MAJOR ARTICLE

Successful Treatment of *Balamuthia* Amoebic Encephalitis: Presentation of 2 Cases

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Case histories are presented of 2 individuals (a 5-year-old girl and 64-year-old man) who developed encephalitis caused by the free-living amoeba *Balamuthia mandrillaris*. Both individuals survived after diagnosis and initiation of effective antimicrobial therapy. Immunostaining for *Balamuthia*-specific antibody levels identified the causative agent of the infections. Antimicrobial therapy with flucytosine, pentamidine, fluconazole, sulfadiazine, and a macrolide antibiotic (azithromycin or clarithromycin) was initiated. Phenothiazines (thioridazine and trifluoperazine) were also used. Both patients recovered, and there was no evidence of recrudescence of the disease at 2 and 6 years after onset of symptoms. Awareness of *Balamuthia* as the causative agent of encephalitis and early initiation of antimicrobial therapy were critical to the recovery of both patients. Although optimal antimicrobial therapy for *Balamuthia* amoebic encephalitis has yet to be determined, the antimicrobials used in these 2 cases effectively controlled the disease. These 2 individuals are the only known survivors of this otherwise fatal type of amoebic encephalitis.

Balamuthia mandrillaris is a free-living amoeba that is found in soil and is responsible for ~100 published cases of amoebic encephalitis globally, approximately one-half of them in the United States. The disease was first recognized ~12 years ago after a pregnant mandrill baboon died at the San Diego Wild Animal Park (San Diego) and the causative agent was isolated in culture and characterized [1, 2]. The earliest case descriptions in humans involved immunocompromised individuals, including those with HIV infection/AIDS, alcohol and drug abusers, and individuals with concurrent disease [1, 3–8]. More recently, the bulk of cases appearing in the literature have involved children [9–18]. In addition to the above-mentioned baboon, *Balamuthia* encephalitis has been diagnosed in other primates [19, 20], as well as in a horse [21] and a sheep [1]. The disease, which is difficult to differentiate from other types of encephalitis, has an insidious course, resulting in death in weeks to months after infection.

In soil, the amoeba may exist in a trophic (feeding) state or, more likely, as a dormant, thick-walled cyst [22]. Infection can result from soil contamination through a break in the skin or from carriage of cysts on wind-blown soil particles to the respiratory tract. In either case, the amoebas that emerge from the cysts are hematogenously transported to the CNS, where they cause a type of granulomatous encephalitis [3, 23]. Several cases have been reported of development of amoebic encephalitis from primary granulomatous facial lesions [11, 16, 18, 24].

Most diagnoses of *Balamuthia* encephalitis are made after death, on the basis of detection of amoebas by indirect immunofluorescence (IIF) or conventional staining of brain tissue obtained during autopsy [1, 2]. Treatment is problematic, and the optimal antimicrobial therapy has yet to be determined. We present here

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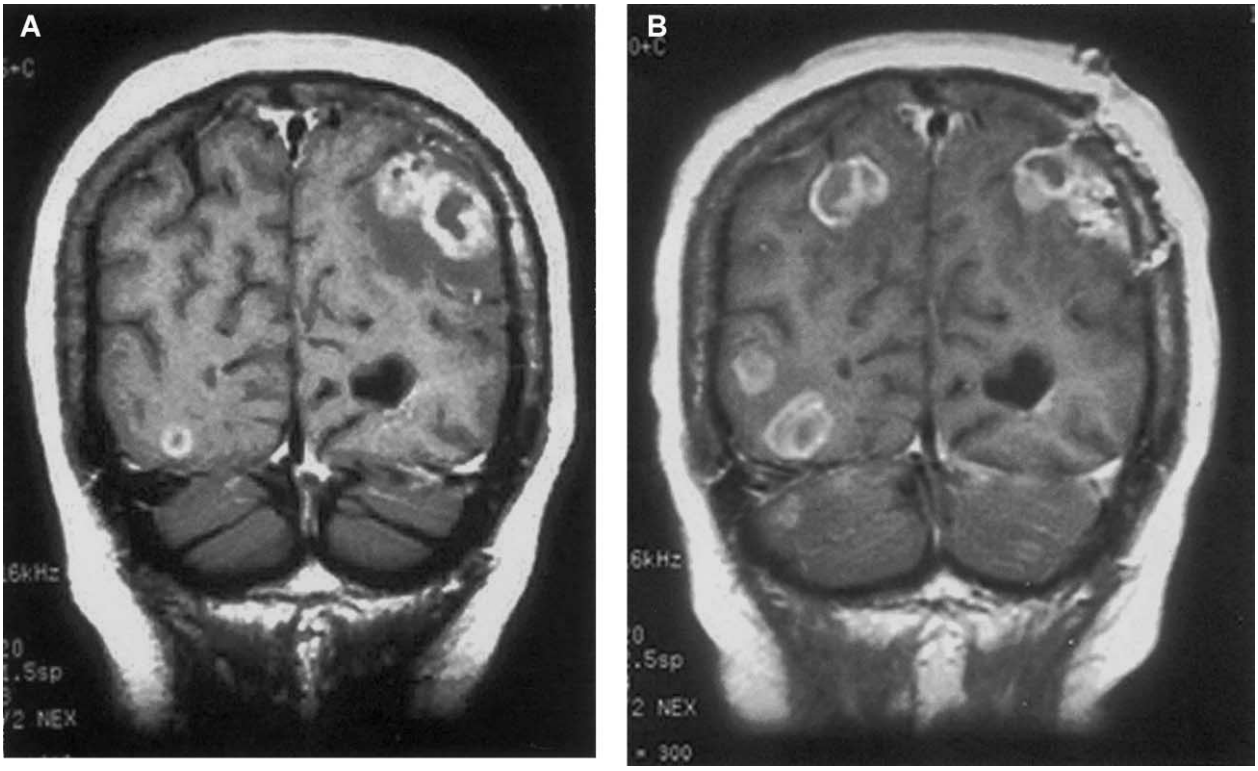

