Granulomatous Amoebic Meningoencephalitis in an Immunocompetent Patient

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Objective: To report a case of granulomatous amoebic encephalitis caused by Balamuthia mandralaris.

Design: Case report.

Setting: University hospital.

Patients: An adult female patient without any apparent suppressor immune system factor had central nervous system infection caused by B mandralaris.

Main Outcome Measures: Clinical, neuroimaging, and pathology findings.

Results: This study shows the diagnosis of B mandralaris encephalitis suspected from a cerebral biopsy specimen and confirmed by immunohistochemical and polymerase chain reaction studies.

Conclusions: This study demonstrates that the diagnosis of amoebic encephalitis represents a clinical challenge and confirming diagnoses are made, in most cases, after death. High suspicion, histopathologic examination, and indirect immunofluorescence, polymerase chain reaction, and cytokine studies from tissue and cerebrospinal fluid are the main devices to reach the diagnosis.

Arch Neurol. 2010;67(12):1516-1520

Granulomatous amoebic encephalitis (GAE) is a rare and sporadic central nervous system infection caused by free-living amoeba. However, the disease has gained importance because of the growing number of immunodepressed patients, its difficult diagnosis, lack of adequate treatment, and high level of mortality.

Most cases have been reported in the United States, Australia, and Europe, which might be because of better identification of patients at these centers and/or publication bias. To our knowledge, only 2 cases have been described in Brazil, one associated with AIDS and the other, with alcoholism as a risk factor.1

Most cases of GAE are related to host immunosuppression and are caused by amoebae of the genus Acanthamoeba.2,3 A case of GAE caused by Balamuthia mandralaris in an adult immunocompetent patient is reported herein. The radiologic and histopathologic findings are also described.

REPORT OF A CASE

A 47-year-old woman from Belo Horizonte, Minas Gerais, Brazil, was admitted to the emergency service reporting a headache in the frontal region that had started 8 days earlier and evolved into a holocranial headache, whose intensity progressively worsened. The patient had had vomiting over the previous 2 days. There was no report of fever at the onset of symptoms, alcohol abuse, diabetes mellitus, or other comorbidities, except for systemic arterial hypertension. Additional examination revealed mild neck stiffness but no cranial nerve abnormalities or focal signs. Funduscoppy was normal. The patient had no lymphadenomegaly, fever, or skin alterations. A cranial computed tomographic scan showed discrete sulcus obliteration (Figure 1A). The patient had a lumbar puncture for analysis of the cerebrospinal fluid, which showed the following results: elevated opening pressure (44 cm of water), protein level of 131 mg/dL, glucose level of 57 mg/dL, and 39 nucleated cells (69% lymphocytes, 12% neutrophils, 15% monocytes, and 4% plasma cells). Results of gram staining, acid-fast staining, and oncotic cytologic analysis were negative. The VDRL test results were non-reactive and the cultures for fungi and Mycobacterium tuberculosis were negative.

The initial diagnostic hypothesis was viral meningitis. The patient was kept under observation and showed stabilization...
of clinical symptoms over the subsequent 2 days. On the third day after admission, the patient developed focal signs characterized by horizontal nystagmus, ataxic gait, and dysmetria on the left side. A cranial computed tomographic scan was repeated and showed hypodensity in the left cerebellar hemisphere (Figure 1B). The diagnostic hypothesis of herpes encephalitis was raised and treatment with acyclovir, ampicillin, and dexamethasone was introduced. The headache improved after 24 hours, but the cerebellar signs persisted. The patient developed drowsiness after 3 days and underwent nuclear magnetic resonance imaging of the brain, which showed multiple brain lesions on both cerebral hemispheres, ranging in diameter from 0.5 to 3 cm. Heterogeneous contrast enhancement was observed especially in the left cerebellar hemisphere (Figure 1C, D, and E). An empirical treatment for neurotuberculosis and neurotoxoplasmosis was tried. Treatment with rifampicin, isoniazid, pyrazinamide, ethambutol, sulfadiazine, and pyrimethamine was introduced. Ampicillin, acyclovir, and dexamethasone treatment was maintained. The patient had a decreased level of consciousness and underwent orotracheal intubation on the same day.

