Neurological Case Reports

Case Report
Published: 21 Oct, 2024

Challenges in Diagnosing and Treating GAE: A Case Report of Fatal *Acanthamoeba* spp. Encephalitis in an Immunocompetent Patient

Khaoula B[1,2]*, Louhab N[1,2], Safae Z[1,2], Chraa M[1,2] and Najib K[1,2]

[1]*Department of Neurology, Mohammed VI University Hospital, Marrakech, Morocco*

[2]*Marrakech Medical School, Cadi Ayyad University, Marrakech, Morocco*

Abstract

Granulomatous Amoebic Encephalitis (GAE) is a rare but fatal infection of the central nervous system with a high mortality rate, due to Free-Living Amoebae (FLA) that are pathogenic to humans and ubiquitous in environment. In this paper, we report the case of an immunocompetent adult female with no relevant medical history who presented acute symptoms resembling a stroke: Altered mental status, slurred speech, brutal proportional right hemiplegia, facial droop and focal to bilateral Tonic-Clonic seizures all concomitant with high fever. Subsequent Magnetic Resonance Imaging (MRI) of the brain revealed diffuse multiple nodular lesions both above and below the tentorium. The initial Cerebrospinal Fluid (CSF) profile was of no great significance however microscopic examination of CSF was able to identify the presence of amoeboid microorganisms and cyst formation, suggestive of a telluric amoeba's infection. The patient was then treated with a combination of fluconazole and trimethoprim-sulfamethoxazole but her neurological state kept on declining until she passed away from GAE. In our case report we highlight the difficulties clinicians encounter handling this disease, since the clinical and radiological presentation are non-specific, additionally to the absence of clear therapeutic guidelines after diagnosis. Our findings point up the urgent need for more precise diagnostic criteria and comprehensive treatment protocols to improve patient outcomes.

Keywords: Granulomatous Amoebic Encephalitis (GAE); Free-living amoebae (FLA); *Acanthamoeba* spp.

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Correspondence:
Khaoula Belaidi, Department of Neurology, Mohammed VI University Hospital, BP2360 Principal, Av. Ibn Sina, Marrakech, Morocco, Tel: 00212669851200;

Received Date: *06 Sep 2024*
Accepted Date: *15 Oct 2024*
Published Date: *21 Oct 2024*

Citation:
Khaoula B, Louhab N, Safae Z, Chraa M, Najib K. Challenges in Diagnosing and Treating GAE: A Case Report of Fatal Acanthamoeba spp. Encephalitis in an Immunocompetent Patient. Neurol Case Rep. 2024; 7(2): 1049.

Background

Granulomatous amebic encephalitis is a rare central nervous system infection that is usually rapidly fatal with a mortality rate exceeding 90% [1]. We have a poor understanding of the disease, and clinical presentation and neuroimaging examination are non-specific, making it easy to be misdiagnosed. Typically, the onset of symptoms is insidious until overwhelming infection results in rapid severe neurological decline, including seizures, altered levels of consciousness, coma, and death. Diagnosis is challenging due to the non-specific clinical presentation and radiological features. The optimal treatment for this infection has not been described. Herein, we report a case in which the diagnosis was promptly made by early CSF examination.

Case Presentation

A 48-years-old immunocompetent female with no relevant medical history arrived at the emergency department with symptoms resembling a stroke: altered mental status (Glasgow Coma Scale at 12/15), slurred speech, brutal proportional right hemiplegia, facial droop, and focal to bilateral Tonic-Clonic seizures. Concurrently, our patient presented high fever at 40°C together with deep deterioration of the general condition and a history of headache and coughing prior to the neurological symptoms. The initial Computed Tomography (CT) scan did not reveal signs of a stroke. However, subsequent Magnetic Resonance Imaging (MRI) revealed diffuse multiple nodular lesions both above and below the tentorium. The patient was then hospitalized in our Neurology Department for further investigations. After admission, the patient began to demonstrate severe altered levels of consciousness, Glasgow Coma Scale dropped to 09/15 with persistent high fever 39°C to 40°C.

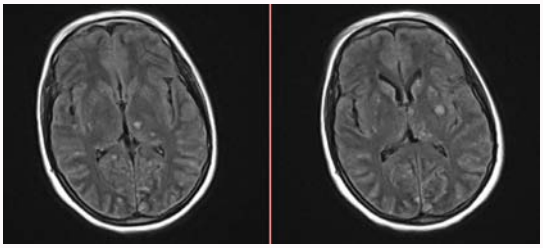

Figure 1a: T1 weighted Brain MRI sections showing multiple nodular lesions in different cortical and sub-cortical areas enhancing with gadolinium.

