Surgical Neurology International

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: James I. Ausman, MD, PhD University of California, Los Angeles, CA, USA

Case Report

Acanthamoeba encephalitis: A Case Report and Review of Therapy

A. Zamora[1], H. Henderson[1], E. Swiatlo[1,2]

[1]Department of Medicine, University of Mississippi Medical Center, [2]G.V. (Sonny) Montgomery VA Medical Center, Jackson, MS USA

E-mail: A. Zamora - azamora@umc.edu; H. Henderson - hhenderson@umc.edu; *E. Swiatlo - edswiatlo@gmail.com
*Corresponding author

Received: 22 January 14 Accepted: 14 March 14 Published: 09 May 14

This article may be cited as:
Zamora A, Henderson H, Swiatlo E. *Acanthamoeba encephalitis*: A Case Report and Review of Therapy. Surg Neurol Int 2014;5:68.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2014/5/1/68/132239

Abstract

Background: *Acanthamoeba* is a rare cause of encephalitis yet is associated with high mortality. Treatment protocols vary greatly and generally include combination therapy across a wide spectrum of antiinfective classes.

Case Description: A 63-year-old male who underwent renal transplantation presented 6 months after transplantation with depressed level of consciousness. Imaging of the head with computerized tomography showed an enhancing lesion suspicious for brain abscess. Biopsy of the lesion showed *Acanthamoeba* cysts. The patient was treated with sulfadiazine, fluconazole, flucytosine, azithromycin, and miltefosine but without success. We review recently published cases of *Acanthamoeba* encephalitis with an emphasis on treatment protocols and outcomes.

Conclusion: Free-living protozoans such as *Acanthamoeba* are ubiquitous in the environment and should be suspected in immunosuppressed persons who present with central nervous system findings and brain abscess. Biopsy is critical to establish the etiology so that appropriate combination therapy can be deployed.

Key Words: *Acanthamoeba*, brain abscess, encephalitis, miltefosine

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.132239

Quick Response Code:

INTRODUCTION

Acanthamoeba was discovered in 1930 and since then at least 24 species have been described.[19,22] It is ubiquitous in nature and has been isolated from soil, fresh and brackish water, bottled mineral water, cooling towers of power plants, heating, ventilating and air conditioning units, and just about any surface that comes in contact with water, including medical and laboratory devices.[22] Here we report a case of cerebral *Acanthamoeba* infection in an immunocompromised host, which was unsuccessfully treated with combination therapy including miltefosine.

CASE REPORT

A 63-year-old male with a history of kidney transplantation presented to the Emergency Department for altered mental status. His wife observed the patient to have intermittent confusion for the previous 2 weeks and also noted that he was sleeping more than usual. She denied fever, nausea, vomiting, neck rigidity, photophobia, or any gross motor or sensory deficits in the patient. The patient had not traveled outside Mississippi since his transplant 6 months prior to the onset of symptoms. He was taking mycophenolate and tacrolimus for his renal allograft. On the night of admission the patient was found unresponsive in his bed. Emergency responders found the patient with marked bradycardia and a temporary pacemaker was placed en route to the hospital.

Upon arrival to the hospital the patient was arousable but unable to answer questions or follow commands.

Laboratory results included the following: white blood cell count – 9000/μL (90% neutrophils, 5% lymphocytes, 4% monocytes, 1% eosinophils), hemoglobin – 10.3 g/dL, hematocrit – 32.4%, platelets – 177,000/mL, sodium – 136 mmol/L, potassium – 6.8 mmol/L, chloride – 105 mmol/L, HCO_3^{-2}- 20 mmol/L, BUN – 42 mg/dL, creatinine – 3.4 mg/dL, lactic acid 3.7 mmol/L, troponin – undetectable. Chest radiograph demonstrated mild cardiomegaly with clear lungs. Computerized tomography (CT) of the head showed low density areas in the left parietal, occipital and frontal lobe thought to potentially be watershed infarcts. He was admitted to the hospital with a diagnosis of ischemic stroke.