Figure 1. MRI of a 64-year-old white man with *Balamuthia* amoebic encephalitis (case 1). *A,* MRI obtained on initial presentation, showing 2 ring-enhancing lesions, one in the left parietal region and the other in the right occipital lobe. *B,* MRI obtained ~22 days after initial presentation. The parietal and occipital lesions have increased in size, and several additional lesions are seen.

2 case histories, one of a 64-year-old man and the other of a 5-year-old girl, both California residents, who received diagnoses of *Balamuthia* encephalitis and who were successfully treated for this almost invariably fatal disease.

METHODS

IIF. IIF staining was used to identify *Balamuthia* amoebas in brain and skin tissue obtained through biopsy. Unstained sections were deparaffinized and treated with anti-*Balamuthia* serum raised in a rabbit, followed by fluorescein isothiocyanate (FITC)–conjugated goat anti-rabbit serum, as described elsewhere [1, 2]. Control staining was done for *Naegleria* and *Acanthamoeba,* 2 other free-living amoebas implicated as causative agents of encephalitis.

IIF staining was also done with acute-phase (or "initial") and convalescent-phase (or "later") serum samples from both patients. Three different clinical isolates of *Balamuthia* (1 isolated from the above-mentioned baboon and 2 from human cases) were pooled, formalin fixed, and deposited to dry on Teflon-coated multiwell slides. Serum samples, diluted from 1:2 to 1:4096, from the 2 patients we describe were applied to the wells, followed by washing and treatment with FITC-conjugated goat anti-human serum. Positive- and negative-control serum samples were run simultaneously. Stained preparations were examined with a fluorescence microscope.

CASE REPORTS

Case 1 (Santa Cruz County, CA). A 64-year-old white man who had been in good health presented with progressive onset of right-side hemiparesis and speech difficulty. He had a focal seizure in the emergency department, where a CT scan revealed a low-density left parietal lobe brain lesion. MRI confirmed the presence of 2 lesions, a left parietal lesion 3 cm in diameter and a smaller, right occipital ring-enhancing lesion (figure 1*A*). Two weeks earlier, a biopsy had been performed on a persistent raised lesion (1.6 × 1.5 cm) on the patient's right forearm. This lesion resulted from the patient's being pricked by a thorn from a rosebush while he was working in his backyard. The tissue revealed chronic inflammation with multinucleated giant cells, and the diagnosis was of a chronic inflammatory nodule with foreign body reaction.

