Neurosurgical intervention in the diagnosis and treatment of *Balamuthia mandrillaris* encephalitis

Report of 3 cases

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The authors describe the unique presentation of *Balamuthia mandrillaris* encephalitis in a kidney donor and two recipients. All three patients suffered acute clinical deterioration, with radiological or clinical evidence of intracranial hypertension. Brain autopsy in the donor and an urgent brain biopsy in a recipient established the diagnosis. First-tier therapy, with mannitol and CSF drainage, successfully treated the intracranial hypertension in both recipients, while administration of a combination of antiamebic drugs was associated with survival in the second recipient. For both recipients, neurosurgical management played a critical role in the rapid diagnosis and treatment of *Balamuthia mandrillaris* encephalitis. (DOI: 10.3171/2011.4.JNS102057)

**KEY WORDS** • *Balamuthia mandrillaris* encephalitis • intracranial hypertension • infection

*Balamuthia mandrillaris* is a free-living ameba that has been identified as a cause of encephalitis in approximately 200 patients since 1991.5,20 The diagnosis of this rare entity is difficult because clinical presentation mimics other forms of encephalitis, and serum and CSF studies as well as neuroradiological examinations are nonspecific. Although a real-time PCR assay has been developed, it is not commercially available, and the definitive diagnosis remains limited to histological or indirect immunofluorescent examinations of brain tissue.14,19,20,24 These clinical hurdles have prevented effective therapeutic strategies, resulting in a mortality rate exceeding 90%.

The role of neurosurgery has been limited to brain biopsy in seriously ill patients, whereas the pathophysiological effects of intracranial hypertension and its treatment have not been analyzed to any extent.18 This report describes the clinical presentations in three patients with *Balamuthia mandrillaris* encephalitis—a kidney donor and two recipients—and the neurosurgical management of the recipients.

**Case Reports**

A 4-year-old boy presented with a 5-day history of a low-grade fever, isolated seizure, and normal findings on neurological examination. There was a history of a febrile illness 1–2 weeks prior to admission that was diagnosed by a rapid influenza test as influenza A and treated with antiviral medication. On admission, MR imaging demonstrated scattered areas of T2, FLAIR, and postcontrast T1 signal changes involving bilateral occipital and left frontoparietal cortices, with nodular enhancement after Gd injection (Fig. 1). Cerebrospinal fluid studies showed a glucose level of 49 mg/dl (normal 40–70 mg/dl), a protein level of 29 mg/dl (normal 12–60 mg/dl), with a WBC count of 170 (76% lymphocytes). Gram stain was negative, as were cultures for bacteria, fungi, and tuberculosis. Cerebrospinal fluid cytology showed a reactive pleocytosis. The patient’s fever resolved and he was discharged home within 3 days. The child returned seven days later, showing agitation, multiple seizures, and low-grade fever. The results of serum and CSF studies were normal, except for a persistently elevated CSF WBC of 150 (85% lymphocytes). A multiple sclerosis panel showed a CSF/serum immunoglobulin ratio of 1.11 (normal 0.17–0.66). Follow-up MR imaging demonstrated increasingly prominent and more diffuse enhancement of the preexisting cortical lesions. Studies for the presence of *Cryptococcus*, herpes simplex, retrovirus, and arbovirus were negative. A tentative diagnosis of acute disseminated encephalomyelitis resulted in the administration of intravenous methylprednisolone. The patient’s level of consciousness deteriorated over the next 5 days. Intravenous immuno-
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![Fig. 1. A, B, and C: Axial T2-weighted, FLAIR, and T1-weighted postcontrast MR images obtained in the kidney donor showing cortical/subcortical signal changes, with nodular enhancement.](image)

globulin was started, but the patient’s condition continued to worsen until Day 10, when he lapsed into a coma. A CT scan showed effacement of the basilar cisterns, focal subarachnoid hemorrhage, and tonsillar herniation. Brain death was declared the following day, and the organs were recovered for kidney donation. Autopsy confirmed death was declared the following day, and the organs were recovered for kidney donation. Autopsy confirmed the radiological findings.