Magnetic resonance imaging (MRI) of the brain showed intracranial masses in the left frontal lobe [Figure 1] as well as the left posterior temporal–occipital interface with edema. Dexamethasone was initiated to reduce edema and antiseizure medications were begun as well. Six days after admission, the patient underwent biopsy of the left frontal lobe lesion. This initial biopsy revealed numerous granulomata with extensive abscess formation and necrosis but no pathogens identified with special staining. Three days following the initial biopsy, another biopsy was performed in an effort to make a specific microbiological diagnosis. This second biopsy, of the left temporal region, showed multiple necrosis, gliosis, and protozoans highly suggestive of *Acanthamoeba* trophozoites [Figure 2]. The patient was started on combination therapy with sulfadiazine, fluconazole, flucytosine, azithromycin, and miltefosine. His hospital course was complicated by declining kidney function, which ultimately required hemodialysis. The patient became pancytopenic and developed intractable fever despite broad-spectrum antibacterial therapy. He expired during his fifth week of hospitalization.

DISCUSSION

Granulomatous amoebic encephalitis (GAE) is an infection of the central nervous system with a mortality rate over 50% and is increasingly recognized as an opportunistic infection of immunocompromised hosts. Reported cases of amoebic encephalitis are increasing as awareness of these pathogens and the population of immunosuppressed patients grows. GAE is caused primarily by free-living amoebae species of *Acanthamoeba*, *Sappinia*, or *Balamuthia*. Most cases are diagnosed postmortem and a limited number of cases have reported successful treatment using various combinations of antimicrobial agents.[3,7,14] Mortality from central nervous system (CNS) amoebic infections remains extremely high and may exceed 90%.[5] Currently, there is no recommended standard therapeutic regimen for CNS infections with these amoebae.

The life cycle of *Acanthamoeba* consist of two stages, a vegetative trophozoite stage and a dormant cyst stage. Under optimal conditions of nutrients, pH and temperature, trophozoitespredominate, however, under stressful conditions, a double-walled cyst is formed. The route of entry into the human body is postulated to be primarily through the lungs or breaks in the skin. The organism then disperses via blood to the brain. The most common manifestations of *Acanthamoeba* infection are related to CNS involvement. Common signs and symptoms are nonspecific and consist of headache, stiff neck, alterations in mental status or cognitive abilities, nausea, vomiting, low-grade fever, lethargy, gait or coordination disturbances, visual disturbance, focal motor deficits, seizures, or coma.[3,22]

Definitive diagnosis is made by examination of tissue and, rarely, by cerebrospinal fluid (CSF) analysis. CSF may show mild pleocytosis, moderately elevated protein,

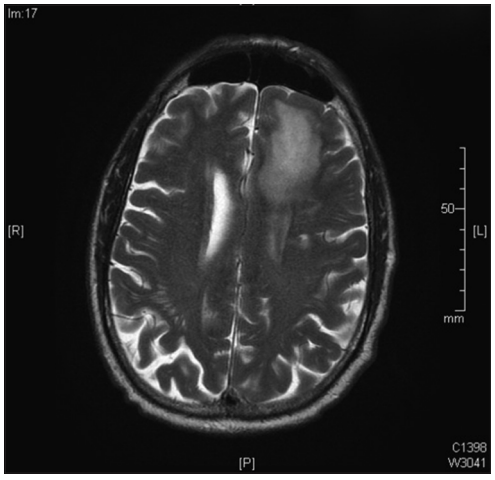

Figure 1: Magnetic resonance image of the brain showing an enhancing lesion in the left frontal lobe consistent with an abscess

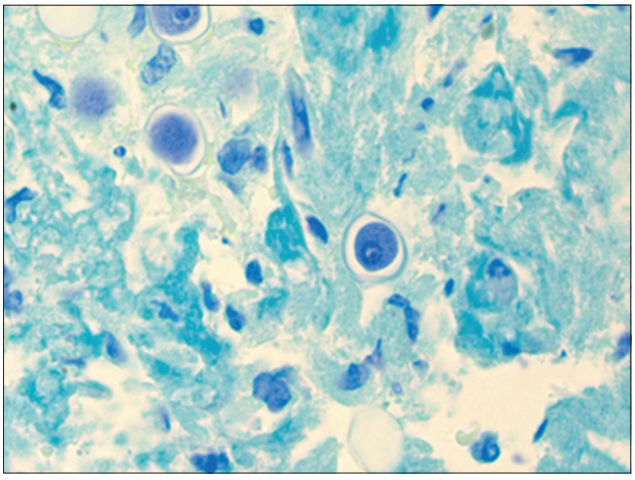

Figure 2: Giemsa stain of brain tissue showing *Acanthamoeba* cysts (×400)

