Balamuthia mandrillaris meningoencephalitis: survival in a pediatric patient

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**abstract**

*Balamuthia mandrillaris* infections are rare and almost always fatal. This ameba is a naturally occurring soil inhabitant that can cause disease in immunocompetent hosts, with early diagnosis typically proving difficult. We recently cared for a previously healthy 2-year-old boy who was diagnosed with meningoencephalitis secondary to *B. mandrillaris* relatively early in his presentation, which enabled us to initiate targeted antimicrobial therapy. Since discharge from the hospital the child has shown slow, steady improvement with dramatic improvements seen on follow-up brain imaging. Our observations suggest that early diagnosis and treatment may significantly reduce mortality and morbidity rates from this highly virulent organism. *Pediatrics* 2010; 125:e699–e703
Infection with *Balamuthia mandrillaris* has been rarely reported in the pediatric population. This protozoan causes significant morbidity and mortality, with almost all cases resulting in death. No age group or geographic area has been spared. Presenting symptoms are nonspecific, and failure to initiate early treatment seems to significantly contribute to the severe morbidity and mortality seen with these infections.

We describe here a 2-year-old boy admitted with abnormal eye movements and unsteady gait. MRI showed multiple areas of hypodensity throughout the cerebral hemispheres suggestive of an infectious or a malignant process. Brain biopsy revealed a necrotizing granulomatous meningoencephalitis with microscopic evidence of amoebic profiles. Additional pathology specimens were reviewed by the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, which confirmed that the offending agent was *B. mandrillaris*. We believe that early identification of the organism and prompt administration of targeted antimicrobial therapy allowed our patient to survive and significantly diminished his morbidity.

**CASE REPORT**

A previously healthy 2-year-old boy was taken to an outside hospital because of vomiting and diarrhea. Examination revealed moderate dehydration that necessitated admission. Initial laboratory values were normal. Despite being made nil per os and receiving intravenous fluids, his vomiting and diarrhea persisted. Repeat chemistries showed a serum sodium level of 132 mEq/L, and the child was transferred to our facility. After administration of intravenous fluids the child improved, his serum sodium level returned to normal, and he was discharged from the hospital within 2 days. Twenty-four hours later the child was readmitted because of drowsiness, gait ataxia, frequent falls, and abnormal eye movements. Examination revealed lethargy, a left esotropia, disconjugate eye movements, and nystagmus on lateral gaze. Routine laboratory study results were normal except for a serum sodium level of 129 mEq/L. Electroencephalography showed diffuse, generalized slowing consistent with a toxic or metabolic encephalopathy. A computed tomography (CT) scan of the brain showed an area of hypodensity in the region of the left basal ganglia associated with surrounding edema. Brain MRI revealed multiple intraparenchymal lesions with surrounding edema consistent with neoplasm or infection (Fig 1). Cerebrospinal fluid (CSF) examination performed on hospital day 2 showed a pleocytosis of 178 white blood cells (WBCs) with lymphocytic predominance (93% lymphocytes) and a protein level of 251 mg/dL. Repeat CSF examination on hospital day 3 again revealed a lymphocyte-predominant pleocytosis (143 WBCs; 98% lymphocytes), protein level of 239 mg/dL, and glucose level of 20 mg/dL. Appropriate stains and cultures of CSF samples showed no bacteria, fungi, or protozoa. A tuberculin skin test and gastric aspirates for acid-fast bacilli were also negative. Empiric treatment for disseminated tuberculosis with

![FIGURE 1](A, Representative axial T1 images after intravenous administration of a gadolinium contrast agent, from inferior to superior (left to right). There is nodular enhancement (arrows) coating the surface of the ventricles and extending out the foramen of Luschka. There are also several intensely enhancing parenchymal lesions (arrowheads). B, An axial fluid-attenuated inversion recovery (FLAIR) image shows significant edema (arrows) associated with the parenchymal lesions. C, Midline sagittal T1 image after intravenous administration of a gadolinium contrast agent shows the intense enhancement within and lining the anterior aspects of the third and fourth ventricles (arrows), as well as within the hypothalamic region (arrowheads).)
isoniazid, rifampin, pyrazinamide, and ethambutol was initiated. By the fourth hospital day the child developed choreoathetoid movements and worsening disconjugate eye movements. CSF from a third lumbar puncture on hospital day 5 was analyzed by using flow cytometry and revealed plasma cells and activated T cells consistent with a reactive or infectious process. He subsequently became lethargic and nonverbal and refused to eat.