The patient's medical history included ankylosing spondylitis, myocardial infarction, glaucoma, and depression. The family medical history included tuberculosis in the patient's father

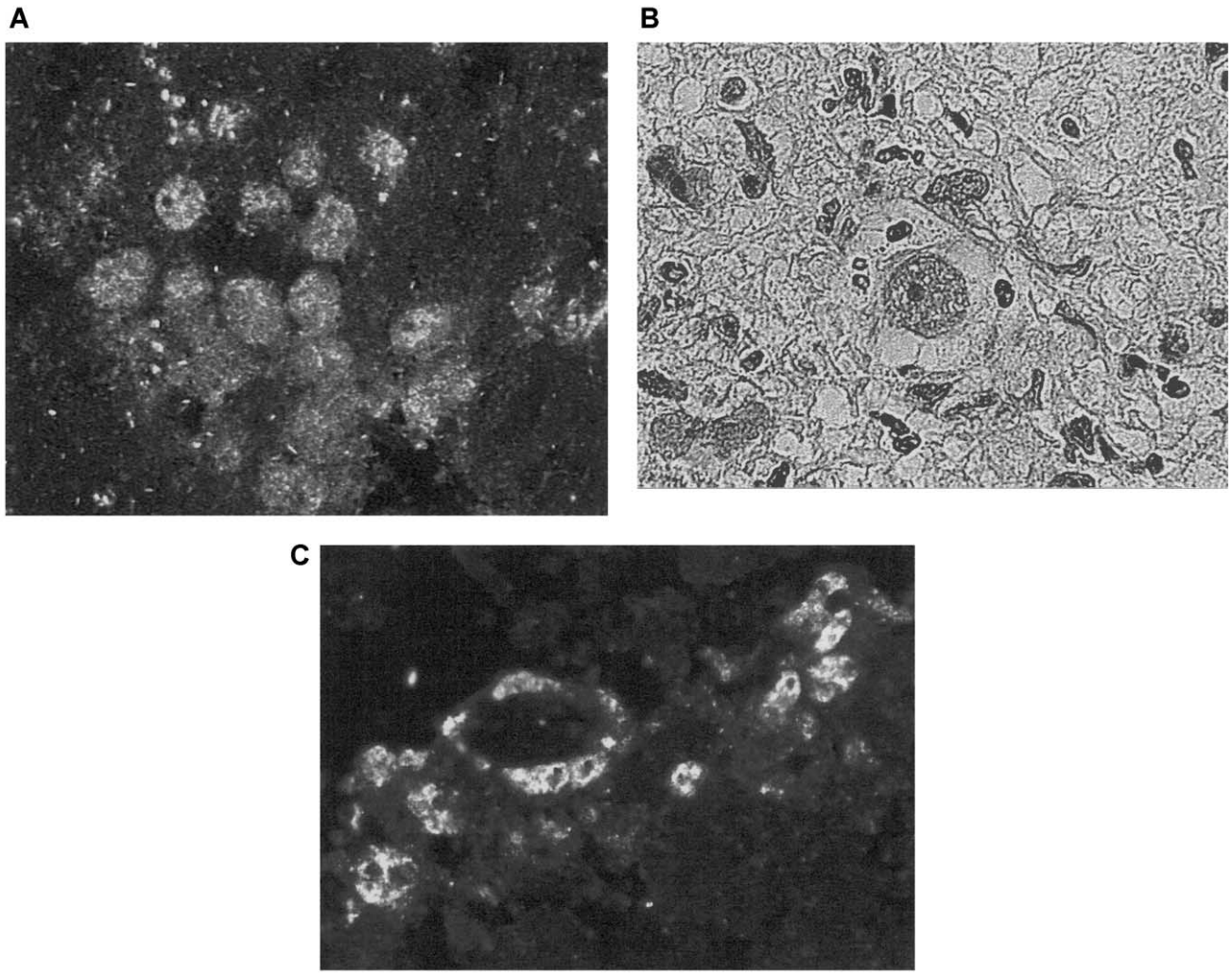

Figure 2. Indirect immunofluorescence– and hematoxylin-eosin–stained tissue sections from a 64-year-old white man (case 1; *A* and *B*) and a 5-year-old Hispanic girl (case 2; *C*) with *Balamuthia* amoebic encephalitis. *A,* Immunofluorescence image of a section of brain tissue from case 1 stained with *Balamuthia*-specific antiserum. The amoebas are clustered around a blood vessel. (Original magnification, ×40.) *B,* Section of skin biopsy specimen from case 1 showing *Balamuthia* amoeba. The nucleus of the rounded amoeba contains a centrally located nucleolus. (Hematoxylin-eosin; original magnification, ×40.) *C,* Immunofluorescence image of a section of brain tissue from case 2, showing a ring of *Balamuthia* amoebas surrounding a blood vessel. (Original magnification, ×500.)

and brother, although the patient had always remained tuberculin negative. Extensive laboratory tests were nondiagnostic. One week after admission to the hospital, the patient underwent a biopsy of the left parietal lesion. Pathologic examination revealed an intense inflammatory vasculitis surrounding vessels and multinucleated giant cells compatible with a granulomatous vasculitis. After the brain biopsy was performed, treatment with dexamethasone was begun. The patient was discharged 10 days after admission; he was receiving treatment with prednisone (80 mg/day), in addition to dexamethasone, and cerebral vasculitis had been tentatively diagnosed.

