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Case Report

A devastating case of a *Balamuthia mandrillaris* pediatric brain infection ☆

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ABSTRACT

Balamuthia mandrillaris is an amoeba that causes an uncommon but deadly encephalitis, referred to as granulomatous amoebic encephalitis (GAE). The highest incidence reported worldwide has occurred in America, and within the United States, it has been highest in the Southwest affecting predominantly children and young men of Hispanic ethnicity. Clinical presentation of GAE includes fever, headache, nausea, vomiting, lethargy, irritability, stiff neck, hallucinations, photophobia, and seizures. Our patient was a Hispanic male child living in Arizona. The patient presented at 3 years of age for severe encephalitis. Symptoms included difficulty with balance, gait, and sitting up and seizure-like activity. Initial CT showed an area of decreased density consistent with edema in the right frontal and left frontoparietal lobes. Rapid progression was seen on further imaging over the length of the patient's hospital stay revealing diffusion restriction, necrosis/blood products, edema, and hemorrhage. The patient expired three weeks after onset of symptoms and one week after admission to our institution. While there are multiple biochemical techniques that can test for *B. mandrillaris*, they are rarely employed for multiple reasons stemming from the rare occurrence of this infection. Because of the fatal nature of this infection, we propose (1) testing should be considered if a patient presents with progressing encephalitis on imaging and other pathogenic etiologies are ruled out and (2) the threshold to treat empirically should be low due to the fatal nature of the infection.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Introduction

Balamuthia mandrillaris is an amoeba that causes an uncommon but deadly encephalitis, referred to as granulomatous amoebic encephalitis (GAE). The highest incidence reported worldwide has occurred in North and South America [1]. Within the United States, most cases have occurred in the Southwest, largely infecting children and young men of Hispanic ethnicity [1]. This case report demonstrates a classic presentation of GAE highlighting imaging findings and discussing diagnostic testing and treatment. This tragic case forewarns of the rapid progression that occurs in GAE necessitating proper diagnosis and treatment.

Case report

The patient was a 3-year-old Hispanic male living in Arizona. He was previously healthy with baseline facial palsy with right lip droop. There was no additional past medical history, no known exposure to pathogens, and no travel history. Symptoms began with only fatigue and progressed with abdominal pain and right cheek pain. The patient was seen by an outpatient provider and given ear drops for right ear redness. Five days later, intermittent fevers developed, and the patient was prescribed penicillin outpatient for potential sinusitis. A few days later, the patient's parents noticed changes in speech, gait, and difficulty sitting up. The patient was tested for Group A *Streptococcus*, was positive, and was switched from penicillin to cephalexin. The next day, the patient experienced seizure-like activity during which he was unresponsive to voice. The parents called EMS, and the patient was taken to the Emergency Department at another medical center. The patient received midazolam en route, and upon evaluation in the ED, the patient was no longer seizing but had altered mental status, fever, and a Glasgow Coma Scale score of 8. The patient developed a generalized tonic-clonic seizure and received lorazepam and levetiracetam. Initial head CT showed an area of decreased density consistent with edema in the right frontal and left frontoparietal lobes (Fig. 1) concerning for diffuse encephalitis. The patient was started on ceftriaxone and vancomycin.

Per outside records, admission labs included normal CMP and CBC with WBC count of 10.1 K/uL, Hgb 14.4 g/dL, and platelets of 321 K/uL. A specimen by bronchiolar lavage, urine analysis, CSF by lumbar punction, and blood for culture were collected, and the differential diagnosis remained broad including bacterial, viral, fungal, or parasitic causes of encephalitis. Lumbar puncture showed elevated WBC count of 75 K/uL, RBC count of 5 K/uL, normal glucose of 53 mg/dL, and elevated protein of 85 mg/dL. CSF analysis by ARUP meningitis/encephalitis PCR panel was negative for bacterial, viral, and fungal DNA (*Streptococcus pneumoniae, Streptococcus agalactiae, E. coli, H. influenzae, Neisseria meningitidis, Listeria monocytogenes, Crytoccous neoformans/gattii*, CMV, HSV 1, HSV-2, HHV-6, enterovirus, VZV, paraechovirus). These results made bacterial, viral, and fungal meningitis less likely, and more unusual causes of encephalitis, including autoimmune and inflammatory etiologies, were investigated. Additional tests included pending CSF oligoclonal bands (elevated in multiple sclerosis and subacute sclerosing panencephalitis), serum aquaporin-4 receptor (diagnostic for neuromyelitis optica), and myelin oligodendrocyte glycoprotein antibody (seen in myelin oligodendrocyte glycoprotein antibody disease [MOGAD]). The patient was started on dexamethasone 2 mg every six hours and received seven doses. Following this, IV immunoglobulin infusion was begun. The goal of these was to empirically treat potential autoimmune and inflammatory processes.

