An unusual case of neutrocytic, culture-negative meningitis in an immunocompetent adult

Kundoly V Suseela¹, Firosh Khan² and Santhosh J Kottoor³
1Department of Microbiology, Amala Institute of Medical Sciences, Thrissur, India
2Department of Neurology, MES Medical College, Perinthalmanna, India
3Department of Medicine, Mother Hospital Pvt Ltd., Thrissur, India
Corresponding author: Santhosh J Kottoor. Email: drsjkottoor@hotmail.com

Abstract
Patient presenting with fever, acute onset seizure and neck stiffness on examination; deteriorating despite initiation of early treatment for meningitis.

Keywords
Primary amoebic meningoencephalitis, Naegleria fowleri, neurologic infection, seizure, miltefosine

Case report
A 62-year-old retired businessman from Thrissur district of Kerala, India, presented to the emergency room with a chief complaint of sudden onset generalised tonic clonic seizures. He had recurrent episodes of vomiting the previous night on a background of fever and headache for the past two days. The fever was low to moderate grade, partially relieved with over-the-counter acetaminophen tablets. The headache that started along with the fever had increased in severity over the past 24 h and was associated with projectile vomiting and photophobia. His medical history was only significant for type 2 diabetes mellitus which was well controlled on oral medications. Being born and brought up in Kerala, he had settled here with family a few years back to enjoy his retired life. He was active and used to go for walking in the morning, visiting temples and swimming in ponds. He had no history of recent travel or exposure to communicable diseases. His medications included metformin 500 mg twice daily and glimepiride 1 mg daily.

On examination, he was stuporous and not responding to commands with a Glasgow Coma Scale of 10. His temperature was 39°C, heart rate 110 beats per minute, oxygen saturation 98% on room air and the blood pressure 140/90 mm Hg. There was no oedema, pallor, cyanosis or clubbing. The neck was hyperextended and had stiffness on passive flexion. Computed tomography of the brain was essentially normal and a working diagnosis of acute meningoencephalitis with symptomatic seizures was made. A lumbar puncture was done immediately, which showed non-bloody, cloudy cerebrospinal fluid and was sent for cytological, biochemical and microbiological examination. He was started on intravenous ceftriaxone, vancomycin, ampicillin, dexamethasone and levetiracetam and was admitted in the neurology intensive care unit (Day 1).

Routine blood investigations showed a white cell count of 15.0 x 10⁹/L with 80% polymorphs, erythrocyte sedimentation rate of 44 mm/h, random blood sugar of 324 mg/dl and serum sodium of 126 mEq/L. Other parameters including the renal function test and liver function test were within normal limits.

Cerebrospinal fluid study showed elevated proteins (248 mg/dl), low sugar (62 mg/dl) and leukocytosis (10,000 cells/mm³) with 90% polymorphs. But cerebrospinal fluid Gram stain and rapid bacterial antigen testing for primary agents of pyogenic meningitis like Streptococcus pneumoniae, Haemophilus influenzae b and Neisseria meningitidis were all negative.

Cerebrospinal fluid sample was also sent for molecular study by cartridge-based nucleic acid amplification test in GeneXpert for Mycobacterium tuberculosis. His hyponatremia was corrected with intravenous 3% saline infusion. His chest X-ray, electrocardiogram and urine routine were within normal limits. While awaiting the culture results, his condition deteriorated further necessitating endotracheal intubation and mechanical ventilation. On the third day, the results of his cerebrospinal fluid culture and cartridge-based nucleic acid amplification test also turned out to be negative giving a picture of neutrocytic, culture-negative meningitis. Taking into consideration a rare possibility of an amoebic meningitis, a wet mount examination with 40x bright field microscopy of the same cerebrospinal fluid sample was done and it showed numerous, motile, amoebic trophozoites suggestive of Naegleria fowleri (Figure 1; see
supplementary material for the video of motile \textit{N. fowleri} trophozoites on wet mount preparation). As the phase contrast microscope was not available, detailed wet mount examination could not be done. On staining with haematoxylin, the amoebae were seen with purple stained-endoplasm and unstained pseudopodia (Figure 2). A preliminary diagnosis of primary amoebic meningoencephalitis was made. He was hence started on Amphotericin B, fluconazole, azithromycin, rifampicin and miltefosin. Despite all aggressive treatment and supportive care, the patient succumbed on the ninth day of admission.