A left lateral suboccipital craniectomy was performed to obtain a biopsy specimen of a lesion in the left cerebellar hemisphere. Blood cell count, coagulogram, erythrocyte sedimentation rate, renal and hepatic function test results, antinuclear factor results, chest radiography, transthoracic echocardiogram, and serologic test results for human immunodeficiency virus were negative and/or showed no alterations. After the procedure, the patient had an increase in intracranial pressure, loss of brainstem reflexes, and hemodynamic instability and died 15 days after hospital admission.

The histopathologic analysis revealed extensive areas of necrosis and hemorrhage in the cerebellum, fibrinoid necrotizing panarteritis, some thrombosis, granulomatous lymphoplasmacytic inflammatory infiltrate, foamy macrophages, isolated multinucleated giant cells, and incipient formation of perivascular granulomas. The in-

Figure 1. Cranial computed tomography and magnetic resonance imaging. A, Cranial computed tomography showing discrete obliteration of the sulci. B, Cranial computed tomography showing hypodensity in the left cerebellar hemisphere. C and D, Fluid-attenuated inversion recovery magnetic resonance imaging showing hyperintensity in the left cerebellar hemisphere and frontal, temporal, and occipital lobes. E, Heterogeneous contrast enhancement.
flammatory infiltrate extended focally to the adjacent leptomeninges. Different structures (isolated or forming small clusters) with the morphological characteristics of amoeba trophozoites were identified in the vascular wall and in areas with and without an inflammatory reaction (Figure 2). Part of the material was sent to the Armed Forces Institute of Pathology, Washington, DC. Immunohistochemical and polymerase chain reaction studies were then performed and revealed the presence of trophozoites of the free-living amoeba B mandrillaris.

**COMMENT**

The involvement of free-living amoebae in human diseases was only recognized after 1965, when the first fatal cases of meningoencephalitis were described in Australia and, almost at the same time, the United States. Free-living amoeba species causing central nervous system injury include Naegleria fowleri, Acanthamoeba species, and B mandrillaris. More recently, Sappinia diploidea has been implicated as a rare cause of meningoencephalitis in humans. B mandrillaris is a free-living amoeba that was first identified in 1989 in the brain of a mandrill baboon that died of encephalitis at the San Diego Zoo. This species causes encephalitis in both immunodepressed and immunocompetent individuals as well as in animals. B mandrillaris and various species of Acanthamoeba are opportunistic agents that cause the clinical presentation of GAE in debilitated and malnourished patients; different types of immunocompromised patients, including those with AIDS; and children. In contrast with Acanthamoeba, which preferentially occurs in immunocompromised patients, Balamuthia is also seen in immunocompetent patients, particularly children. By 2007, approximately 150 cases of infection with Balamuthia had been reported worldwide since the recognition of the disease in 1990.

Balamuthia and Acanthamoeba species show a ubiquitous distribution, with organisms being found in soil, water, heaters, and air-conditioning units. The former species is probably transmitted by inhalation of airborne cysts or by direct contamination of skin lesions. The few patients with GAE caused by B mandrillaris had not been exposed to water but had a history of skin lesions before the emergence of neurological symptoms. In a review including 24 patients with B man-
drillaris infection, 92% had skin lesions. The present patient had no skin lesions and the probable route of invasion of the pathogen might have been the respiratory tract, followed by hematogenic dissemination to the central nervous system.

The risk factors of Balamuthia encephalitis are not well established. In a series of 10 patients, 5 had comorbidities such as diabetes, heart disease, a previous splenectomy, nephrotic syndrome associated with prolonged steroid treatment, and possible lymphoma. Five of the 10 patients had been exposed to soil. Alcoholism and prolonged antibiotic therapy have also been considered to be risk factors. Balamuthia encephalitis was a fatal complication in 2 patients who underwent renal transplant at the University of Mississippi and it appears that the donor had asymptomatic Balamuthia encephalitis. Because of this, organ transplant should always be considered as a risk factor for this infection. There is a predominance of cases in young (<15 years) and elderly (>60 years) individuals, which may be attributed to some what weaker immune systems. However, no risk factors could be identified in most cases reported in the literature or in the present case.

