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Subacute Meningoencephalitis by free-living amoebae. Case presentation.

José Moisés Águila Figueroa[1], Jorge Luis Vázquez Cedeño[2*], Virginia Capo de Paz[3], Alexander Morales Fontaine[4], Mabel Brito Bartumeu[5]

[1]Specialist in Pathological Anatomy, Hospital "Héroes del Baire" Isla de la Juventud, Cuba
[2]Specialist in Intensive Medicine and Emergencies, Hospital "Héroes del Baire" Isla de la Juventud, Cuba
[3]Specialist in Pathological Anatomy, Pathological Anatomy Department of the "Pedro Kourí" Institute of Tropical Medicine, Havana. Cuba
[4]Specialist in Pathological Anatomy, Institute of Tropical Medicine "Pedro Kourí", Havana. Cuba
[5]Pediatric Specialist. Intensive Care, Hospital "Héroes del Baire" Isla de la Juventud, Cuba

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[*]**Corresponding author:** Jorge Luis Vázquez Cedeño, [2]Specialist in Intensive Medicine and Emergencies, Hospital "Héroes del Baire" Isla de la Juventud, Cuba. Email: jlvazquez@infomed.sld.cu

Abstract

Free-living amoeba (FLA) meningoencephalitis is uncommon, but with high mortality rate. All five previously reported FLA in Cuba were due to Naegleria fowleri. An elderly patient with a three-day history of upper respiratory and neurological symptoms is presented, clinically interpreted as bacterial meningoencephalitis. He died 48 hours later was admitted due to ischemic heart disease. The autopsy showed findings consistent with subacute meningoencephalitis by FLA. The importance of the clinical suspicion and the use of diagnostic methods for early detection are highlighted.

Keywords: Amebic meningoencephalitis; Autopsy; Free-living amoeba; Cuba

Introduction

Free-living amoeba (AVL) were considered safe commensals for years. In the middle of the 20th century, it was shown that they were capable of producing serious diseases in humans, which, despite their low morbidity, are associated with a relatively high mortality.

Four main tissue conditions are described, two of the central nervous system (CNS) with a high lethality, above 90-95%: an acute form that affects apparently healthy children and young people: Primary amoebic meningoencephalitis (MAP) caused by Naegleria fowleri and Paravahlkampfia francinae **[1, 2]** and another subacute or chronic form, which mainly affects elderly and / or immunocompromised individuals such as AIDS or hematological diseases: granulomatous amoebic encephalitis (GAE) caused by Acanthamoeba spp, Balamuthia mandrillaris and Sappinia pedata. Two other forms of presentation described are keratitis **[3, 4]** and skin lesions caused by Acanthamoeba spp and Balamuthia mandrillaris. These amoebas can also cause severe infections in the lungs, ears and nose **[5-9]**.

These parasites live in the soil and in stagnant fresh water with a warm temperature, capable of contaminating recreational and bottled waters because they resist chlorination, adopting the form of a trophozoite or cyst.[7, 8] they are usually acquired through the mucosa of the nasal region. Where they induce inflammation, they reach the olfactory neuroepithelium, the olfactory bulb, the cerebellum and, finally, the parenchyma and the cerebral cortex. They can also reach the CNS, from a primary focus: lung, skin or cornea, by hematogenous route, crossing the blood-brain barrier.[6, 10] Experiments and reports indicate that an alternative invasion route could be through a tympanic membrane, traumatic ruptured or weakened by infection, to access the acoustic nerve and basal ganglia **[6]**.

The infected individuals have a recent history of contact with polluted waters, especially swimming pools, hot springs or others for recreational or work purposes.[7] They are thermophilic amoebae, grow in tropical and subtropical climates.[2, 7, 8] They are globally distributed with an increase in exposures in the summer

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months, however, at present, the density of amoebas in the waters has increased, among other possible causes of climate change **[2, 7, 8]**.

AVLs can harbor endosymbiotic pathogens (bacteria, viruses, fungi) with clinical importance, acting as vectors and enhancing their environmental survival ("Trojan horse" effect) **[2, 10, 11]**.

In 1958 Culbertson demonstrated the pathogenicity of Acanthamoeba and in 1965 Fowler and Carter reported the first case of MAP in Australia caused by amoeba of the genus Naegleria. Since then (until 2016) the reports of AVL infections worldwide have been around 300 cases of MAP caused by Naegleria fowleri, approximately 150 cases of SAE due to Acanthamoeba sp, about 200 cases due to Balamuthia mandrillaris[12] and a single case due to Acanthamoeba sp. Sappinia pedata in 2001 **[13]**.
In a work published by Sierra in 2011, García-Tijera is cited in a report of the first Cuban case in 1978, based solely on clinical suspicion (including improvement with amphotericin B treatment and observation of the microorganism in nasal lavage) **[14]**. And Sotolongo, who in Havana in 1986, a patient from the Isla de la Juventud, Cuba was exposed, when observing the mobile amoeba by studying the cerebrospinal fluid (CSF) **[14]**.