The patient was transferred to our institution for specialist assessment and was received by the PICU. At that time, he was intubated without sedation and was without brainstem reflexes on exam. Neurology, infectious disease, rheumatology, and genetics were consulted. The patient continued to receive IV immunoglobulin, methylprednisolone, and levetiracetam. Routine EEG demonstrated diffusely slow background with decreased reactivity and decreased variability suggestive of moderate encephalopathy with nonspecific etiology. MRI brain upon arrival to our hospital and four days after initial admission demonstrated extensive bilateral supratentorial and infratentorial, cortical/deep gray, and diffuse white matter diffusion restriction, T2 hyperintense signal and necrosis/blood products, subarachnoid/meningeal enhancement, and patchy enhancement within the bilateral frontal lobes (Fig. 2) indicating rapidly progressive inflammatory changes. Pupils became non-reactive and decerebrate posturing was noted. Rapid progression was again seen on repeated brain imaging. MRI brain three days after the last showed interval progression of extensive parenchymal diffusion restriction and T2 FLAIR hyperintense signal, increased periventricular and cerebellar involvement, increased edema within the basal nuclei lesions, extensive involvement of the frontotemporoparietal cortex and subcortical white matter, both medial thalami and medial temporal lobes, brainstem, and central cerebellum, petechial hemorrhage, and patchy leptomeningeal and parenchymal enhancement (Fig. 3). The patient's rapid deterioration inhibited further disease workup.

After one week of hospitalization and three weeks after initial symptoms, the patient experienced two episodes of asystole and expired with findings of extensive brain parenchymal edema and tonsillar herniation. Parents made the decision to make the patient DNR and withdraw life-sustaining interventions. Family agreed to brain autopsy in which the patient was diagnosed postmortem with parasitic encephalitis secondary to a *B. mandrillaris* CNS infection.

Discussion

Balamuthia mandrillaris is a free-living amoeba and opportunistic pathogen [1]. It is transmitted through broken skin exposure or inhalation of aerosols and is commonly found in soil and dust [2]. *B. mandrillaris* may spread to multiple organ systems, with a notable ability to cross the blood-brain-barrier and infiltrate the central nervous system (CNS). CNS infections caused by *B. mandrillaris*, referred to as granulomatous amoebic encephalitis (GAE) [2], lead to rapid patient deterioration by producing necrotizing hemorrhagic encephalitis [3].

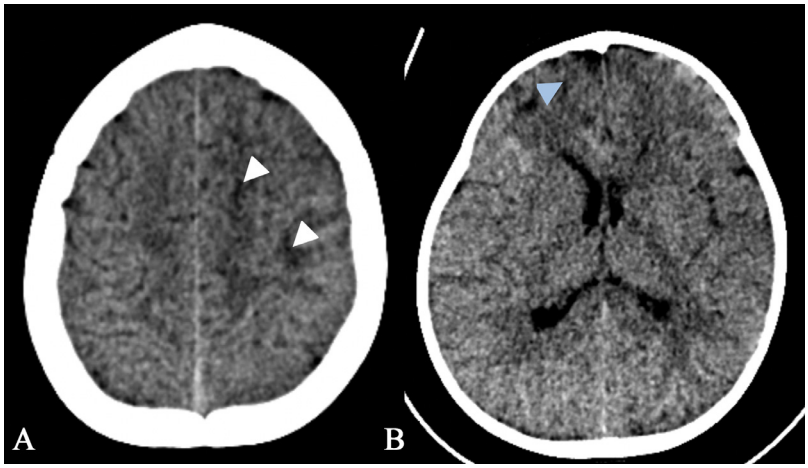

Fig. 1 – Brain CT on admission, two weeks after symptom onset, showing (A) hypoattenuation of the cortical and subcortical white matter of the left frontal lobe vertex (white arrows) and (B) subtle hypoattenuation of the frontal lobes (blue arrow).