The kidney recipients developed headaches and seizures 20 and 21 days following transplantation. Both patients received immunosuppressive therapy; both were admitted 23 days following transplantation and both were placed on multiple antibiotics. Cerebrospinal fluid findings on the day of admission in the first recipient showed an elevated glucose level of 114 mg/dl and a mild elevation of protein level to 75 mg/dl. The WBC was 3. The CSF in the second recipient showed a normal glucose level and a protein level of 74 mg/dl with a WBC of 19 (28% polymorphonuclear leukocytes, 29% lymphocytes, and 17% monocytes). On Day 23 MR images were obtained in the second recipient and on Day 25 in the first recipient. Both studies demonstrated multiple scattered, enhancing masses with surrounding signal changes in both supra- and infratentorial compartments, primarily involving cortices and adjacent subcortical white matter. These findings were similar in appearance to features on the donor’s MR images (Fig. 2).

The neurological condition of the first recipient, a 31-year-old female, with endstage renal disease, secondary to diabetes mellitus and hypertension, deteriorated just prior to and after admission. On posttransplant Day 26, she underwent an urgent brain biopsy of the right temporal lobe. In collaboration with the Centers for Disease Control, the autopsy tissue of the donor and the brain biopsy tissue of this recipient were examined. A diagnosis of *Balamuthia mandrillaris* encephalitis was made the following day from histopathological and immunohistochemical examinations (Fig. 3) and PCR assay. The patient was given pentamidine, sulfadiazine, flucytosine, fluconazole, and azithromycin; miltefosine was added on Day 35. During surgery, the brain was markedly swollen, but it responded to the administration of mannitol. First-tier therapy with mannitol was continuously administered after surgery, but her condition deteriorated and an EVD was placed on Day 28. The opening pressure was 9 mm Hg. Intermittent CSF drainage was used for ICP control over the next 5 days, following which there were no additional problems. She remained in coma until her death on Day 75.

The second recipient, a 27-year-old man, with endstage renal disease, secondary to focal segmental glomerulosclerosis, improved following admission, but his level of consciousness acutely deteriorated on Day 27 to a Glasgow Coma Scale score of 4. Antiamebic therapy similar to that of the first recipient was started; insertion of an EVD revealed an opening pressure of 40 mm Hg. Cerebrospinal fluid diversion controlled the intracranial hypertension until Day 32, at which time the elevated pressure resolved. On Day 39, a CSF sample was sent to the Centers for Disease Control; *Balamuthia mandrillaris* was confirmed by PCR assay on Day 46. *Balamuthia* was cultured from the fluid on Day 74. The patient’s condition improved slowly. On Day 126, MR imaging revealed hemorrhagic ring enhancement of the previous lesions, with minimal decrease in surrounding vasogenic edema (Fig. 4). Following rehabilitation, the patient was discharged on Day 199, with a GOS score of 3, to family care.

**Discussion**

Previously regarded as an innocuous soil organism, the ameba *Balamuthia mandrillaris* was isolated in 1990 from brain tissue of a pregnant mandrill baboon, who died of hemorrhagic encephalitis. The first 2 cases of human encephalitis were reported the following year.

In the initial case, a 36-year-old American man, who was an intravenous drug user, with undiagnosed HIV, received dexamethasone and antibiotics for a suspected encephalitis. The patient died 23 days after onset of symptoms that included headaches, nausea, fever, and eventually deterioration in his level of consciousness. The second patient, a 12-year-old Argentinian boy, had a 2-year history of maculopapular facial skin lesions diagnosed by biopsy examination as lupus vulgaris. After 6 months of antibiotic treatment, the diagnosis was revised to sarcoid, for which he received prednisone. The patient’s neurological condition deteriorated abruptly and he died 14 days after the onset of neurological symptoms. Over the past 19...
years, approximately 200 cases have been reported, with 11 survivors, including the patient in this report. The taxonomy, life cycle, ecological distribution, and epidemiology of this organism have been outlined in detail.20