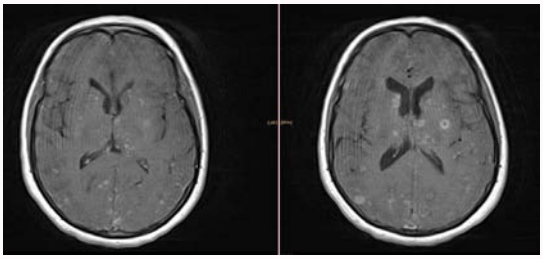

Figure 1b: T2 weighted Brain MRI sections showing multiple hyperintense nodular lesions in different cortical and sub-cortical areas.

Pathological Findings

The initial Cerebrospinal Fluid (CSF) profile was as follows: Leukocyte count, 17 cells/mm^3 with predominant lymphocytes (80%), erythrocyte count, 778 cell/mm^3, glucose concentration, 0.7 g/l, and total protein concentration 0.4 g/l. Results from Gram staining and culture of Cerebrospinal Fluid (CSF) were negative. Specific PCR testing for herpes simplex virus also were negative, as did testing with India ink for *Cryptococcus neoformans* (Figures 1-3).

Brain MRI scans showed multiple isointense nodular lesions on T1-weighted imaging, hyperintense lesions on T2-weighted imaging with restricted diffusion and without ADC restriction. Many of those lesion's ring enhanced and some were hemorrhagic, there was meningeal enhancement as well. An infectious origin was primary suspected.

A second lumber punction was preformed 5 days after, CSF profile was as follows: Leukocyte count, 27 cells/mm^3 with predominant lymphocytes (80%), erythrocyte count, 0 cell/mm^3, glucose concentration, 0.5 g/l, and total protein concentration, 0.6 g/l. microscopic examination of CSF revealed the presence of amoeboid microorganisms and cyst formation, suggestive of a telluric amoeba's infection (*Acanthamoeba* sp. / *Balamuthia mandrillaris*).

To identify the route of entry, and given the patient's history of coughing, we performed a Computed Tomography (CT) scan of the lungs. The scan revealed alveolar consolidation with air bronchograms, highly suggestive of an infectious origin due to the clinical context. The decision was then to start treatment using fluconazole and trimethoprim-sulfamethoxazole. The patient was transferred to the intensive care unit, where she remained hospitalized for 15 days before she passed away from granulomatous amebic encephalitis 5 weeks after the onset of neurological symptoms.

Discussion

Granulomatous Amoebic Encephalitis (GAE) is a rare fatal infection of the central nervous system with a mortality rate exceeding

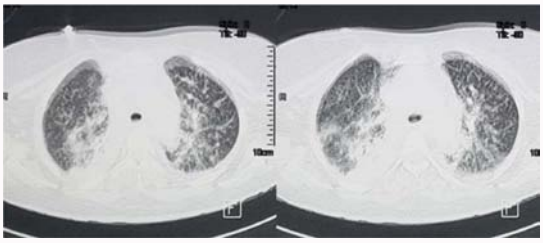

Figure 2: CT scan of the lungs showing alveolar consolidation with air bronchograms.

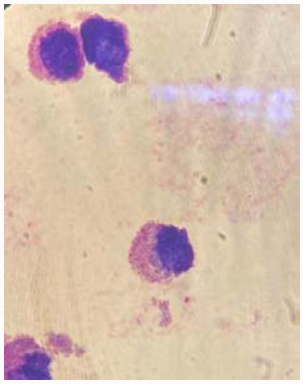

Figure 3: Microscopic examination of CSF after MMG staining showing amoeboid microorganisms.

97% to 98% [2]. Since 1990 to 2020, 75 cases of patients with GAE caused by *Acanthamoeba* spp. have been published, only 19 of the cases had survived [2]. GAE is caused by Free-Living Amoebae (FLA) that are pathogenic to humans and ubiquitous in natural environment [3]. Three genera of FLA are known to infect human hosts: *Acanthamoeba* spp., *Balamuthia mandrillaris*, and *Naegleria fowleri* [3]. GAE is caused by *Acanthamoeba* or *Balamuthia* species. *Acanthamoeba* spp. is ubiquitous and can be found in soil and water, both indoors and outdoors environments. *Balamuthia* is more likely to be from soil. Entry sites for infection include skin, as well as upper respiratory and urogenital tracts [4]. It has been noted all those patients infected with *Acanthamoeba* spp. developed symptoms of upper respiratory tract infection followed by acute meningitis [5]. In our case the portal route is considered to be upper respiratory on account of respiratory symptoms and pulmonary lesions on CT scan the patient had presented. The origin of FLA is presumed to be outdoor water since the patient entourage had reported her direct consumption of raw water from a river near-by her household. The amoebas break into the nasal mucosa and can penetrate the olfactory tracts, then invade the cribriform plate into the subarachnoid space [4]. Amoebas infiltrate the brain and form granulomatous lesions. The progression of the disease is subacute to chronic often causing death. Clinical features are typically severe but common and nonspecific. Symptoms include headache, fever, altered mental status, seizures and focal motor deficit [6]. In our case, the patient presented with symptoms resembling a stroke, consequently, GAE could easily be misdiagnosed as stroke, brain tumors, and other CNS infections which delays diagnosis and worsens prognosis [7]. At the time of writing, most of the reported cases of Granulomatous Amebic Encephalitis (GAE) occurred in immunocompromised patients [6]. These cases were identified in individuals who had undergone kidney, liver, or allogeneic hematopoietic stem cell transplants, patients