Brain biopsy was performed on hospital day 7 and showed a free-living ameba later identified as *B mandrillaris* (Fig 2). Antituberculous therapy was discontinued, and the child was placed on a regimen of pentamidine (4 mg/kg per day), fluconazole (12 mg/kg per day), flucytosine (150 mg/kg per day), sulfadiazine (200 mg/kg per day), clarithromycin (14 mg/kg per day), and thioridazine (0.5 mg/kg per day). Quantitative immunoglobulins were collected, and levels were normal. Repeat brain MRI showed mild ventricular enlargement, inflammation of the basilar cisterns, and persistent parenchymal lesions.

The child continued to deteriorate and was placed on a ventilator. On the 14th hospital day, brain MRI revealed significant obstructive hydrocephalus requiring a ventriculoperitoneal shunt. The patient slowly improved over the next 2 months and was removed from the ventilator on hospital day 62. He remained poorly responsive but was stable enough to be transferred to a rehabilitation facility. Treatment for amebic encephalitis has been continued with clarithromycin, sulfadiazine, flucytosine, and fluconazole.

At his last infectious disease clinic follow-up ~22 months after his initial presentation, he continued to show gradual improvement without evidence of active disease and continued participation in outpatient rehabilitation. At the time of discharge from his initial hospitalization he was unable to follow commands, communicate, or walk. Since then he has shown improved postural stability, developed a social smile, will follow simple commands, and is attempting speech.

Subsequent brain MRI has shown marked improvement with decreases in both the size and number of ring-enhancing lesions throughout the cerebral hemispheres (Fig 3). Additional brain MRI has been scheduled for 1 month after this last physician encounter. After receiving results of this scan, documentation of recent visits from other specialists (including child neurology and rehabilitative medicine), and consultation with experts at the CDC, a decision will be made concerning a timetable for tapering antimicrobial therapy and the longevity of antimicrobial therapy, which will be particularly challenging because of the lack of information regarding this disease process in the few patients who have survived infection.

**DISCUSSION**

*B mandrillaris* has been known as a distinct clinical entity since 1986.1,2 This ameba is difficult to culture, and diagnosis usually requires indirect immunofluorescence staining. *Balamuthia* is known to cause disease in both immunocompetent and immunodeficient patients but has rarely been reported in the young. Infections seem to have no seasonal or geographic variation, and cases have been reported worldwide.3 *Balamuthia* is a soil ameba that is likely transmitted by inhalation of airborne cysts or acquired through a break in the patient’s...
skin with hematogenous spread to the central nervous system (CNS). Uncertainty exists whether water can serve as an effective vehicle for transmission as it does for *Naegleria fowleri* and *Acanthamoeba* infections. Disease prevention and control is poorly understood, with no clearly delineated ways of preventing infection with this ameba. Patients can present with a wide range of symptoms that, when coupled with the often insidious nature of the disease, make early diagnosis and treatment difficult.