and low glucose, however, amoebae are frequently seen by any staining or microscopic technique. Serology for amoeba-specific antibodies is available, however, these assays are not widely available and their specificity for active disease is low since most people have been exposed to this organism at one or more times in their life. The most expeditious and common way to make the diagnosis of GAE is to demonstrate trophozoites or cysts in tissue samples.[3] A unique characteristic feature of *Acanthamoeba sp.* is the presence of fine, tapering, thorn-like acanthopodia protruding from the cell. Trophozoites are 15-50 μm in size with a centrally located nucleus and a densely staining nucleolus. Cysts are 10-25 μm with two cell walls usually discernible and also demonstrate a nucleus with a dense nucleolus. The organism can also be cultivated quite readily *in vitro* in special media.[3]

Currently, there is no reliably effective drug therapy for *Acanthamoeba* infection of the CNS. Most published cases have used multiple drug combinations with varying success.[1,2,4,6,8,9-13,15-18,20,23] A review of the English language literature for cases of CNS infection with *Acanthamoeba* diagnosed antemortem since 2000 and which described treatment protocols is summarized in Table 1.

Of the 18 cases in the literature, 83% (15/18) were males and 61% (11/18) had identifiable underlying immunosuppressive conditions. Mortality was 44% (8/18) and the survivors were evenly divided by the concurrence of an immunosuppressive condition. The number of cases is too small to draw any reliable conclusions about efficacy and there is a large overlap of drugs used between patients who survived and those who succumbed to infection. The Infectious Diseases Society of America (IDSA) guidelines for *Acanthamoeba* CNS infection have a CIII-level recommendation for either trimethoprim-sulfamethoxazole + rifampin + ketoconazole or fluconazole + sulfadiazine + pyrimethamine.[21] Recently, the Centers for Disease Control and Prevention (CDC) announced the availability of miltefosine as an investigational drug to treat amoebic CNS infection.[5] Two cases included in Table 1 used miltefosine as part of combination therapy and both patients survived. Although the patient presented in this report was also treated with miltefosine, this drug should be strongly considered as part of combination therapy for amoebic infections of the CNS.

CONCLUSION

Because of the rarity of amoebic encephalitis, it is unlikely there will be randomized clinical trials to rigorously test treatment options. Case reports and small series will remain important for identifying trends in epidemiology, natural history, and treatment of amoeba infections of the CNS. As human population demographics shift, and the number of immunosuppressed patients rises, this information will be critical to provide clinicians and laboratory workers with the most effective diagnostic and therapeutic options.

Table 1: Published cases of *Acanthamoeba* encephalitis since 2000

Case (age, sex)	Underlying medical condition	Treatment regimen	Outcome	Reference
25 months, male	Acute lymphoblastic leukemia	TMP/SMX[1], Flu[2], PTD[3]	Survive	6
53 years, male	HIV	SFZ[4], PYR[5], Flu	Death	7
79 years, male	Autoimmune hepatitis	PTD, Vor[6], AZM[7]	Death	8
38 years, male	Immunocompetent	Vor, MFS[8]	Survive	9
51 years, male	Systemic lupus erythematosus	Flu, IMI9, MTZ[10], intrathecal AmB[11]	Death	10
17 years, male	Immunocompetent	TMP/SMX, Flu, Rif[12]	Survive	11
13 years, male	Fragile X syndrome	AmB, Vor	Death	12
25 year, male	Disseminated tuberculosis	AN[13], MFS	Survive	13
25 years, male	Seizure disorder	Rif, TMP/SMX, Flu	Survive	14
63 year, female	Hypertension	AmB, Flu, Rif	Death	15
42 years, male	Liver transplant	Rif, TMP/SMX	Survive	16
51 years, male	Renal transplant	AmB, PTD, Rif, AZM, 5-FC[14], SFZ, MTZ	Death	17
24 year, female	Unknown	AmB	Death	18
33 years, male	HIV	SFZ, PYR, Flu	Survive	19
45 year, female	Immunocompetent	ABZ[15], CFX[16], Flu	Survive	20
8 years, male	Mandibular tuberculosis	TMP/SMX	Death	21
8 years, female	Immunocompetent	TMP/SMX, Ket[17], Rif	Survive	21
3 years, male	Immunocompetent	TMP/SMX, Ket, Rif	Survive	21