\textbf{Discussion}

This is a case of primary amoebic meningoencephalitis, an extremely rare and sporadic central nervous system (CNS) infection caused by \textit{N. fowleri}, commonly referred to as brain eating amoeba.\textsuperscript{1} Fresh water bodies are identified as the habitat of this pathogen.\textsuperscript{2} There are three morphological forms for this organism such as amoeboid, flagellate and cyst; of these, amoebae are the invading forms. The organism enters the nasal passages, invades the nasal mucosa and reaches brain through the olfactory nerve.\textsuperscript{1} The disease usually affects children and young adults who are being in good health.\textsuperscript{3} History of contact with water as swimming or diving in ponds or streams may or may not be elicited and it depends on the conscious state of the patient. Laboratory studies of cerebrospinal fluid, like cytology, of these patients may point to bacterial meningitis and antibiotic treatment is opted for majority.\textsuperscript{4}

Even though it is termed as a rare infection, the true occurrence of these cases is not very well known. Very often they are being underdiagnosed and hence underestimated. The Centers for Disease Control and Prevention data from 1962 to 2018 show an average of just three to four cases being reported per year in the United States,\textsuperscript{5} while an epidemiological study estimates an average of 16 deaths due to primary amoebic meningoencephalitis in the United States.\textsuperscript{6} Only 15 cases of amoebic meningoencephalitis have been reported from India so far. Global data show only about 133 reported cases from year 1992 to 2014, out of which 10 were from India and 97\% of the victims died due to the infection resulting in very few survivors.\textsuperscript{7} Recently, few events have been reported from other parts of Kerala as well.\textsuperscript{8} The recent increase in the number of cases could be due to better awareness of the disease and the availability of modern diagnostic facilities like polymerase chain reaction. Some also propose a change in the climate and global warming to be a cause of spike in the incidence as the free-living amoebae are thermophilic organisms.\textsuperscript{9,10}

Patients typically present with high fever, headache, nausea, vomiting and meningeal signs. Rapid progression to seizure and coma may follow and most patients die within a week. Hence, it is very essential to identify the disease at the earliest and provide prompt treatment. But it often becomes a diagnostic challenge as the initial symptoms of the disease are indistinguishable from bacterial meningitis.\textsuperscript{11} The presence of motile amoebae in cerebrospinal fluid wet mount along with a typical history and clinical picture would most likely confirm the diagnosis. Subsequent identification of the pathogen on Wright-Geimsa staining may also be considered. In our case, we attempted staining the amoeba using
haematoxylin (Figure 2). Diagnostic polymerase chain reaction, immunohistochemistry, indirect immunofluorescence or next-generation sequencing are currently available in advanced centres, which can be used for confirmation. But lack of advanced diagnostic techniques should not delay or limit the diagnosis of primary amoebic meningoencephalitis.

A rapid progression of meningoencephalitis in a patient in spite of initiating protocol-based intravenous antibiotic therapy should always raise an index of suspicion for primary amoebic meningoencephalitis. *N. fowleri* should always be considered in any patient who has purulent meningitis without evidence of bacteria on Gram stain, antigen detection assay or culture. A cerebrospinal fluid wet mount can immediately be performed after a Gram stain to look for any motile amoeba instead of waiting for antigen detection or culture results. Several unidentified cases of primary amoebic meningoencephalitis are mostly misdiagnosed as bacterial meningitis and treated with antibiotics.

Very few survivors have been reported and no specific guidelines have been published for the treatment of primary amoebic meningoencephalitis. Miltefosine, a new antiparasitic drug has been shown to be active against *naegleria* in vitro. Other recommended drugs are amphotericin B and rifampin. A recent study by Gharpure et al. identified 381 cases of primary amoebic meningoencephalitis from 1965 to 2016. Out of the 32 survivors reported, only 7 were laboratory confirmed cases while others had a clinical picture similar to primary amoebic meningoencephalitis but confirmatory testing was not done due to technical limitations. All the seven confirmed survivors received amphotericin B and the majority received a combination of azole with rifampin, azithromycin, miltefosine and/or dexamethasone. Other factors that might have contributed for survival include early identification and treatment using these recommended antimicrobials and effective management of elevated intracranial pressure.