Three days later, the patient was readmitted to the hospital. The results of fungal cultures of the initial brain biopsy specimen were negative, as were the results of acid-fast bacterial staining. A lumbar puncture was not performed. A second MRI showed multiple new enhancing lesions in the right and cerebellar hemispheres (figure 1*B*), and antituberculous therapy, as well as therapy with amphotericin B, doxycycline, and ceftriaxone, was initiated. Examination of brain tissue sections (figure 2*A*) and review of the original skin biopsy specimen (figure 2*B*) by IIF and hematoxylin-eosin staining identified the amoebas present as *B. mandrillaris.* Therapy with 5-fluorocytosine (flucytosine; 2 g q6h po), fluconazole (400 mg/day), pentamidine isethionate (4 mg/kg/day iv), and sulfadiazine (1.5 g q6h po) was begun. After brief use of azithromycin (500 mg/day), a change was made to clarithromycin (500 mg/day), because CNS penetration of azithromycin is thought to be minimal. Trifluoperazine (10 mg q12h) was briefly administered

but was discontinued from the regimen because of increasing muscle rigidity.

The course of the patient's illness while he was in the hospital was marked by focal seizures; coma requiring ventilatory support; frequent myoclonus; renal insufficiency; elevation of hepatic enzyme levels; pancreatitis; and hyperglycemia (presumably secondary to pentamidine therapy, which was discontinued). The patient was in the intensive care unit for 7 weeks. Several MRIs showed no change in the number and size of lesions. At the time of his discharge to a rehabilitation unit (~3 months after the initial hospitalization), the patient was dysarthric, alert, and oriented to person and place but had severely increased muscle tone, coarse tremor, and weakness. He was nonambulatory. His condition continued to improve while he remained in the rehabilitation unit. Fluconazole therapy was discontinued because of elevated levels of hepatic enzymes.

The patient was readmitted to the hospital for a third time (at approximately day 180) because of worsening mental status, increasing CNS lesions (in number and size) on MRI, and uncontrollable seizures. Fluconazole therapy was reinitiated, and the patient's condition gradually improved over the course of 11 days. This time, his hepatic enzyme levels remained normal, and he could again verbalize and was able to follow simple commands, but he remained markedly stiff and had frequent myoclonic jerking. Over the course of the next 5 years, he learned to walk independently and to perform all activities of daily living, and he was able to communicate well. MRI continued to show decreases in the size and enhancement of the numerous lesions. The patient continued to receive a regimen of fluconazole (400 mg/day) and sulfadiazine (1.5 g q6h).

Serum samples obtained during the initial phase of his illness (at approximately day 50) and at various subsequent stages were tested for *Balamuthia* antibody by IIF staining. The initial serum sample yielded a titer of 1:128 (at approximately day 50) for *Balamuthia* antibody, and later serum samples yielded titers of 1:64 (at approximately day 260), and 1:32 (after ~5 years). The results of control staining for *Naegleria* and *Acanthamoeba* antibodies were negative. Table 1 provides a chronologic summary of the case history of this patient.

Case 2 (San Diego County, CA). A 5-year-old Hispanic girl presented with generalized seizures, fever, and MRI findings of edema in the left temporal/parietal area of the brain (figure 3*A*). She had been in good health, with normal growth and development and without hospitalizations. Her immunizations were current, and she was receiving no medications before admission. She traveled frequently to Mexico to visit relatives.

Evaluation of the patient revealed CSF pleocytosis (WBC count, 162 cells/mm^3, with 65% neutrophils, 27% lymphocytes, and 8% monocytes; RBC count, 2 cells/mm^3; glucose level, 73 mg/dL; and protein level, 41 mg/dL) and abnormal electroencephalographic findings with focal changes in the left temporal lobe. Her fever persisted for several days, but seizures did not recur. She was treated presumptively with acyclovir for 21 days for herpes simplex virus (HSV) encephalitis. The results of 2 PCR assays of CSF were negative for HSV-1, as was a PCR assay for enterovirus. Also negative were the results of tests for CSF neurocysticercosis antibody, CSF *Cryptococcus* antigen, and serum toxoplasmosis antibody. She had elevated levels of serum IgM and IgG to *Mycoplasma,* and Epstein-Barr virus antibody titers consistent with past infection were found. After she completed the course of acyclovir, she was thought to be neurologically intact, and her physical condition had returned to baseline.