The diagnosis of GAE in the living requires caution and suspicion, since its symptoms mimic various types of encephalitis. Few appropriate laboratory tests for diagnosis are available and many physicians are unaware of the disease. The methods available for the diagnosis of GAE caused by B mandrillaris include histologic analysis of hematoxylin-eosin-stained specimens and detection of amoebae in tissue samples and serum antibodies using indirect immunofluorescence. Cell culture, polymerase chain reaction, and cerebrospinal fluid analysis may also be done. Immunochemical analysis permits the detection of trophozoites, which are difficult to identify by hematoxylin-eosin staining in areas of necrosis or when macrophages are abundant. Immunochemical analysis also can show granular antigens inside macrophages and the blood vessel wall. Most cases are identified in retrospective postmortem studies. Recently, the California Department of Public Health study revealed that in Balamuthia encephalitis, cerebrospinal fluid may show elevations in the levels of cytokines interleukin 6 and interleukin 8, which could differentiate it from other types of encephalitis. There is also a triple real-time polymerase chain reaction assay for Naegleria, Acanthamoeba, and Balamuthia developed by the Centers for Disease Control and Prevention.

An anatomopathologic examination of central nervous system lesions requires diligence and experience. In the present case, this analysis involved consideration of important differential diagnoses, such as primary angitis of the central nervous system, vasculitis, giant cell arteritis, and infection by viruses, fungi, and other protozoa. There are no specific characteristics in clinical, laboratory, or radiologic findings for the diagnosis of GAE. Computed tomography and magnetic resonance imaging generally show 1 or more contrast-enhanced lesions that are nonspecific and can be seen in other conditions such as fungal or bacterial infections, tuberculosis, toxoplasmosis, or neoplasms. Magnetic resonance imaging reveals hyperintense multifocal lesions on T2-weighted images that show a heterogeneous or ringlike enhancement. The lesions are preferentially located in the diencephalon, brainstem, and structures of the posterior fossa. A brain biopsy is important for the diagnosis of GAE and can be part of the treatment in cases in which no dissemination of isolated lesions to the brain is observed.

Various alternatives have been proposed for the treatment of GAE. Combination treatments with pentamidine, fluconazole, sulfadiazine, flucytosine, azithromycin, and clarithromycin have been described. This combination was administered to 2 patients who successfully recovered and there was no evidence of recrudescence of the disease 2 and 6 years after the onset of symptoms in these cases. The prognosis is generally obscure and mortality is approximately 100%.

Granulomatous amoebic encephalitis caused by B mandrillaris is a rare disease and barely known among physicians. Because of the lack of pathognomonic symptoms and diagnostic difficulties, numerous complementary tests are generally performed and different empirical treatments are indicated, as in the present case. The diagnostic hypothesis of GAE caused by B mandrillaris should therefore be considered in the case of symptoms of acute and subacute meningoencephalitis, even in countries where this infection is rarely described, such as Brazil, and in immunocompetent patients who do not have any risk factors. A biopsy should always be performed because of the possibility of treatment if the disease is diagnosed at an early stage.

Accepted for Publication: March 15, 2010.

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Author Contributions: Study concept and design: Silva, Araujo, Avellar, Oliveira, and Christo. Acquisition of data: Silva, Araujo, Avellar, Oliveira, and Christo. Analysis and interpretation of data: Silva, Araujo, Avellar, Pittlea, Oliveira, and Christo. Critical revision of the manuscript for important intellectual content: Silva, Araujo, Avellar, Pittlea, Oliveira, and Christo. Study supervision: Silva, Araujo, Avellar, Pittlea, Oliveira, and Christo.

Financial Disclosure: None reported.

REFERENCES


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**Announcement**

**New Initiatives: Clinical Trials and Videos.** We have embarked on 2 new initiatives: Clinical Trials and video presentations. We welcome manuscripts that describe double-blind, randomized, placebo-controlled clinical trials as our primary area of interest. We plan on expediting the review process and time to publication and to include them online ahead of print as these studies are time sensitive and of direct benefit to our patients. We hope you will take advantage of this new initiative. Please refer to the Instructions for Authors when submitting a Clinical Trials paper, including the requirement to register the trial with an accepted clinical trials site.

We plan to utilize videos as part of published papers that highlight and provide convincing information about the observational and visual features of a patient’s neurologic findings. Please refer to Instructions for Authors for instructions on submitting video presentations.