[1]Trimethoprim/sulfamethoxazole, [2]Fluconazole, [3]Pentamidine, [4]Sulfadiazine, [5]Pyrimethamine, [6]Voriconazole, [7]Azithromycin, [8]Miltefosine, [9]Imipenem, [10]Metronidazole, [11]Amphotericin B, [12]Rifamycin, [13]Amikacin, [14]5-flucytosine, [15]Albendazole, [16]Ceftriaxone, [17]Ketoconazole, HIV: Human immunodeficiency virus

REFERENCES

1. Abd H, Saeed A, Jalal S, Bekassy AN, Sandstrom G. Ante mortem diagnosis of amoebic encephalitis in a hematopoietic stem cell transplanted patient. Scand J Infect Dis 2009;41:619-22.
2. Aichelburg AC, Walochnik J, Assadian O, Prosch H, Steuer A, Perneczky G, *et al*. Successful treatment of disseminated *Acanthamoeba* sp. infection with miltefosine. Emerg Infect Dis 2008;14:1743-6.
3. Akpek G, Uslu A, Huebner T, Taner A, Rapoport AP, Gojo I, *et al*. Granulomatous amebic encephalitis: An under-recognized cause of infectious mortality after hematopoietic stem cell transplantation. Transpl Infect Dis 2011;13:366-73.
4. Alkhunaizi AM, Dawamneh MF, Banda RW, Daabil RA, Al-Tawfiq JA, Akkad SA, *et al*. *Acanthamoeba* encephalitis in a patient with systemic lupus treated with rituximab. Diagn Microbiol Infect Dis 2013;75:192-4.
5. Centers for Disease Control and Prevention. Investigational drug available directly from CDC for the treatment of infections with free-living amoebae. MMWR Morb Mortal Wkly Rep 2013;62:666.
6. Fung KT, Dhillon AP, McLaughlin JE, Lucas SB, Davidson B, Rolles K, *et al*. Cure of *Acanthamoeba* cerebral abscess in a liver transplant patient. Liver Transpl 2008;14:308-12.
7. Gene AH, Gardner PA, Counce Matovelle ME. Rapidly expanding brain mass. Transpl Infect Dis 2007;9:211-3.
8. Hamide A, Sarkar E, Kumar N, Das AK, Narayan SK, Parija SC. *Acanthamoeba* meningoencephalitis: A case report. Neurol India 2002;50:484-6.
9. Kaushal V, Chhina DK, Kumar R, Pannu HS, Dhooria HP, Chhina RS. *Acanthamoeba* encephalitis. Indian J Med Microbiol 2008;26:182-4.
10. Lackner P, Beer R, Broessner G, Helbok R, Pfausler B, Brenneis C, *et al*. Acute granulomatous *acanthamoeba* encephalitis in an immunocompetent patient. Neurocrit Care 2010;12:91-4.
11. Maritschnegg P, Sovinz P, Lackner H, Benesch M, Nebl A, Schwinger W, *et al*. Granulomatous amebic encephalitis in a child with acute lymphoblastic leukemia successfully treated with multimodal antimicrobial therapy and hyperbaric oxygen. J Clin Microbiol 2011;49:446-8.
12. Mayer PL, Larkin JA, Hennessy JM. Amebic encephalitis. Surg Neurol 2011;2:50.
13. McKellar MS, Mehta LR, Greenlee JE, Hale DC, Booton GC, Kelly DJ, *et al*. Fatal granulomatous *Acanthamoeba* encephalitis mimicking a stroke, diagnosed by correlation of results of sequential magnetic resonance imaging, biopsy, *in vitro* culture, immunofluorescence analysis and molecular analysis. J Clin Microbiol 2006;44:4265-9.
14. Meersseman W, Lagrou K, Sciot R, de Jonckheere C, Haberler C, Walochnik J, *et al*. Rapidly Fatal *Acanthamoeba* encephalitis and treatment of cryoglobulinemia. Emerg Infect Dis 2007;13:469-71.
15. Ndiaye M, Diop AG, Dieng Y, Seydi M, Diouf FS, Diop BM, *et al*. A case of meningoencephalitis caused by *Acanthamoeba* sp. In Dakar Med Trop 2005;65:67-8.
16. Pietrucha-Dilanchian P, Chan JC, Castellano-Sanchez A, Hirzel A, Laowansiri P, Tuda C, *et al*. *Balamuthia mandrillaris* and *Acanthamoeba* amebic encephalitis with neurotoxoplasmosis co-infection in a patient with advanced HIV infection. J Clin Microbiol 2012;50:1128-31.
17. Ranjan R, Handa A, Choudhary A, Kumar S. *Acanthamoeba* infection in an interhemispheric ependymal cyst: A case report. Surg Neurol 2009;72:185-9.
18. Seijo Martinez M, Gonzalez-Mediero G, Santiago P, Rodriguez De Lope A, Diz J, Conde C, *et al*. Granulomatous amebic encephalitis in a patient with AIDS: Isolation of *Acanthamoeba* sp. group II from brain tissue and successful treatment with sulfadiazine and fluconazole. J Clin Microbiol 2000;38:3892-5.
19. Siddiqui R, Khan NA. Biology and pathogenesis of *Acanthamoeba*. Parasit Vectors 2012;5:6.
20. Singhal T, Bajpai A, Kalra V, Kabra SK, Samantaray JC, Satpathy G, *et al*. Successful treatment of *Acanthamoeba* meningitis with combination oral antimicrobials. Pediatr Infect Dis J 2001;20:623-7.
21. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, *et al*. The management of encephalitis: Clinical practice guidelines by the Infectious Disease Society of America. Clin Infect Dis 2008;47:303-27.
22. Visvesvara GS, Moura H, Shuster FL. Pathogenic and opportunistic free living amoebae: *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia diploidea*. FEMS Immunol Med Microbiol 2007;50:1-26.
23. Webster D, Umar I, Kolyvas G, Bilbao J, Guiot MC, Duplisea K, *et al*. Case report: Treatment of granulomatous amoebic encephalitis with voriconazole and miltefosine in an immunocompetent soldier. Am J Trop Med Hyg 2012;87:715-8.

