International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
DOI: 10.22192/ijarbs Coden: IJARQG (USA) Volume 7, Issue 8 -2020

Review Article

DOI: http://dx.doi.org/10.22192/ijarbs.2020.07.08.003

A Review of Balamuthiasis

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Abstract

Balamuthia mandrillaris was first discovered in 1986 from brain necropsy of a pregnant mandrill baboon (Papio sphinx) that died of a neurological disease at the San Diego Zoo Wild Animal Park, California, USA. Because of the rarity of Balamuthiasis, risk factors for the disease are not well defined. Though soil, stagnant water may serve as sources of infection for balamuthiasis. Right now, the predisposing factors for *B. mandrillaris* encephalitis remain incompletely understood. Though, BAE may occur in healthy individuals, immunocompromised or weakened patients due to HIV infection, malnutrition, diabetes, those on immunosuppressive therapy, patients with malignancies, and alcoholism are predominantly at risk. While the number of infections due to *B. mandrillaris* is fairly low, the difficulty in diagnosis, lack of awareness, problematic treatment of GAE or BAE, and the resulting fatal consequences highlights that this infection is of great concern, not just for humans but also for animals

Current methods of treatment require increased awareness of physicians and pathologists of GAE or BAE and strong suspicion based on clinical findings. Early diagnosis followed by aggressive treatment using a mixture of drugs is crucial, and even then the prognosis remains extremely poor.

Keywords: *Balamuthia mandrillaris,* balamuthiasis, immunocompromised patients, HIV

Introduction

Discovery, biology and classification

Balamuthia mandrillaris was first discovered in 1986 from brain necropsy of a pregnant mandrill baboon (Papio sphinx) that died of a neurological disease at the San Diego Zoo Wild Animal Park, California, USA (Visvesvara *et al.*, 1990). It was named after the late professor William Balamuth of the University of California Berkeley, for his contributions to its study.

As an emerging protist pathogen; a free-living amoeba resembling Acanthamoeba in microscopic tissue sections, *Balamuthia mandrillaris* is found naturally in the environment. Although closely related to Acanthamoeba, based on light and electron microscopic studies, animal pathogenicity testing, antigenic analyses and ribosomal RNA sequences, a new genus, Balamuthia was created(Visvesvara and Stehr-Green, 1990; Amaral Zettler *et al.*, 2000; Booton *et al.*, 2003).

In literature, it is referred to as a “Leptomyxid amoeba” and causes a serious infection of the brain known as “Balamuthia or Granulomatous amoebic encephalitis” (BAE or GAE) in both immune-competent and immune-compromised humans, horses, dogs, sheep, and non-human primates. Other organs like the skin, liver, kidneys, and rarely spinal cord may be affected.

The first human infections were reported in 1990, and in 1993. About 200 cases of infection have been reported worldwide (Lorenzo-Morales *et al*., 2013, Bravo and Seas, 2012 and Cary *et al*., 2010). Since 1993, cases have been reported in western and central Europe, Canada, Argentina, Brazil, Peru, Venezuela, Mexico, Australia, Thailand, Japan, and India.

Early reports of the disease in humans suggested that the infection occurred primarily in immune-compromised persons (e.g. HIV/AIDS patients, injection-drug users, the elderly, and persons with concurrent health problems).

Because of the rarity of Balamuthiasis, risk factors for the disease are not well defined. Though soil, stagnant water may serve as sources of infection for balamuthiasis. Right now, the predisposing factors for *B. mandrillaris* encephalitis remain incompletely understood. Moreover, unlike Acanthamoeba; Balamuthia can produce encephalitis in relatively immunocompetent individuals, leading almost frequently to death, and consequently presents a significant threat to human health. This remains a big concern in view of

i. The increasing rise in the numbers of immunocompromised patients
ii. The rising use of antibiotics world-wide
iii. Global warming with increased outdoor activities adding to the ubiquity of these pathogens, hence increases people's exposure or susceptible hosts and so on.