Despite the benign clinical course of this patient's illness, follow-up MRI performed 19 days after initial presentation demonstrated that she now had 2 large (3.0 and 3.5 cm in diameter), distinct ring-enhancing lesions surrounded by edema in the left temporal and parietal lobes, one of which is shown in figure 3*B* [25]. This prompted a CT-guided biopsy; examination of a biopsy specimen revealed acute suppurative and necrotizing inflammation and structures consistent with amoebas. A second opinion on the patient's condition was then sought in Mexicali, Mexico, and a partial excisional biopsy of one of the lesions was performed. Samples from this biopsy were submitted to the Centers for Disease Control and Prevention (Atlanta), and the amoebas were identified as *B. mandrillaris* by IIF staining (figure 2*C*). The patient was treated in Mexico with ketoconazole and metronidazole.

On returning to the United States for care, the patient was reevaluated for amoebic brain abscess. Clinically, she continued to do well and was without fever and headache. The only neurologic finding was mild dysphasia. The ketoconazole and metronidazole regimen was discontinued, and therapy with clarithromycin (14 mg/kg/day) and flucytosine (~110 mg/kg/day) was initiated. After ~2 weeks, this treatment regimen was changed to one containing azithromycin (14 mg/kg/day), flucytosine (110 mg/kg/day), fluconazole (14 mg/kg/day), thioridazine (1 mg/kg/day), and pentamidine (1 mg/kg/day).

The patient tolerated pentamidine therapy for ~2 weeks, and then it was stopped because her creatinine level was increasing. Pentamidine therapy was started again (at approximately day 140) but was permanently discontinued after ~1 week because of increases in the patient's serum glucose level. Azithromycin was changed to clarithromycin (14 mg/kg/day) because of persistent elevation of creatinine levels and concern about interstitial nephritis caused by azithromycin. Clinically, the patient's condition remained stable throughout this period, and she had minimal CNS symptoms (occasional headache and slight dysphasia). The patient required insulin therapy for 9 months to treat pentamidine-induced hyperglycemia. This eventually resolved, and she was maintained on the same 4-drug regimen

Table 1. Chronologic summary of the case history of a 64-year-old white man with *Balamuthia* amoebic encephalitis.

Timeline	Presentation/status	CNS imaging results	Laboratory findings	Treatment
Two weeks before first hospital admission; biopsy performed on skin lesion	Raised lesion on right forearm with chronic inflammation	…	Foreign-body granuloma; PAS staining negative for fungi	Metronidazole, ceftriaxone
Day 1 (first hospital admission)	Hemiparesis (right side), speech difficulty, focal seizure in emergency department	CT 1/MRI 1: 2 brain lesions noted	…	…
Day 7 (brain biopsy performed of left parietal lesion)	…	…	Intense inflammatory reaction, granulomatous vasculitis	Dexamethasone, prednisone
Day 10 (patient returned home)	…	…	…	…
Day 13 (second hospital admission)	Increased lethargy, headache and vomiting, afebrile	CT 2: new lesions	AFB staining and fungal cultures of brain biopsy specimen negative	…
Days 15–17	…	MRI 2: new lesions in right and cerebellar hemispheres	*Balamuthia* identified in brain biopsy specimen by IIF and HE staining; *Balamuthia* also seen on examination of skin biopsy specimen	Started anti-TB drugs (isoniazid, rifampin, ethambutol, pyrazinamide), amphotericin B, ceftriaxone, doxycycline; regimen discontinued after 4 days
Day 18	…	…	…	Started pentamidine, fluconazole, flucytosine, rifampin, sulfadiazine, azithromycin, trifluoperazine
Day 36	…	…	…	Discontinued pentamidine (because of hyperglycemia), trifluoperazine (because of increased rigidity)
Days ~50–90	…	MRIs 3–5: lesions unchanged	IIF staining of serum for *Balamuthia* antibody; titer of 1:128	Changed from azithromycin to clarithromycin
Days ~100–150 (transferred to rehabilitation unit)	Dysarthric, with increased muscle tone and coarse tremor; nonambulatory	MRI 6: lesions unchanged	…	Discontinued fluconazole (because of persistently elevated hepatic enzyme levels)
Days ~180–190 (third hospital admission)	Worsening mental status, seizures; able to verbalize	MRI 7: new lesions; some enlargement of previous lesions	…	Restarted fluconazole (hepatic enzyme levels remained normal)
Day ~200 (transferred to rehabilitation unit)	Stiffness, with myoclonic jerking	…	…	Receiving sulfadiazine, flucytosine, fluconazole, clarithromycin
Day ~260	…	…	IIF staining of serum for *Balamuthia* antibody; titer of 1:64	…
Years 1–2	Ambulatory	MRIs 8 and 9: no increase in no. of lesions	…	Discontinued clarithromycin
Years 4–5	…	MRI 10: no new lesions; slight decrease in size of existing lesions	IIF staining of serum for *Balamuthia* antibody; titer of 1:32	…
Present status	Able to walk independently and communicate	…	…	Discontinued flucytosine; still receiving fluconazole, sulfadiazine