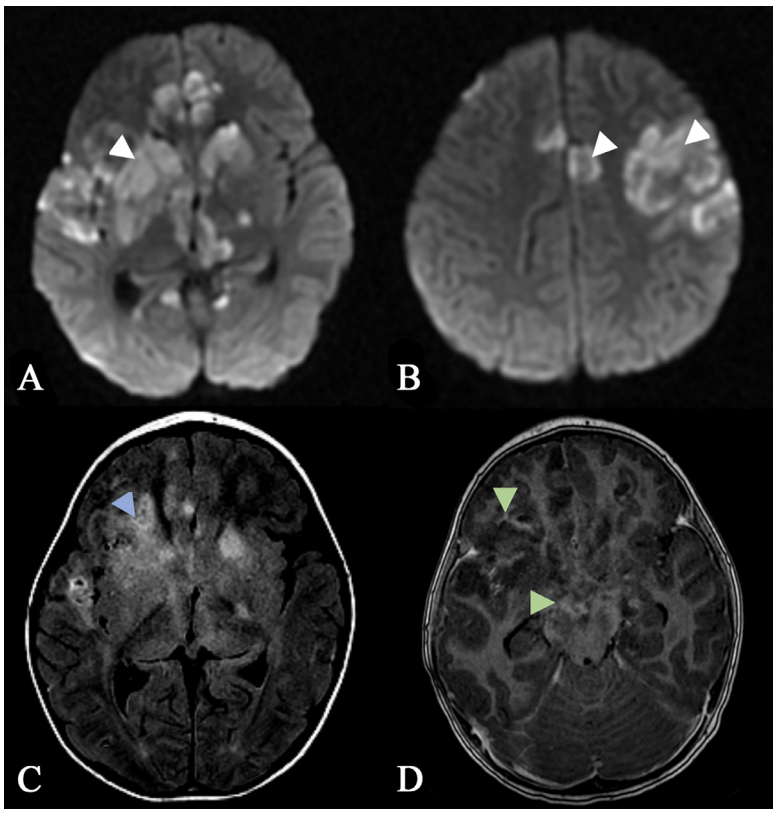

Fig. 2 – Brain MRI four days after admission with increased DWI signal shown by white arrowing in (A) and (B) consistent with true diffusion restriction on ADC (not shown), corresponding hyperintensity on FLAIR shown with a blue arrow in (C), and patchy enhancement shown with green arrows on post-contrast T1 in (D).

Clinical presentation of GAE may include skin lesions, fever, headache, nausea, vomiting, weight loss, lethargy, irritability, stiff neck, hallucinations, photophobia, hemiparesis, slurred speech, and seizures [1,2,4]. Patients may first present with skin involvement prior to encephalitis. However, patients in the United States have predominantly only presented with encephalitis [5]. Similarly, our patient presented with fever, lethargy, and seizures without skin involvement.

Neuroimaging findings are nonspecific, with multifocal lesions and edema affecting any cortical lobe or extracortical site [5]. The temporal lobe and frontal lobes are most frequently affected (52% and 42% of cases, respectively) [3]. Le-

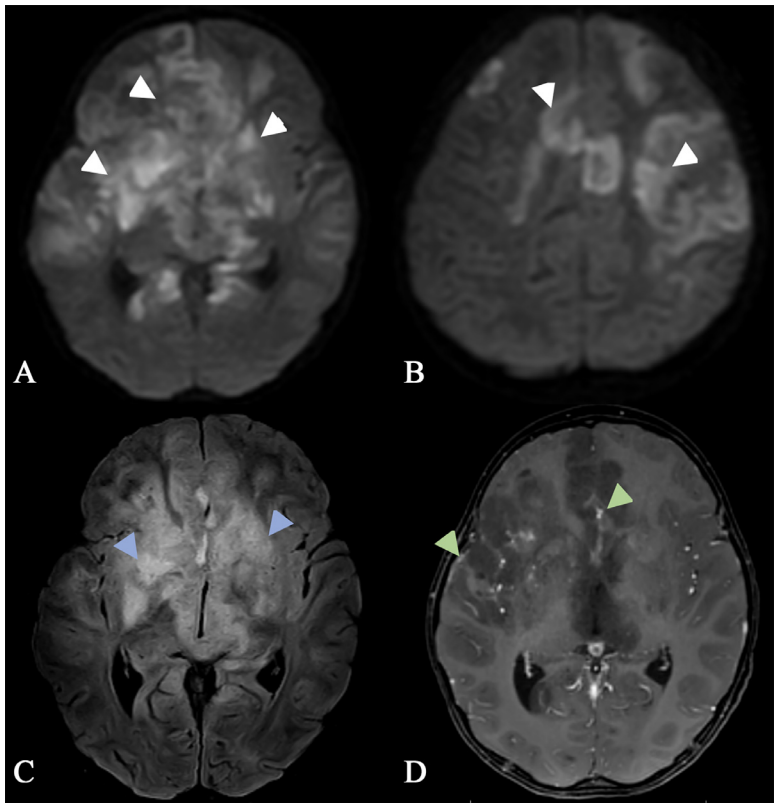

Fig. 3 – Brain MRI three days after the previous MRI and three weeks after symptom onset seen with progressive increased signal shown with white arrows on DWI in (A) and (B), progressive extensive hyperintense FLAIR signal shown with blue arrows in (C), and patchy meningeal and parenchymal enhancement shown with green arrows on fat-sat post-contrast T1 in (D).

sions may be small and solid or large and either nodular or with ring enhancements [1,2,4,5]. Aggressive and rapid progression of disease is characteristic of GAE. Imaging of our patient showed multifocal lesions affecting multiple lobes and extracorticol sites and rapid progression.

Differential diagnoses include viral or bacterial meningoencephalitis, acute disseminated encephalomyelitis, toxoplasmosis, or neurocysticercosis [1,5]. More common viral and bacterial pathogens should be ruled out first through CSF analysis and meningitis/encephalitis panel. Unfortunately, with current practice, misdiagnosis is frequent, and correct diagnosis is often made postmortem [1,5].

The limited cases of *B. mandrillaris* contribute to the difficulty in its diagnosis. Pathologists may be unable to diagnose it on biopsy due to unfamiliarity with the appearance of the amoebae in tissue sections [3]. Alternatively, *B. mandrillaris* can be diagnosed by PCR, immunofluorescence or immunoperoxidase staining, ELISA, flow-cytometry, or next-generation sequencing (NGS) using serum of CSF [1,3,4]. The majority of cases in the United States from 1974 to 2016 were diagnosed by indirect immunofluorescence followed by PCR and histopathology [4]. Unfortunately, testing materials are not readily available due to the uncommon nature of GAE. While NGS is a promising diagnostic tool, it is not available at all institutions. Additionally, false positives can be expected, as anti-*Balamuthia* antibodies are also found in the healthy population [6].

Infrequent diagnosis has prevented controlled studies required to elucidate effective treatment. There is no standardized treatment for GAE [1]. Therefore, most optimal treatment is somewhat unclear, and no single agent has been proposed. Patients are usually treated with multi-drug regimens. Success has been found using a combination of flucytosine, pentamidine isethionate, fluconazole, sulfadiazine, and macrolide with or without other drugs and with the combination of miltefosine, albendazole, and fluconazole or itraconazole [1,2]. In vitro activity of miltefosine against *B. mandrillaris* has been reported [7]. Length of treatment is a few months to >5 years [1].

Conclusion

B. mandrillaris is an uncommon and deadly parasite. Symptoms coincide with encephalitis, prompting CT and/or MRI. Imaging demonstrates edema affecting any cortical lobe or extracortical site. If routine tests for bacteria, viruses, and fungi are negative, *B. mandrillaris* may be considered. Rapid diagnosis and treatment are critical to increase patient survival. Though an uncommon diagnosis, its deadly nature requires consideration among the differential diagnosis. We propose testing should be considered if the patient presents with progressing encephalitis on imaging and other pathogenic etiolo-

gies are ruled out and the threshold to treat empirically should be low due to the fatal nature of the infection.

Patient consent

Consent was provided for this case report.

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