Given all these, the most disheartening aspect to *B. mandrillaris* encephalitis, is the inadequate availability of effective and/or recommended treatment. Therefore the purpose of this review is to broaden our current understanding of the organism's morphology and biology, life cycle, the disease it causes, virulence, culture and diagnosis, pathogenesis of its infection amongst others, and to recommend ways we can increase people's awareness especially medical health personnel, on detecting the organism, treatment, prevention and possibly control its spread among others.

Balamuthia mandrillaris is classified in the;

- Kingdom: Amoebozoa
- Class: Lobosea
- Order: Centramoebida
- Family: Balamuthiidae
- Genus: Balamuthia
- Specie: *B. mandrillaris*

Morphology

Using Atomic force microscopy, that involves the study of the precise description of shape, surface and feature of an organism. The two-dimensional and three-dimensional images shows that *B. mandrillaris* has an irregular surface with a mean height of 2.76 µm and a diameter of approximately 10 µm (Aqeel *et al.*, 2014). Morphologically it has two stages in its life cycle, a vegetative trophozoite stage and a dormant cyst stage. The trophozoites form broad pseudopodia and exhibit filamentous structures (Schuster and Visvesvara, 2004; Jayasekera *et al*., 2004; 2005).
The trophozoite stage is approximately 30–60 µm in diameter and contains a single nucleus (although binucleated forms have been observed). Under harsh conditions (i.e. lack of food, extremes in osmolarity, pH and temperatures, increasing density of parasite populations), the amoebae switch by encystation into a dormant cyst stage which are spherical, uninucleate and approximately 10–30 µm.

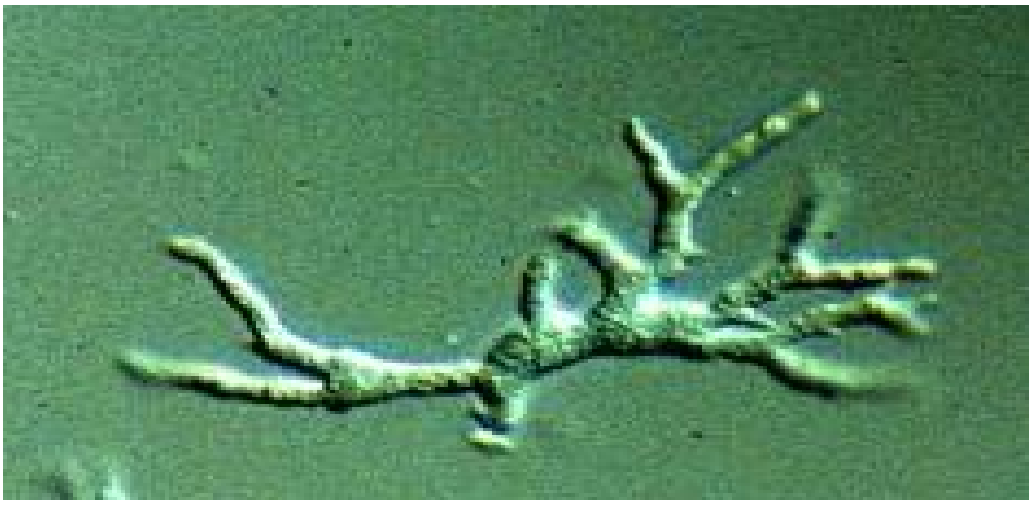
Transmission electron microscopic studies show that cysts in *B. mandrillaris* have three walls: An inner endocyst, and an outer wrinkled ectocyst. Both separated by an undefined thick amorphous, fibrillar middle layer, the mesocyst (Martinez *et al.*, 2001).