In another more recent publication, the third case of AVL Meningoencephalitis is cited, the only one confirmed by molecular biology in our country, reported by Cubero in 2004 in Havana and from a brain autopsy study as Naegleria fowleri etiology **[15]**, other two cases were identified by the Sierra itself in Santiago de Cuba / 2011, from a CSF study, confirmed as Naegleria fowleri by ANNE culture, flagellation test and electron microscopy **[14]**. In short, only one of the five reported cases has been internationally recognized due to Its confirmation by molecular techniques, which together with PCR techniques are considered the gold standard for diagnosis of this infectious entity, very few reference laboratories have this capacity installed in Cuba **[15]**.

The present work aims to report the 6th case of AVL meningoencephalitis in Cuba diagnosed by necropsy, for the first time, a subacute clinicopathological variant.

Case presentation

Male patient, 65 years old, rural residence in Isla de la Juventud with a health history. He developed a sore throat and fatigue three days before going to the hospital. Prior to admission, a fever of 39oC began, associated with headache, nausea and drowsiness. He arrives at the emergency department with irritability, psychomotor agitation and nuchal rigidity. A lumbar puncture was performed with a CSF cytochemical study: yellow, cloudy appearance, positive Pandy reaction, 8000 cells / mm3 predominantly neutrophils, 0.4 mmol / L glucose, 204.6 g / L proteins.

He was admitted to intensive care (ICU) with clinical deterioration where antibiotic treatment was started (Ceftriaxone 2 grams every 12 h / Vancomycin 1 gram every 12 hours both drugs intravenously), mannitol and mechanical ventilation due to neurological deterioration (Glasgow 7 points). Evolutionarily, he presented ST segment elevation in the electrocardiogram, for which he was diagnosed with acute myocardial infarction (AMI), he presented serious ventricular arrhythmias and died 48 hours after admission to the ICU. Clinical diagnosis of death: Ventricular arrhythmia secondary to AMI. Basic cause: Bacterial meningoencephalitis. Microbiological organisms were identified in direct microbiological examination or in CSF culture.

Autopsy Report

Macroscopic examination: Brain: cerebral atrophy and edema, slight opacity of the leptomeninges in parasagittal convexity, towards the base and cerebellum. Serial sections of the cerebral and cerebellar parenchyma did not show alterations. Histological examination: A mixed inflammatory process is observed with an infiltrate rich in polymorphonuclear cells, lymphocytes and histiocytes, as well as plasma cells of perivascular, meningeal, parenchymal location in the cortico-subcortical region, nuclei of the base and cerebellum, accompanied by a moderate glial reaction. Vasculitis with fibrinoid necrosis and arteriolar thrombosis, as well as focal cerebral colliquative necrosis, is evident. Perivascularly, numerous rounded or ovoid nucleated structures are identified, with a large pink nucleolus with a light halo, resembling macrophages, morphologically compatible with amoeba trophozoites. **(Figure 1-4)** The Department of Pathological Anatomy of the "Pedro Kouri" Institute of Tropical Medicine is consulted, where it is reported that the morphological findings strongly suggest that they correspond to AVL trophozoites, without the possibility of carrying out molecular diagnosis or immunofluorescence in this center. PAS staining was performed and thick-walled structures were identified, which morphologically may correspond to cysts of Acanthamoeba spp **[12]**.

