Pathologic Quiz Case

Headache in an 8-Year-Old Child

Joshua D. Stephany, MD; Gary S. Pearl, MD, PhD; Orlando R. Gonzalez, MD

An 8-year-old, 30-kg, previously healthy boy presented with frontal headaches, nausea, fever (40°C), and vomiting. His family denied any history of trauma. Upon further questioning, it was discovered that he had been swimming in a local pond several days prior to admission. His medical history consisted of attention deficit hyperactivity disorder treated with methylphenidate. On admission, laboratory studies disclosed the following values: hemoglobin, 13.4 g/dL; hematocrit, 38.5%; and white blood cell count, 13 100/μL, with a differential of 86% polymorphonuclear neutrophils, 10% lymphocytes, and 4% monocytes. His urinalysis and chemistry profile were within normal limits. A lumbar puncture yielded 2.4 mL of clear, colorless cerebrospinal fluid (CSF) containing 17 red blood cells, 19 white blood cells (74% polymorphonuclear neutrophils, 24% lymphocytes, and 2% monocytes), a glucose level of 56 mg/dL (3.1 mmol/L), a protein level of 0.058 g/dL, and a lactic acid level 3.1 mg/dL. A Gram stain of the CSF demonstrated no organisms. A further workup included a viral screen, a computed tomographic scan, magnetic resonance imaging studies, and an electroencephalogram. None of these tests showed any diagnostic abnormalities. A ventriculostomy was performed to alleviate his elevated intracranial pressure; however, he rapidly deteriorated and died 3 days after admission. An autopsy was performed.

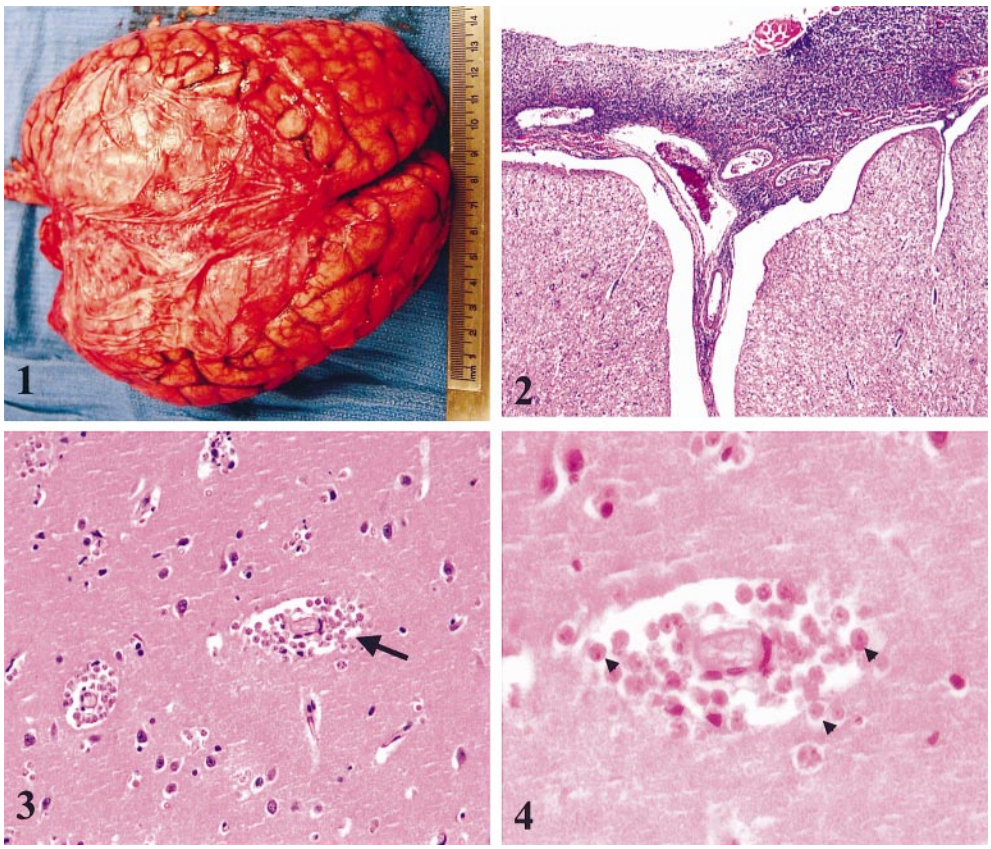
Significant gross autopsy findings included a 1610-g swollen, edematous brain (Figure 1). The meninges were slightly cloudy. Histologic sections of the central nervous system (CNS) stained with hematoxylin-eosin showed a diffuse acute inflammatory infiltrate involving the leptomeninges (Figure 2). Characteristic histiocyte-like cells were identified in the perivascular spaces of the cortical gray matter and basal ganglia (arrows in Figure 3, arrowheads in Figure 4).

What is your diagnosis?

Accepted for publication October 3, 2003.

From the Department of Pathology, Orlando Regional Health Care, Orlando, Fla.

Corresponding author: Joshua D. Stephany, MD, 1414 Kuhl Ave, Orlando Regional Health Care, Department of Pathology, Orlando, FL 32806 (e-mail: jdsmd2@yahoo.com).