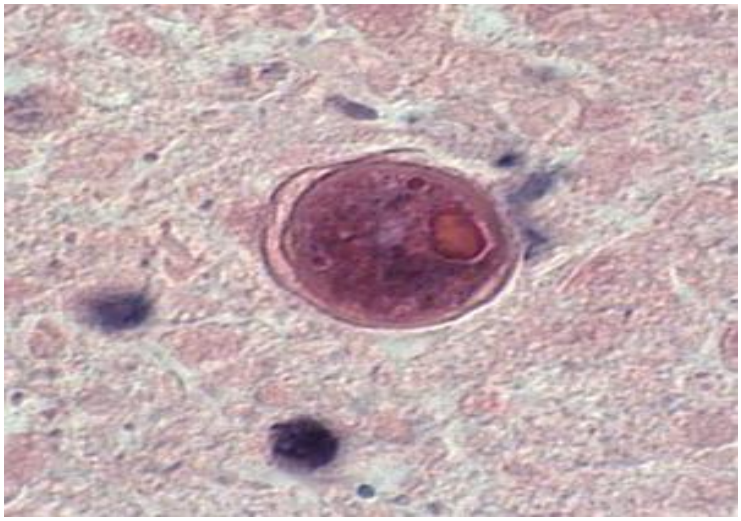
Siddiqui *et al.* (2008) also found that *B. mandrillaris* cysts are resistant to repeated freeze–thawing (5 times), temperatures of up to 70°C, 0.5% SDS, 25 ppm chlorine, 10 mg pentamidine isethionate per mL and 200 mJ ultraviolet irradiation cm^2.

These studies reveal that the cysts are resistant to denaturing conditions, and that cyst walls are composed following linkage analyses, at least in part, of carbohydrates. Examination of the carbohydrate composition of the cyst wall revealed that the major components are mannose (20.9 mol%) and glucose (79.1 mol%) with trace amounts of galactose present.

Linkage analysis shows cyst wall carbohydrates with apparently linear and branching saccharides and suggests the presence of cellulose (Siddiqui *et al.*, 2010).

Below is the structure of the organism's Trophozoite and cyst.





Life cycle

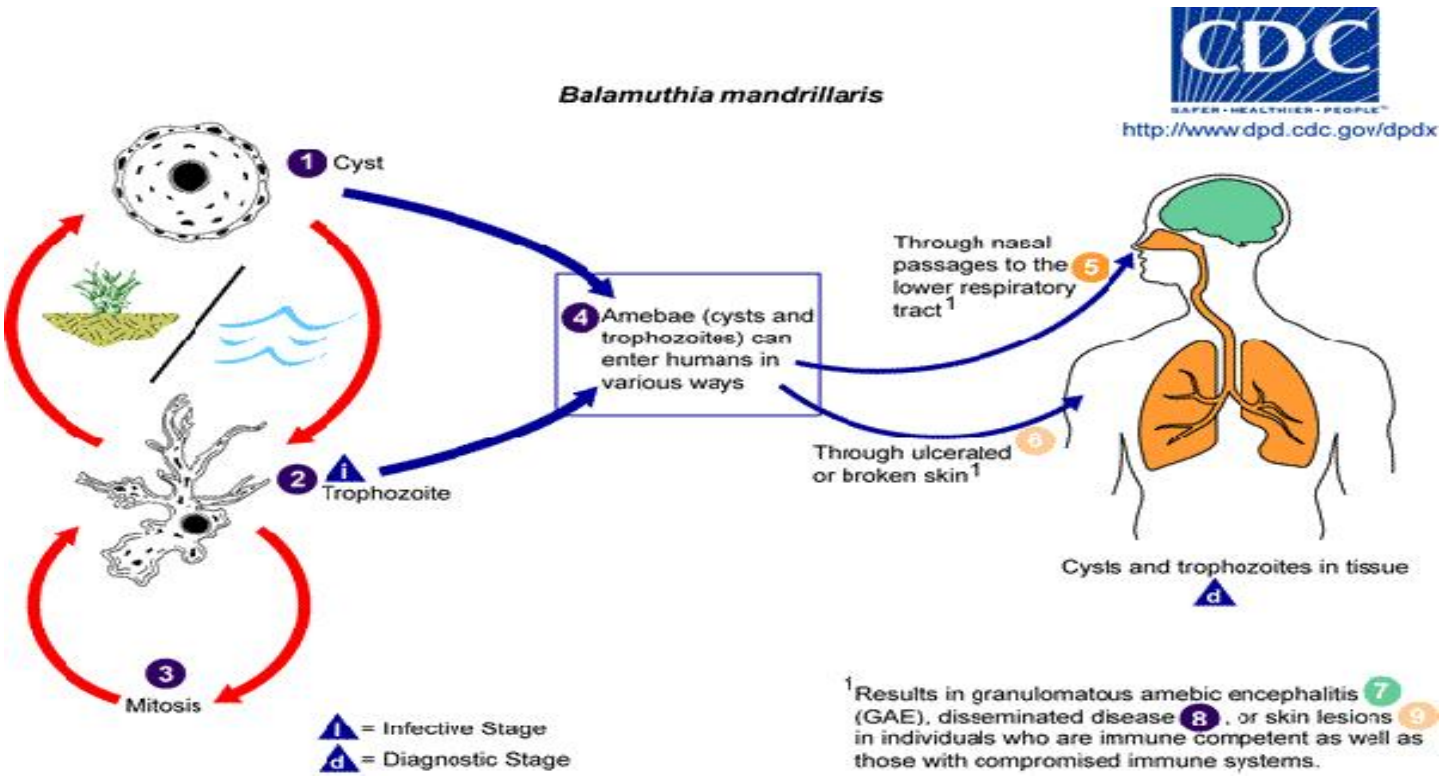
Balamuthia's life cycle, like Acanthamoeba, consists of only two stages; a cystic stage and a trophozoite stage which is pleomorphic, both of which are infectious, and which can be identified as inclusions in the brain biopsies of infected individuals.