Commentary

Acanthamoeba Granulomatous Amebic Encephalitis: A Challenging and Often Fatal Diagnosis

In the article "*Acanthamoeba* encephalitis: A case report and review of therapy", the authors describe a classic case of *Acanthamoeba* granulomatous amebic encephalitis (GAE) in an immunocompromised patient. Given its rarity and the specific expertise needed to make the diagnosis, *Acanthamoeba* GAE remains a challenging diagnosis. The differential diagnosis is usually that of a space-occupying brain lesion and includes more common infections like bacterial brain abscess, tuberculosis, fungal infection, neurocysticercosis, and toxoplasmosis as well as noninfectious etiologies such as malignancy or stroke. The incubation period of *Acanthamoeba* GAE is unknown although, in disseminated infections with preceding cutaneous involvement, several weeks or months may elapse between the appearance of skin lesions and the recognition of central nervous system (CNS) disease.[6] Patients with *Acanthamoeba* GAE are usually immunocompromised and frequently present with an insidious and protracted onset of low-grade fever, headache, fatigue, weakness, and nausea. Patients will then progress to neurologic symptoms that may include altered mental status, hemiparesis, seizures, blurred vision, and diplopia. Other neurologic symptoms can also occur later in the course of illness such as cranial nerve palsies, dizziness, ataxia, confusion, and personality change.[7] Delayed diagnosis is common because of the slowly progressive and nonspecific nature of early disease as well as a lack of awareness of this infection among clinicians. Over the course of a week to several months from the onset of neurologic symptoms, the disease almost universally progresses to coma and death from increased intracranial pressure and brain herniation.

Cerebrospinal fluid (CSF) from patients with *Acanthamoeba* GAE typically demonstrates a moderate

lymphocytic pleocytosis. Protein may be elevated and glucose may be normal or low. *Acanthamoeba* organisms are rarely seen in the CSF. Computed tomography and magnetic resonance imaging scans of the brain frequently reveal single or multiple hypodense, ring-enhancing, space-occupying lesions. The diagnosis of *Acanthamoeba* GAE is usually made once affected brain tissue is obtained, whether via premortem biopsy as in the case presented here or postmortem, and amebic cysts and trophozoites are directly visualized in the tissue with hemotoxylin and eosin (H and E) staining by an experienced pathologist. The diagnosis of *Acanthamoeba* infection can be confirmed with immunohistochemical techniques that detect amebic antigen in the tissue or polymerase chain reaction (PCR) testing to detect *Acanthamoeba* DNA in the tissue.[5] Confirmatory testing is only available at selected reference diagnostic laboratories including at the U.S. Centers for Disease Control and Prevention (CDC).