Pathologic Diagnosis: Primary Amebic Meningoencephalitis Due to *Naegleria fowleri*

Naegleria fowleri is a ubiquitous free-living ameba with a worldwide distribution. It is the etiologic agent of primary amebic meningoencephalitis and the only *Naegleria* sp known to cause disease in humans.[1] The earliest finding of human disease associated with *N fowleri* dates back to 1937 in Virginia but went unreported until a retrospective study in 1968 by Dos Santos.[2] In 1965, Rodney Carter and Malcolm Fowler of Australia described an infection of the CNS by an ameba that they attributed to the *Acanthomoeba* sp. The organisms were later identified as *N fowleri*. In 1966, Cecil Butt of Florida coined the term *primary amebic meningoencephalitis* and reported the first case in the United States of *N fowleri* causing CNS disease.[3–5]

This organism primarily infects immunocompetent children and young adults who have a recent history of diving or swimming in warm fresh water. It is thermophilic and can survive in water with temperatures up to 45°C.[5] The route of exposure begins by contaminated water being forcibly flushed into the nasal cavity. The organisms penetrate the nasal mucosa and submucosal nerve plexuses and then cross the cribiform plate. They migrate along the mesoaxonal spaces of the unmyelinated olfactory nerve to the subarachnoid space surrounding the olfactory bulb and invade the CNS.[6] High concentrations of oxygen, glucose, and protein in the CSF provide an ideal environment for their rapid growth and reproduction. Once within the CNS, the organism thrives by phagocytosing erythrocytes and leukocytes. It destroys brain tissue by secreting lysosomal hydrolases and phospholipases into its amebostome or food cup, where it digests small portions of brain in a piecemeal fashion. The ameba are capable of killing any cell they come in contact with by secreting destructive heat-stable hemolytic proteins.[7]

Naegleria fowleri has 3 stages in its life cycle. The trophozoite form is pear-shaped, measures 10 to 30 μm, and has a single clear nucleus containing a centrally placed karyosome. It moves via pseudopods and reproduces by binary fission. The trophozoites feed on bacteria in the free state and on blood cells and nervous tissue in the infected host.[5] The trophozoite transforms into a flagellate when challenged by a change in ionic concentration such as distilled water or nonnutrient agar.[7] It encysts when exposed to unfavorable conditions such as cold and can survive for up to 8 months at 4°C. No cyst form is present in infected tissue. Cysts measure 7 to 14 μm and are made up of a single nucleus surrounded by a dense cell wall with one or two flat pores sealed with mucus. The trophozoite form emerges through the pores during more favorable conditions.[8]

As of 1997, 179 cases of primary amebic meningoencephalitis caused by *N fowleri* had been reported worldwide, with 81 cases in the United States. Of the reported case-patients, only 6 have survived.[8] There is no predilection by race. The male-female ratio is 3:1, but this most likely reflects a difference in exposure rather than a true gender-related risk. Healthy children and young adults are affected the most, with the youngest reported age being 8 months.

There is invariably a history of recent exposure to warm fresh water through activities such as swimming or diving. Symptoms usually appear 2 to 5 days after the last exposure and consist of abrupt frontal headache, nausea, vomiting, and altered mental status. Occasionally, there are prodromal symptoms such as altered taste and smell.[6] The disease course is rapid with a fatal result greater than 95% of the time.

The workup for a suspected case of primary amebic meningoencephalitis must be expeditious because of its rapid course and high rate of mortality. The peripheral white blood cell count is elevated. The CSF pressure is elevated. The CSF white blood cell count may be normal early in the infection but is usually elevated to 400 to 26 000 cells/μL with a neutrophilic predominance. Glucose is normal to low, and protein is elevated. A Gram stain will be of little help, as the organisms are destroyed during heat fixation. Antemortem diagnosis is by direct visualization of motile trophozoites in a wet mount preparation of the CSF. Careful examination must be stressed, as the trophozoites closely resemble macrophages in appearance and motility. A definite diagnosis is usually made postmortem. Findings include edema, purulent meningeal exudate, and hemorrhagic necrosis. Histologically, there is an inflammatory infiltrate composed of neutrophils, lymphocytes, and monocytes involving the leptomeninges. Trophozoites are identified throughout the infected nervous tissue mainly in the cortical gray matter and periventricular tissue. The organisms, which resemble macrophages, surround the perivascular spaces of midsize-to-small arteries and arterioles. Trichrome and Giemsa stains are often helpful in elucidating the trophozoites. In 50% of the reported postmortem cases, a neutrophilic myocarditis was identified. No organisms are seen in the cardiac muscle. The etiology of this sterile myocarditis is unknown.[6]

Once primary amebic meningoencephalitis is suspected, treatment must be initiated immediately. A ventriculostomy to relieve pressure serves as only a palliative treatment. Of the 6 known cases of survival, 5 were treated with intrathecal and systemic amphotericin B, and the other was treated with intrathecal and systemic miconazole, rifampin, and sulfisoxazole.

References

1. Martinez AJ, Visvesvara GS. Laboratory diagnosis of pathogenic free-living amoebas: Naegleria, Acanthomoeba, and Leptomyxid. *Clin Lab Med.* 1991;11:861–872.
2. Dos Santos JG. Fatal primary amebic meningoencephalitis: a retrospective study in Richmond, Virginia. *Am J Clin Pathol.* 1970;54:737–742.
3. Butt CG. Primary amebic meningoencephalitis. *N Engl J Med.* 1966;274:1473–1476.
4. Butt CG, Baro C, Knorr RW. Naegleria (sp.) identified in amebic encephalitis. *J Clin Pathol.* 1968;50:568–574.
5. John DT. Primary amebic meningoencephalitis and the biology of Naegleria fowleri. *Annu Rev Microbiol.* 1982;36:101–123.
6. Ma P, Visvesvara GS, Martinez A, Theodore F, Daggett PM, Sawyer TK. Naegleria and Acanthomoeba infections: review. *Rev Infect Dis.* 1990;12:490–513.
7. Marciano-Cabral F. Biology of Naegleria spp. *Microbiol Rev.* 1988;52:114–133.
8. Martinez AJ, Visvesvara GS. Free living, amphozoic, and opportunistic amebas. *Brain Pathol.* 1997;7:583–598.