NOTE. AFB, acid-fast bacilli; HE, hematoxylin-eosin; IIF, indirect immunofluorescence; PAS, period acid–Schiff; TB, tuberculosis.

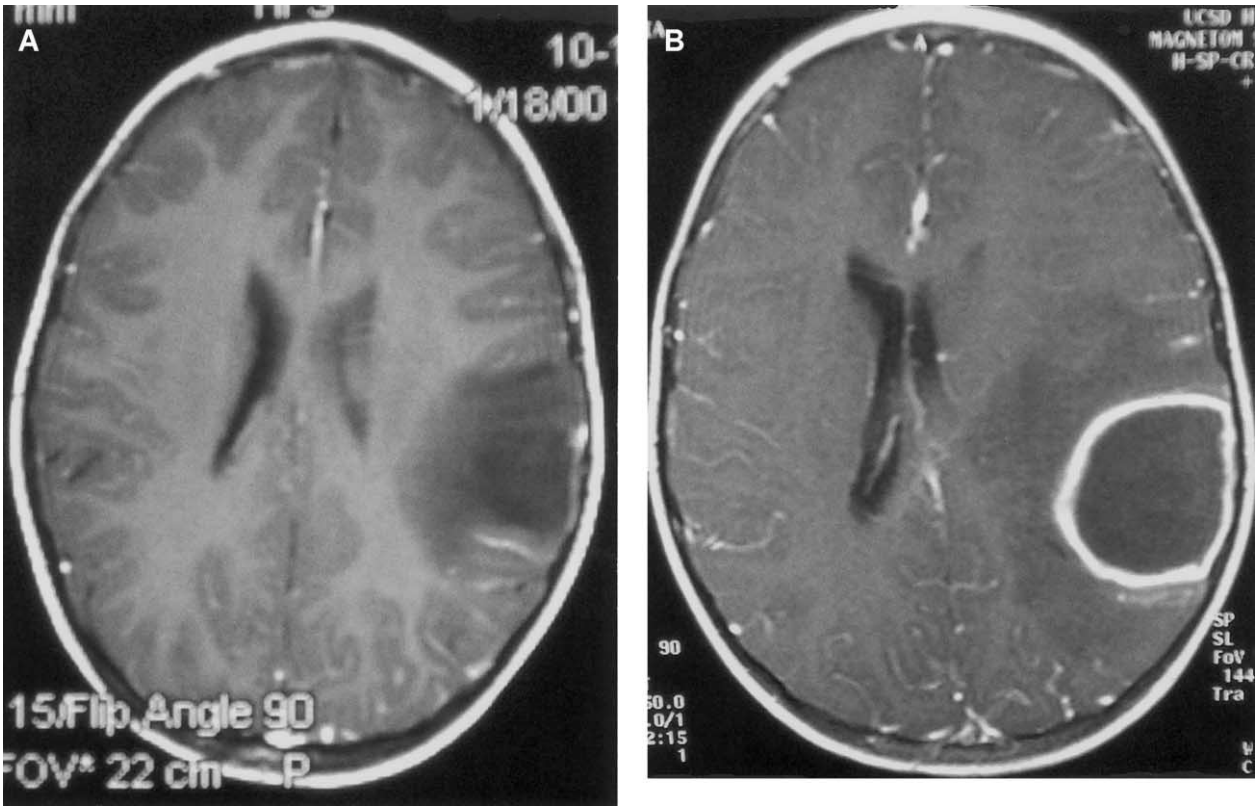

Figure 3. MRI of a 5-year-old Hispanic girl with *Balamuthia* amoebic encephalitis (case 2). *A,* Contrast-enhanced MRI obtained on initial presentation, demonstrating edema in the left parietal lobe. *B,* Contrast-enhanced MRI obtained 70 days after initial presentation, demonstrating a discrete encapsulated lesion in the left parietal lobe that enhances with surrounding edema.