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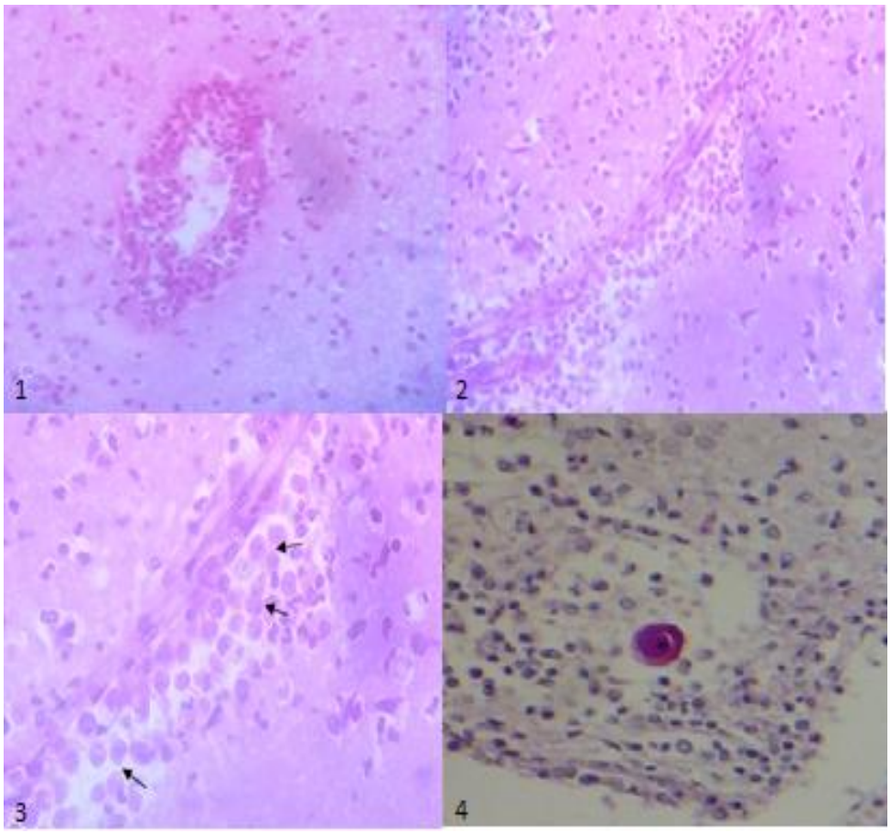

Figure 1: Histological section of the brain showing chronic cerebral vasculitis characterized by moderate to severe inflammatory infiltrate. (H&E, 25X). **Figure 2:** Greater detail of the histological section of the brain showing tissue edema, abundant inflammatory, interstitial and perivascular cells, as well as numerous AVL trophozoites, and abundant perivascular inflammatory infiltrate. (H&E, 40X. **Figure 3:** Enlargement of the previous image showing the presence of ovoid trophozoites, with fine granular, eosinophilic cytoplasm and nucleus with prominent nucleolus, probably from Acanthamoeba spp. perivascular location (arrows). Tissue neutrophils are also seen. (H&E, 100X). **Figure 4:** AVL cyst of thick wall, possible Acanthamoeba, spp, neighboring chronic inflammatory infiltrate (Periodic Acid Schiff 40X).

Severe vessel atheromatosis of the circle of Willis. Hemorrhagic inflammatory condensation of both lungs with a predominance of basal lobes that histologically corresponded to mild bibasal bronchopneumonia and chronic pulmonary congestion. Left ventricular cardiac hypertrophy with normal myocardial staining, which histologically showed recent ischemic lesion due to coagulation myocytolysis, edema and moderate cardiac interfiber polymorphonuclear infiltrate. Severe aortocoronary atheromatosis. No endocardial or pericardial alterations. Digestive system: acute gastritis, diverticular disease of the colon. Cholelithiasis. Severe chronic passive stasis liver and moderate steatosis. Nodular prostatic hyperplasia.

Conclusions of the case:

Heart rhythm disorder as a direct cause of death, acute myocardial infarction as an intermediate cause, and basic cause is subacute AVL meningoencephalitis, probably Acanthamoeba spp.

Discussion

The sixth Cuban case of AVL meningoencephalitis is reported, this time of a subacute clinical and pathological nature, which, in turn, reinforces the probable morphological suspicion of amoeba of the genus Acanthamoeba spp in postmortem brain tissue. The histological study can reveal subtle differences between species, however, the morphology of the parasite is insufficient to conclude an aetiological diagnosis of certainty, due to the morphological similarity between them, especially between Acanthamoeba spp and Balamuthia mandrillaris **[10]**.

Due to the tropical nature of the Cuban archipelago with high temperatures almost all year round and the population's trend towards bathing for recreational purposes, it is likely that the true incidence is under-registered due to low clinical and pathological suspicion, as well as the current low level of autopsy. in many hospital institutions **[1, 8-10, 14, 15]**.

For granulomatous amoebic encephalitis, invasion of the CNS through the blood-brain barrier is the most important form of infection and species of Acanthamoeba, Balamuthia mandrillaris and Sappinia pedata participate because their life cycle involves only 2 stages: cysts and trophozoites, responsible Frequent subacute and chronic symptoms, these amoebas lack the amoeboflagellate transition stage, characteristic only of Naegleria sp that favors direct invasion of the CNS via the nasal passage, causing more acute and fulminant pictures **[8-10, 13]**.