More often than not, *Acanthamoeba* infection is a fatal disease. Among 94 cases of *Acanthamoeba* infection reported to CDC from 1955 through 2013, mortality was 85% (CDC unpublished data). The rarity of this infection precludes the use of rigorous studies to examine effective treatment regimens; therefore, treatment recommendations rely solely on individual case reports of successful outcomes. Survivors were given multidrug regimens consisting of various combinations of pentamidine, sulfadiazine, flucytosine, fluconazole, itraconazole or voriconazole, trimethoprim-sulfamethoxazole, and miltefosine. The drug miltefosine has shown particular promise in treating free-living ameba infections, including those caused by *Acanthamoeba* and *Balamuthia mandrillaris* (a free-living ameba similar to *Acanthamoeba* that also causes GAE). Although the number of *B. mandrillaris* and *Acanthamoeba* infections treated with a miltefosine-containing regimen is small, it appears that a miltefosine-containing treatment regimen does offer a survival advantage for patients with these often fatal infections.[1]

Finally, this patient's immunocompromised status was the result of an immunosuppressive regimen prescribed following a kidney transplant 6 months prior to symptom onset. In addition to the resulting immunosuppression, the patient's organ transplant also represented a possible route of exposure to *Acanthamoeba*. While there has not yet been a documented case of *Acanthamoeba* infection transmitted via solid organ transplant, the related free-living ameba, *Balamuthia mandrillaris*, has caused three clusters of organ transplant-transmitted infection when an infected donor's organs were transplanted into multiple recipients.[2-4] In the case presented here, transplant transmission was investigated and donor testing was negative for *Acanthamoeba*. However, the potential for transplant transmission remains and clinicians should be aware of the possibility when considering the diagnosis of *Acanthamoeba* infection.

With increasing populations of immunocompromised patients, the diagnosis of *Acanthamoeba* GAE should be considered in an immunosuppressed patient with encephalitis and aggressively treated with a combination of antimicrobials. In solid organ transplant patients, the possibility of transplant-transmitted infection should be investigated so that other recipients can be prophylactically treated to prevent this deadly infection.

REFERENCES

1. Centers for Disease Control and Prevention. Investigational drug available directly from CDC for the treatment of infections with free-living amebae. MMWR Morb Mortal Wkly Rep 2013;62:666.
2. Centers for Disease Control and Prevention. Balamuthia mandrillaris transmitted through organ transplantation — Mississippi, 2009. MMWR Morb Mortal Wkly Rep 2010;59:1165–70.
3. Centers for Disease Control and Prevention. Transplant-transmitted Balamuthia mandrillaris — Arizona, 2010. MMWR Morb Mortal Wkly Rep 2010;59:1182.
4. Lea AS, Kulkarni1 RD, Schain DC, Casey MJ, Zendejas-Ruiz IR, Chung WK, *et al.* Transmission of Balamuthia mandrillaris through solid organ transplantation: Utility of organ recipient serology to guide clinical management. Am J Transplant 2014. [In press].
5. Qvarnstrom Y, Visvesvara GS, Sriram R, da Silva AJ. Multiplex real-time PCR assay for simultaneous detection of Acanthamoeba spp., Balamuthia mandrillaris, and Naegleria fowleri. J Clin Microbiol 2006;44:3589-95.
6. Visvesvara GS, Moura H, Schuster FL. Pathogenic and opportunistic free-living amoebae: Acanthamoeba spp., Balamuthia mandrillaris, Naegleria fowleri, and Sappinia diploidea. FEMS Immunol Med Microbiol 2007;50:1-26.
7. Visvesvara GS. Free-living amebae as opportunistic agents of human disease. J Neuroparasitol 2010;1.

Jennifer R. Cope

Waterborne Disease Prevention Branch, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA