowleri* necessitates its inclusion in the differential of patients with meningoencephalitis, particularly those who report a recent history of swimming in warm freshwater, regardless of geographic location, or use of nonsterile water for nasal irrigation or ritual ablution. Since 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. In the presence of signs of increased ICP, we recommend placement of an EVD and administration of intrathecal amphotericin (Table 1). Elevated ICP should be aggressively managed, maintaining an ICP below 20 mmHg. Administer dexamethasone concurrently with the antimicrobials as it was utilized in all three documented survivors, and has shown benefit in central nervous system insults due to infectious etiologies.^{1–3, 24} Consider also lowering the patient's core body temperature (32–34°C) as this may have beneficial effects beyond lowering ICP. Additional data are needed to determine 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.

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Abbreviations

PAM	Primary amebic meningoencephalitis
CSF	Cerebrospinal fluid
EVD	Extraventricular drain
ICP	Intracranial pressure
PCR	Polymerase chain reaction
MRI	Magnetic resonance image
CDC	Centers for Disease Control and Prevention

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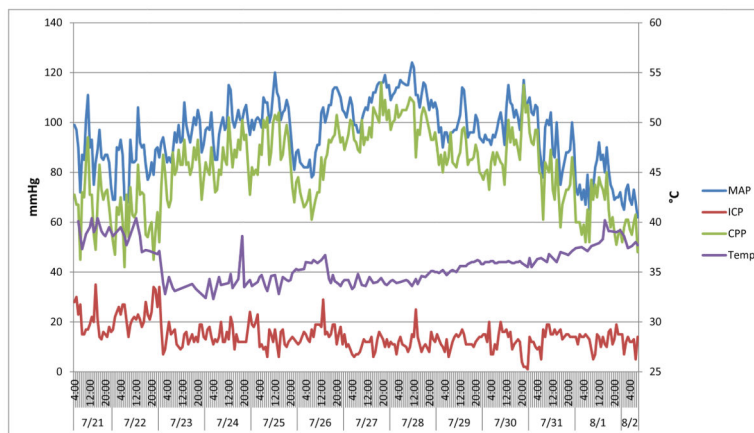


Figure 1. The Relationship Between Mean Arterial Pressure, Cerebral Perfusion Pressure, Intracranial Pressure and Core Body Temperature During the Management of a Twelve-Year-Old Female with *Naegleria fowleri* Primary Amebic Meningoencephalitis

MAP is mean arterial pressure. ICP is intracranial pressure. CPP is cerebral perfusion pressure. Temp is temperature. The graph above illustrates our management strategy of maintaining CPP above 60mmHg and ICP below 20mmHg. With induction of hypothermia (7/22 22:00), ICPs were sustained under 20mmHg. Please note early attempts to rewarm the patient on 7/24 and 7/26 led to elevations of ICP. After 5 days of cooling, rewarming the patient was met with minimal ICP elevations.

Figure 2a

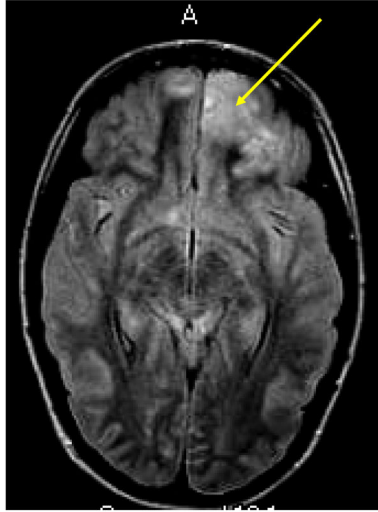


Figure 2b



Figure 2c

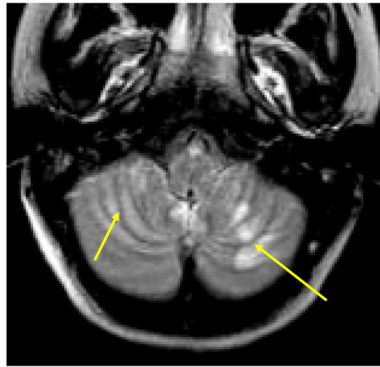


Figure 2d

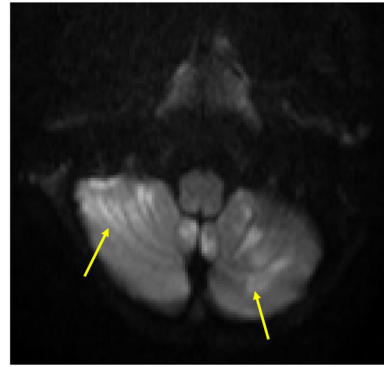


Figure 2. Noncontrast Axial Magnetic Resonance Images of the Brain of a Patient with *Naegleria fowleri* Primary Amebic Meningoencephalitis

Figure 2a: The axial fluid attenuated inversion recovery (FLAIR) image shows focal edema in the left frontal lobe (arrow). Figure 2b: Axial susceptibility-weighted image shows hemorrhage within the left frontal edematous lesion (arrow). Figure 2c: Axial FLAIR image demonstrates multiple areas of edema in the cerebellum bilaterally (arrows). Figure 2d: Axial diffusion-weighted image shows areas of restricted diffusion consistent with acute cerebellitis (arrows).

Table 1
Recommended Treatment Regimen for *Naegleria fowleri* Primary Amebic Meningoencephalitis

Medication	Dose	Route	Maximum Dose	Duration	Comments
Amphotericin B *1	1.5 mg/kg/day in 2 divided doses	IV	1.5 mg/kg/day	3 days	
then	1 mg/kg/day once daily	IV		11 days	14-day course
Amphotericin B *1	1.5 mg once daily	Intrathecal	1.5 mg/day	2 days	
then	1 mg/day every other day	Intrathecal		8 days	10-day course
Azithromycin ¹²	10 mg/kg/day once daily	IV/PO	500 mg/day	28 days	
Fluconazole ³	10 mg/kg/day once daily	IV/PO	600 mg/day	28 days	
Rifampin ^{1,3}	10 mg/kg/day once daily	IV/PO	600 mg/day	28 days	
Miltefosine ¹³	Weight < 45 kg: 50 mg BID				
	Weight > 45 kg: 50 mg TID	PO	2.5 mg/kg/day	28 days	50 mg tablets
Dexamethasone ^{3,24}	0.6mg/kg/day in 4 divided doses	IV	0.6mg/kg/day	4 days	

* Conventional amphotericin preferred.

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/symptoms of increased intracranial pressure. Miltefosine should be started once available.

Data from references 1, 3, 12, 13, and 24.