The patient had a history of upper respiratory involvement, associated with rural residence and regular use of well water with inadequate sanitary parameters, which could be the source of contamination. In the postmortem stage, a history of skin lesions and ophthalmological care was collected without other specifications, which could correspond to entry points of the causative agent **[10]**.

The observation of the parasite in the CSF in GSD is not the diagnostic method of choice since they only usually appear in the early stage of the disease and usually in the form of few or absent trophozoites, while the cystic form is more frequent. behavior contrary to that observed in the clinical form MAP **[1, 3, 10, 15]**.

Given that the symptoms and imaging findings are nonspecific, for the diagnosis of amoebic meningoencephalitis it is imperative to document the presence of trophozoite or amoeba cysts in the CSF or in brain tissue obtained by stereotaxic or postmortem biopsy **[1, 5, 8-10, 16, 17]**. Immunomolecular methods are currently recommended as the gold standard for confirmatory diagnosis and that also allow to demonstrate the gender of AVL involved **[15]**.

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Ggranulomatous amoebic encephalitis (GAE) as a subacute, chronic, mixed granulomatous or granulomatous infection, caused by Acanthamoeba spp, B. Mandrilari, and Sappinia Pedata, affects elderly, weakened or immunocompromised individuals; considered opportunistic infection with exceptional reports in the literature in immunocompetent individuals, and a prolonged period of evolution of weeks or months, although the history of immunocompromise is relevant in infections by Acanthamoeba spp, it is not in cases produced by B. mandrillaris **[3, 8, 10, 15, 16]**.

In this work, an immuno-senescent patient is presented, with no apparent opportunistic disease, a short period of evolution of the neurological manifestations, which could be influenced by the virulence of the germ, the size of the inoculum and the systematicity of exposure to the possible source. Histologically, there was no complete development of granulomatous changes, possibly due to the truncated evolution of the disease, as the patient died of arrhythmia secondary to acute myocardial infarction (AMI) before completing the natural evolution of the infectious process in the CNS. A large series study **[18]** reported 35% of SAEs cases in which mixed tissue inflammation predominated, even without elements of classic granuloma, with a predominance of association with Balamuthia sp, intermediate histopathological findings when compared with MAP, which may also mean alterations in the Immune status of the patient **[16, 18, 19]**. Nakamura reports a case diagnosed as primary acute meningoencephalitis, caused by Acanthamoeba, Japan. 1979 **[19]**.

The diagnosis in the vast majority of cases is made postmortem. Neuroinfection by Naegleria spp, which can be rapidly fatal, causes death generally due to direct complications of central nervous system involvement such as marked cerebral edema and intracranial hypertension, while elderly patients with associated or immunocompromised comorbidities who suffer from CNS infection due to Acanthamoeba spp and B Mandrilari, death frequently occurs from other causes such as bronchopneumonia or other lung lesions, liver or kidney failure, or other disease not related to direct brain damage **[2, 3, 5, 10, 13, 15, 20]**. The literature exposes cases in which sterile neutrophilic myocarditis is identified post-mortem as a complication of free-living amoeba neuroinfection **[2,3,5,9]**. The authors found no reports of death from AMI in the course of AVL meningoencephalitis.

The golden rule of successful treatment is early diagnosis. The usual antimicrobials have a limited capacity to cross the blood-brain barrier and reach the CNS, which, associated with the low sensitivity of amoebae to these agents, reduces their effectiveness. However, several combined agents, administered intrathecally and intravenously, could increase therapeutic success **[1, 8, 13, 17]**.

To prevent AVL infection, avoid exposing the skin with a breakdown and the nasal mucosa to water from natural and artificial deposits. Contact lenses should be disinfected and avoid wearing them during bathing.

Conclusions

We document the first case of AVL meningoencephalitis, of subacute anatomoclinical nature, that has been reported in Cuba, which corresponds to the clinical variant: SAE, in which the etiological agent must correspond to the genus Acanthamoeba spp or B. Mandrilari, which is difficult to differentiate between them if more sensitive diagnostic methods such as PCR and immunochemicals are not available. It is important to collect well the data of the current disease and clinical-epidemiological history as well as the risk behaviors of the patient, to suspect the diagnosis and consider AVL infections as a differential diagnosis in CNS infections, especially in atypical conditions, if they are knows the presence of the etiological agent in the country. Laboratory diagnosis with specific cultures and CSF and histological findings can guide these pathogens, which would contribute to early diagnosis and could improve the prognosis, since there is no specific effective treatment.

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Conflict of Interest

All authors declare that they have no conflict of interest.

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