(clarithromycin, fluconazole, flucytosine, and thioridazine) until approximately day 520. Thioridazine therapy was discontinued but was restarted when the patient had a brief generalized seizure and because of concern about reactivation of *Balamuthia* infection. Evaluation showed no change in her lesions, and she had no abnormal neurologic signs. Thioridazine therapy was continued until approximately day 680 (approximately year 1.9), at which time it was permanently discontinued. The patient continued receiving clarithromycin and fluconazole.

Serial MRI and CT scans showed gradual resolution of the surrounding edema but persistence of 2 ring-enhancing lesions (which decreased in size from 3.5 and 3.0 cm in diameter to 2.4 and 2.7 cm, respectively), which partially calcified. The patient had no gross neurologic sequelae but experienced moderate performance problems in school.

Immunostaining of a serum sample obtained from the patient ~7 months after her initial visit yielded a *Balamuthia* antibody titer of 1:64–1:128. Approximately 2 months later, the titer was 1:64, as it was again ~2 months later. The results of control immunostaining were negative (titers of 1:2 and 1:4). Table 2 provides a chronologic summary of this patient's case history.

DISCUSSION

Because of the difficulty in diagnosing *Balamuthia* amoebic encephalitis and the resultant delay in initiating antimicrobial therapy, whether patients with this disease will survive is uncertain. What makes the 2 cases described in this report particularly noteworthy is (1) that diagnosis was made before death and (2) that antimicrobial therapy was initiated early enough to halt the course of disease, leading to survival of the 2 individuals.

Both patients underwent brain biopsies because of the nature of the lesions and the difficulty in making a diagnosis on the basis of the results of routine serologic and CSF testing. Brain tissue sections stained by immunofluorescence demonstrated *Balamuthia* amoebas in tissue. Other free-living amoebas have been implicated in amoebic encephalitis, including *Naegleria fowleri* and *Acanthamoeba* species [3, 22, 23]. *Naegleria* infections are of a fulminant type and are most often associated with swimming or other water activities, and *Acanthamoeba* infections typically occur in immunosuppressed or immunocompromised persons, which was not true of either of the 2 cases presented in this report.

Table 2. Chronologic summary of the case history of a 5-year-old Hispanic girl with *Balamuthia* amoebic encephalitis.

Timeline	Presentation/status	CNS imaging results	Laboratory findings	Treatment
Day 1 (first hospital admission)	Generalized seizures, fever	MRI 1: edema noted	Negative results of tests for HSV, enterovirus, neurocysticercosis, *Cryptococcus, Toxoplasma*	Acyclovir
Day 19	…	MRI 2: 2 large brain lesions seen	…	…
Day 38	CT-guided biopsy performed	…	Acute suppurative and necrotizing inflammation; amoebas seen in biopsy tissue specimen	…
Day 48 (excisional biopsy performed in Mexico)	…	…	*Balamuthia* identified in brain biopsy specimen by IIF and HE staining	Ketoconazole, metronidazole
Day 82 (returned to United States for reevaluation of amoebic brain abscess)	Fever, headache, slight dysphasia	…	…	Discontinued ketoconazole, metronidazole; started clarithromycin, flucytosine
Day 96 (change in treatment regimen)	…	…	…	Discontinued clarithromycin; started azithromycin, fluconazole, pentamidine, thioridazine
Day ~120	…	…	…	Changed from azithromycin back to clarithromycin; discontinued pentamidine (because of rising creatinine level)
Day ~140	…	…	…	Restarted pentamidine
Day ~150	Occasional headaches and dysphasia	…	…	Discontinued pentamidine (because of increasing serum glucose level)
Days ~510–520	…	…	IIF staining of serum for *Balamuthia* antibody; titer of 1:128	Discontinued thioridazine
Year ~1.4	No abnormal neurologic signs	MRI: no change in brain lesions	…	Restarted thioridazine because of seizure
Year ~1.8–1.9	…	…	IIF staining of serum for *Balamuthia* antibody; titer of 1:64	Thioridazine permanently discontinued; receiving clarithromycin, fluconazole, flucytosine
Year ~2	…	…	IIF staining of serum for *Balamuthia* antibody; titer of 1:64	…
Year ~2.4	…	MRI/CT: persistence of 2 lesions, with partial calcification; resolution of edema	…	Discontinued flucytosine
Present status	No gross neurologic sequelae; returned to school with moderate performance problems	…	…	Still receiving clarithromycin, fluconazole

NOTE. HE, hematoxylin-eosin; HSV, herpes simplex virus; IIF, indirect immunofluorescence.