We attempted to define common clinical features of *Balamuthia* infections by reviewing all reported cases from the English literature during the past 10 years by performing a Medline search. Our search revealed 14 applicable publications that described patients who were found to have infections caused by *Balamuthia*. Fifteen of the 29 cases reported during this time period were of children aged 1 to 12 years, with only 1 reported survivor. Presenting symptoms varied widely, with children presenting with seizures, headaches, fever, otitis media, vomiting, and abdominal pain. Empiric therapy against CNS *Mycobacterium tuberculosis* infection and herpes simplex virus (HSV) infection was commonly used in the treatment of these patients. Diagnostic testing was also commonly performed to rule out the possibility of a malignant CNS lesion. The only previously reported surviving pediatric patient presented with generalized seizures and fever. The child was a Hispanic girl who traveled frequently to Mexico but had a benign past medical history and current immunizations. She received empiric treatment for HSV encephalitis with acyclovir for 21 days and seemed to improve. Initial CSF analysis showed a pleocytosis (WBC count: 162 cells per µL, with 65% neutrophils, 27% lymphocytes, and 8% monocytes), glucose level of 73 mg/dL, and protein level of 41 mg/dL. An electroencephalogram was also obtained, which showed focal changes within the left temporal lobe. CSF cultures for bacterial, viral, fungal, and protozoan infections were all negative, as were polymerase chain reaction assays for HSV-1 and enterovirus. Brain MRI obtained 19 days after her presentation revealed 2 large ring-enhancing lesions surrounded by edema in the left parietal and temporal lobes. CT-guided biopsies revealed acute suppurative and necrotizing inflammation with structures present consistent with amebas. After a second evaluation in Mexico an excisional biopsy was performed. Tissue sent to the CDC confirmed infection with *B. mandrillaris*. While in Mexico the patient was treated with ketoconazole and metronidazole. After returning to the United States her examination was significant only for a mild dysphasia. Her previous drug regimen was discontinued, and clarithromycin and flucytosine were begun and later changed to azithromycin, flucytosine, fluconazole, thioridazine, and pentamidine. Serial MRI and CT scans of the patient showed a gradual resolution of the edema surrounding the 2 ring-enhancing lesions. The patient had no gross neurologic sequelae but was reported to have experienced moderate performance problems in school.

Unlike the previous survivor, our patient had a more fulminant course with rapid deterioration and organ fail-

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**FIGURE 3**

Follow-up MRI 15 months after treatment. A. Shown are representative axial T1 images after intravenous administration of a gadolinium contrast agent, from inferior to superior (left to right). There has been complete resolution of pathologic enhancement within the parenchyma and coating the surface of the brain/ventricles. B, An axial fluid-attenuated inversion recovery (FLAIR) image demonstrates resolution of edema associated with the parenchymal lesions. Changes within the frontal lobes are present from a previous ventriculostomy. C, A midline sagittal T1 image after intravenous administration of a gadolinium contrast agent shows resolved enhancement within the ventricles and the hypothalamic region.
ure. It was fortunate that specific therapy against *Balamuthia* was begun within 10 days of presentation, which we believe was key to the patient’s ability to survive an otherwise lethal infection.

Among all age groups there have been 4 reported survivors in the United States, and they have had varied outcomes. All were able to return home and participate in activities of daily living. Of the reports that have documented specific antimicrobial treatment regimens, all have shown similar treatment regimens consisting of pentamidine, fluconazole, flucytosine (5-fluorocytosine), sulfadiazine, and a macrolide antibiotic (azithromycin or clarithromycin). The lone pediatric patient was also treated with thioridazine. No author has yet commented on a finite duration of treatment, because all documented survivors remained on antibiotics at the time of reported follow-up.

Our patient was initially treated with all the aforementioned antimicrobial agents, with discontinuation of pentamidine secondary to hyperglycemia and thioridazine secondary to worsening hyponatremia. We have been unable to identify a source or cause of infection in our patient. The child displayed symptoms consistent with viral gastroenteritis before his admission. He was previously healthy without any significant previous medical history. Our patient represents only the second pediatric survivor documented in this country in the last 10 years. Recent reports have suggested that the incidence of *Balamuthia* encephalitis has increased in the United States. Infection seems to disproportionately affect Hispanic individuals and may be underreported in areas where surveillance mechanisms are not readily available.

Our experience and review suggest that *Balamuthia* infections should be considered in children who present with an atypical encephalitis and MRI findings of multiple parenchymal lesions with surrounding edema. Cerebral biopsy may lead to early diagnosis resulting in prompt treatment with increased survival and less morbidity.

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