The 2 index cases, subsequent case reports, and the patients in this report exhibited several common patterns in this infection. First, immunocompromised patients or patients receiving immunosuppressant agents have a significant risk for infection or rapid progression of the illness. While Balamuthia encephalitis has occurred in immunocompetent patients, particularly children and adolescents, the suppression of antibody production may lead to rapid clinical decline, as seen in the patients in this series.19–21 Second, the infection in the recipients presumably spread by blood via the host kidney cells, supporting experimental work showing that Balamuthia grows well in monkey kidney (E6) cells or African green monkey fibroblast-like kidney (CoS-7) cells.20 More common portals of entry include skin or respiratory tract, presumably due to contamination from water or soil.19–21

The amebae, however, are ubiquitous and in many instances the portal of entry cannot be determined. Interviews with the donor’s family indicated that the child had lived in Kentucky, Florida, and Mississippi before onset of symptoms, with soil and water exposure in all 3 locations. There was no clinical evidence of skin, pulmonary, or kidney lesions. Interestingly, the donor’s heart and liver were transplanted into 2 other recipients, without evidence of infection. Finally, initial diagnoses are clouded by considerations of more common illnesses, such as acute disseminated encephalomyelitis in the donor. Clinical, laboratory, and neuroradiological examinations are non-specific. Histological examinations, including electron microscopy of brain tissue, can achieve a rapid diagnosis, but require experienced neuropathological analyses. Indirect immunofluorescent and PCR assays are specific and rapid, but available in few laboratories whereas tissue culture is time consuming. The sensitivity and specificity of serum and CSF titers, particularly in immunosuppressed patients, have not been determined.19,20

Other than the unique passage of the infections from kidney donor to 2 recipients, there are several unusual clinical characteristics in these patients. Balamuthia mandrillaris encephalitis has been characterized as a chronic granulomatous infection lasting 3 months to several years. The time frame from initial symptoms to death or coma in the patients in our series was 25–27 days, although several reports, including the index cases, described periods of 14–66 days. What is apparent from many studies is that the deterioration of the level of consciousness to coma can be followed by long periods of survival to death, as seen in the first recipient. Thus, neurological deterioration is an ominous prognostic sign. In the 11 survivors with adequate clinical descriptions, 3 progressed to coma. All 3, including the second recipient in the present series, were left with significant neurological deficits—that is, a GOS score of 2 in one and a GOS score of 3 in two. These data indicate that the time window for the initiation of treatment is

**Fig. 2.** Axial FLAIR and T1-weighted postcontrast MR images obtained in the first kidney recipient (A and B) and the second kidney recipient (C and D). Images demonstrate cortical/subcortical enhancing lesions bilaterally, some of which show ring enhancement. There is mild leptomeningeal enhancement noted (D).

**Fig. 3.** Balamuthia mandrillaris in patient specimens. A: Brain autopsy specimen acquired in the kidney donor. The organisms appeared as scattered cells with cytoplasmic vacuoles loosely clustered around the thin-walled blood vessel. PAS, original magnification x 200. B: Brain biopsy obtained in a kidney recipient. Amebae are in dense aggregates, again arranged around a capillary. PAS, original magnification x 100. C: Closer view of the image in B showing the prominent vacuoles and nucleosomes in the ameba. PAS, original magnification x 400. D: Brain autopsy specimen obtained in a kidney donor. Perivascular amebea labeled by an antibody to Acanthamoeba/Balamuthia, original magnification x 100. (A subsequent PCR assay amplified antigens specific for Balamuthia mandrillaris.)
small. The index of suspicion must be high, and rapid diagnosis, including brain biopsy, is essential for functional recovery.

The clinical patterns in our patients may offer several clues to the diagnosis. The donor and second recipient presented with normal or slightly altered levels of consciousness, while in the first recipient deterioration occurred just prior to admission. Magnetic resonance images taken within several days of presentation showed similar multiple, scattered lesions, with nodular enhancements throughout the brain. These findings were particularly evident on the FLAIR sequences. Although these images were not specific for *Balamuthia* encephalitis, the MR imaging findings, coupled with the high level of consciousness, may indicate a potential physiological instability prior to rapid generalized structural damage to the CNS. The characteristic ring enhancement and restricted central cortical diffusion within the center of the lesion, as seen in the second recipient several months into treatment, may be a late finding, indicating an adequate immune response or pharmacological control of the infection. These latter MR imaging findings have been seen in long-term survivors irregardless of their neurological condition.