receiving immunosuppressive treatments, those with autoimmune disorders, or patients who had tested positive for HIV [8]. On that account, GAE was primarily recognized as an opportunistic infection of immunocompromised hosts. However, several cases have been reported in healthy patients [2,6]. In most cases, diagnosing GAE is challenging and often only confirmed postmortem [3]. Definitive diagnosis relies on real-time PCR, immunohistochemistry, and indirect immunofluorescence assays of brain biopsies [9]. CSF (Cerebrospinal Fluid) examination is crucial for diagnosis. Analyzing CSF can reveal an increased white blood cell count, elevated protein levels, and occasionally the presence of amoebas [9-11], as found in our tests. However, the cysts of *Balamuthia mandrillaris* and *Acanthamoeba* spp. are morphologically very similar, generally, they cannot be reliably distinguished without molecular confirmation. Nonetheless, since *Acanthamoeba* spp. is known to be ubiquitous in raw water and that it causes pneumonia right before the onset of meningoencephalitis [5], we believe that our patient was infected with this particular species. Real-time PCR of cerebrospinal fluid may confirm diagnosis GAE in the early stage, nevertheless amoebas are rarely found in the cerebrospinal fluid [9,10,12], and this test is not readily available. Serology for amoeba specific antibodies is available, but these assays are not widely available and their specificity for active disease is low since most people have been exposed to this organism at one or more times in their life [6]. Early diagnosis is crucial for a good prognosis. However, the rarity of the disease and the limited number of reported cases often lead to delayed diagnosis or even misdiagnosis of GAE. There is no standard therapeutic recommendation for GAE. In most surviving cases various drug combinations were used. Since 2000, twenty-three surviving cases of Acanthamoeba encephalitis have been reported [2,5,6,9,12-16]. Fourteen of these cases occurred in healthy, immunocompetent patients [2,6,13-15], while two involved post-transplantation patients (hematopoietic stem cell transplant [9] and liver transplant [8]. Two patients were HIV-positive [2,12], and the remaining five cases involved individuals with different underlying conditions: Disseminated tuberculosis [2], seizure disorder [6], ulcerative colitis [9], chronic malnutrition [2] and acute lymphoblastic leukemia [17]. In each of these cases, a different combination of medications was used. Trimethoprim-sulfamethoxazole, Rifampicin, and ketoconazole or fluconazole were the most common agents administered, often simultaneously in surviving cases [2,6].

Other medications, such as pentamidine, sulfadiazine, pyrimethamine, voriconazole, azithromycin, miltefosine, and metronidazole, were also used but not as frequently [2,6]. The same drugs were used in cases where patients did not survive, making it difficult to draw reliable conclusions about the efficacy of any particular drug combination. Trimethoprim- sulfamethoxazole has the highest frequency of drug usage, 47% of patients treated with these drugs survived [18]. Fluconazole was the most commonly used azole in GAE treatment, with a 40% survival rate among those treated [18]. Ketoconazole, however, proved to be the most effective azole, showing a 46% efficacy rate [18].

Miltefosine, an anti-leishmanial agent, had shown peculiar efficacy in curing GAE, it has shown the highest efficacy of drug usage and it may be associated with the highest rate of survival, although this finding holds borderline clinical significance. In our case, we attempted to cure the patient using a combination of Trimethoprim-sulfamethoxazole and Fluconazole in high doses. The patient remained comatose for 20 days after diagnosis before she succumbs to death. Based on the data gathered through this case report, we believe a combination of fluconazole, trimethoprim-sulfamethoxazole, miltefosine and rifampicin could make a highly effective therapeutic regime.

Further research and clinical studies are needed to improve diagnostic methods and establish effective treatment strategies for GAE. Cases such as ours can contribute valuable information to the medical community and may help raise awareness about this uncommon but severe disease. Simple microscopic examination of CSF can help identify at times the presence of amoeboid micro-organisms. Early diagnosis and prolonged multi-agent treatment improve prognosis and enhance chances of survival.

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