**Conclusion**

Primary amoebic meningoencephalitis is a very deadly disease with over 97% mortality rate, yet frequently misdiagnosed and undertreated. Early recognition of primary amoebic meningoencephalitis is crucial as it has a rapidly deteriorating course and has no empirical treatment options available. Wet mount preparation of cerebrospinal fluid should be routinely performed as it is a simple, fast and inexpensive method to rule out primary amoebic meningoencephalitis in patients with pyogenic meningitis if no bacterial agent is identified on Gram stain.

**Declarations**

**Competing Interests:** None declared.

**Funding:** None declared.

**Ethics approval:** Written informed consent for publication was obtained from the patient or next of kin.

**Gurantor:** Dr. Firosh Khan MD,DNB,DM,DNB, Consultant Neurologist, email: firoskhans@gmail.com

**Contributorship:** VSK performed the microbiological examination of the cerebrospinal fluid, identified the organism, thereby contributing to the diagnosis of the condition, and contributed in writing the manuscript. FK analysed and interpreted the patient condition, had the major contribution in treating the patient and contributed in preparing the manuscript. SJK managed the patient throughout the hospital course, did Lumbar puncture, resuscitated the patient and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

**Acknowledgements:** None.

**Provenance:** Not commissioned; peer-reviewed by Herbert, Oliver Budka, Lloyd.

**ORCID iD:** Santhosh J Kottoor [https://orcid.org/0000-0002-4863-6804](https://orcid.org/0000-0002-4863-6804)

**Supplemental material:** Supplemental material for this article is available online.

**References**

1. John DT. Opportunistic amebae. In: Cox FEG, Wakelin D, Gillespie SH, et al (eds) *Topley & Wilson’s microbiology and microbial infections*. London: Edward Arnold, 2005, pp.226–240.
2. Heggie TW. Swimming with death: *Naegleria fowleri* infections in recreational waters. *Travel Med Infect Dis* 2010; 8: 201–206.
3. Visvesvara GS, Moura H and 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.
4. Chomba M, Mucheleng’anga LA, Fwoloshi S, Ngulube J and Mutengo MM. A case report: primary amoebic meningoencephalitis in a young Zambian adult. *BMC Infect Dis* 2017; 17: 532.
5. Centers for Disease Control and Prevention. *Case report data & graphs | Naegleria fowleri*. See https://www.cdc.gov/parasites/naegleria/graphs.html (last checked 16 June 2020).
6. Matanock A, Mehal JM, Liu L, Blau DM and Cope JR. Estimation of undiagnosed *Naegleria fowleri* primary amebic meningoencephalitis, United States. *Emerg Infect Dis* 2018; 24: 162–164.
7. Prasad K, Varghese N, Biju S, Jiju V and Abraham E. *Naegleria fowleri*. See http://www.journalijdr.com (last checked 16 June 2020).
8. *Primary Amebic Encephalitis in Kerala* [Internet]. [cited 2020 Jun 20]. Available from: http://www.cidsindia.org/
9. Kemble SK, Lynfield R, Devries AS, Beach MJ, Visvesvara GS, Silva AJ, et al. Fatal *Naegleria fowleri* infection acquired in Minnesota: possible expanded range of a deadly thermophilic organism. *Clin Infect Dis* 2012; 54: 805–809.

10. Gompf SG and Garcia C. Lethal encounters: the evolving spectrum of amoebic meningoencephalitis. *IDCases* 2019; 15: e00524.

11. Andrade RM and Reed SL. Amebiasis and infection with free-living amebae. In: Jameson JL, Fausi AS, Kasper DL, Hauser SL, Longo DL and Loscalzo J (eds) *Harrison’s Principles of Internal Medicine*, 20th edn. New York: Mc Graw Hill Education, 2018, pp.1573–1574.

12. Gharpure R, Bliton J, Goodman A, Ali IKM, Yoder J and Cope JR. *Naegleria fowleri*: a global review. *Clin Infect Dis* See https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa520/5830738 (last checked 1 April 2021).