The rapid neurological decline in all the patients in the series was associated with intracranial hypertension. The CT scan obtained in the donor documented tentorial herniation that was confirmed at autopsy. Just prior to and after admission, the first recipient exhibited precipitous decline that was associated with marked temporal lobe swelling at the time of biopsy. This swelling responded to the administration of mannitol, which was continued after surgery. The patient’s condition continued to decline, however, and an EVD was inserted, which indicated an opening pressure of 9 mm Hg. For the next 4–5 days, intermittent CSF diversion successfully controlled the intracranial hypertension until the pressure spikes ceased. The second recipient did not receive mannitol. An EVD inserted at the time of his neurological decline registered an opening pressure of 40 mm Hg. Intermittent CSF drainage controlled intracranial hypertension over the next 7 days until the pressure reverted to normal levels. Because the patients’ neuroradiological studies did not show ventriculomegaly, the rapid neurological decline and intracranial hypertension may be attributed to a generalized vasogenic edema triggered by the breakdown of the microvasculature and blood-brain barrier. One patient described in a prior report, a 32-year-old Mexican man, exhibited this pattern. This possible mechanism corroborated the MR imaging findings of multiple lesions throughout the brain in all patients and it confirms the angiotropism by the ameba that has been demonstrated in numerous histopathological studies, including the index cases. There are, however, other reports that have shown intracranial hypertension produced by solitary mass lesions, occasionally associated with brain biopsy or acute ventriculomegaly. Due to incomplete reporting, the incidence of high ICP associated with fatalities cannot be calculated with certainty, but treatment in every case was initiated following the onset of coma. Two of three survivors, who progressed to coma, required treatment for intracranial hypertension. These data suggest that high ICP may be more common in *Balamuthia* encephalitis than is generally recognized and can be produced by several pathophysiological mechanisms, leading to a rapid decline in the level of consciousness. Finally, because amebae have been found in the CSF in several previous cases, the risk of seeding the ventricles with ameba by the placement of an EVD through infected tissue cannot be proven in our second recipient. In all circumstances, this potential risk must be weighed against the benefit of rapid reduction of intracranial hypertension.

The two kidney recipients received pentamidine, sulfadiazine, flucytosine (5-fluorocytosine), fluconazole, azithromycin, and mifepronosine for treatment of *Balamuthia* encephalitis. The latter drug was administered through an emergency investigational new drug protocol. Other antiamebic regimens have been used in survivors, and a lengthy list of antimicrobials that show in vitro sensitivity to *Balamuthia mandrillaris* isolates has been outlined. One survivor required continued therapy over 5 years; the second recipient remains on sulfadiazine and azithromycin 11 months after transplantation (K. Kokko, personal communication, August 30, 2010). These extensive therapeutic efforts underscore the need for continued investigation into the management of this forbidden infection.

**Conclusions**

These three cases of *Balamuthia mandrillaris* encephalitis corroborated reports that demonstrated the significant risk of infection in immunosuppressed patients, and the difficulty in the diagnosis of a rare infection, with nonspecific clinical presentation, laboratory, and neuroradiological findings. The cases also showed the potential of a rapid decline in the level of consciousness and the poor prognosis in comatose patients.

The patients in this series also exhibited clinical patterns that may aid in diagnosis and treatment. Early stages of the infection include symptoms of headaches, with signs of low-grade fever, isolated seizures, focal neurological deficits, and normal or slightly altered level of consciousness associated with multiple enhancing lesions, particularly evident on the FLAIR sequences of the MR images throughout the brain. The discontinuity
between the level of consciousness and neuroradiological findings suggests the need for rapid diagnosis that includes brain biopsy in collaboration with a laboratory capable of testing for the presence of \textit{Balamuthia mandrillaris}. Monitoring of ICP or the placement of an EVD associated with antiamebic therapy should be considered for these patients with potentially unstable symptoms.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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**Addendum**

Based on genetic sequencing, the genus \textit{Balamuthia} is closely related to \textit{Acanthamoeba}, and it is placed in the family Acanthamoebidae. There is one species in this genus. The genus is named for Professor William Balamuth (1914–1981), a respected protozoologist and academic mentor, who taught at the University of California, Berkeley.$^{16}$

**References**


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