Methods for diagnosis of *Balamuthia* encephalitis include microscopic examination of hematoxylin-eosin–stained biopsy specimens, detection of amoebas in sectioned tissue by IIF, and detection of serum antibodies using IIF. Because *Balamuthia* encephalitis is chronic rather than fulminant, there is ample time for a build-up of antibodies that can be detected by IIF. When fresh (unfixed) brain tissue obtained through biopsy that contains lesions is available, it is possible to isolate amoebas in tissue cultures used as feeder layers, but the process is slow—often requiring days or weeks—and not realistically usable as a diagnostic aid [1, 22, 26]. The absence of specific symptoms and the difficulty in recognizing *Balamuthia* amoebas generally results in diagnoses being made after death. CT and MRI have been helpful in determining the size, location, and dynamics of amoebic brain lesions and have been used in ~12 of the cases published in the literature. Given the numbers of immune-impaired individuals globally, it is likely that the disease is underreported.

The differential diagnosis for *Balamuthia* encephalitis includes mycobacterial tuberculosis [6, 7, 10, 12, 14, 27] and neurocysticercosis [12, 27, 28]. In one case described in the literature, in which neurocysticercosis was initially diagnosed, histologic study after autopsy led to reporting of the case as *Acanthamoeba* encephalitis [29], and the case was subsequently identified by immunostaining to be *Balamuthia* encephalitis (G.S.V., unpublished observations). The patient in case 1 in this report was initially treated for tuberculosis before amoebas were identified in brain tissue, and cysticercosis was considered as a possibility in case 2. Until MRI findings became available, at approximately day 60, the patient in case 2 was treated as if she had HSV encephalitis, despite negative results of 2 HSV PCR assays. *Balamuthia* encephalitis should be considered as a possible diagnosis for patients being treated for presumptive HSV encephalitis when the diagnosis of HSV infection is not supported by PCR or other test results. It should also be considered for patients with cutaneous lesions and nonspecific granulomatous pathology in the absence of microbial involvement [16], as was true for the patient in case 1.

The optimal antimicrobial therapy for *Balamuthia* infection has yet to be determined. The selection of antimicrobials used to treat these 2 patients was based on unpublished and published in vitro studies of drug efficacy against clinical isolates of *Balamuthia*. In both cases, the core of antimicrobials administered included pentamidine, flucytosine, fluconazole, a macrolide antibiotic (azithromycin or clarithromycin), and sulfadiazine. Amphotericin B, which is effective against *Naegleria* species [30], varies in its efficacy against *Balamuthia* isolates [31]. Amphotericin B was used unsuccessfully in treating 2 other patients with *Balamuthia* encephalitis, along with trimethoprim-sulfamethoxazole [13] and fluconazole [32]. In vitro testing of pentamidine isethionate indicated that it was effective against clinical isolates of *Balamuthia* [31, 33]. A study of pentamidine distribution in patients with HIV infection/AIDS reported slow uptake (~30 days) into the CNS [34]. Therapy with pentamidine, which was administered over the course of ~25 days in both of the cases we describe (tables 1 and 2), was discontinued because of hyperglycemia that developed and that, for the patient in case 1, has persisted. Phenothiazine compounds have shown in vitro efficacy against *Balamuthia,* although these tend to be toxic to tissue culture cells at concentrations that are amoebicidal [33]. Thioridazine was used in case 2, and trifluoperazine was used in case 1, but it is difficult to assess the efficacy of these drugs, among the other antimicrobial agents used, in the patients' recovery. In neither of the 2 cases were amoebas isolated from the patients' biopsied brain tissue, and thus the antimicrobial sensitivity of the infecting amoebas is unresolved.

The source of the infection in case 1 would appear to have been the wound that the patient received while working in his garden. Given the circumstances, it is likely that the wound was contaminated with soil, offering a portal of entry for the amoeba. No focal source of infection was evident in case 2.

The recovery of these 2 patients after timely diagnosis and treatment indicates that *Balamuthia* amoebic encephalitis cases need not invariably be fatal. With greater awareness that this amoeba can be a causative agent of encephalitis, earlier diagnosis can be made either by immunostaining or by recognizing the amoebas in histologic sections of brain tissue after biopsy. At present, the Centers for Disease Control and Prevention and the California State Department of Health Services are able to perform IIF testing of serum samples and tissue sections as an aid to diagnosis. Premortem diagnosis, coupled with effective antimicrobial therapy, may significantly reduce the mortality associated with this type of encephalitis.

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