No flagellated stage exists as part of the life cycle. The trophozoites are the infective forms, though cysts can gain entry into the body through various means.

Among these are nasal passages to the lower respiratory tract, ulcerated or broken skin. When *B. mandrillaris* enters the respiratory system or through the skin, it can invade the central nervous system by hematogenous dissemination causing BAE or GAE or disseminated disease

Skin lesions may also be seen in immune-competent or compromised individuals.

Life cycle image



Pathogenesis/ Immune reactions

Despite improvements in the diagnosis of Balamuthia or Granulomatous Amoebic Encephaliti (Huang *et al.*, 1999; Booton *et al*., 2003a, b; Yagi *et al*., 2005; Qvarnstrom *et al*., 2006; Tavares *et al*., 2006), the pathogenesis and pathophysiology of this disease remains however incompletely and poorly understood.

The routes of entry include the respiratory tract, leading to amoebae invasion of the intravascular space, followed by hematogenous spread. Alternatively, skin lesions may provide direct amoebal entry into the bloodstream. The Amoebae enter the body via the nose and either enter into lungs or travel along the olfactory neuroepithelial route, finally leading to amoebae invasion of the central nervous system (CNS).

The precise molecular mechanisms of *B. mandrillaris* transmigration of the blood-brain barrier are not known. Several events may combine to disrupt the blood-brain barrier, including its adhesion, proteolytic attack, and/or host inflammatory responses leading to blood-brain barrier injury.

Recent studies invitro show that the organism exhibit binding to Human Brain Mascrovascular Endothedial Cells (HBMEC) which model the blood-brain barrier in a galactose-inhibitable manner, thus indicating the presence of a galactose-binding protein on the surface membranes of *B. mandrillaris* (Matin *et al.*, 2007).

Overall, *B. mandrillaris* stimulate the activation of host intracellular Signaling pathways leading to inflammatory responses. The cumulative effects of these events eventually lead to blood-brain barrier perturbations as demonstrated by HBMEC cytotoxicity (Jayasekera *et al*., 2004; Matin *et al*., 2006).

The immunity is predominantly T-lymphocyte mediated and therefore depletion of CD_{4+} and T-helper cells results in replication of amoebae. The route of invasion is the bloodstream, the trophozoites and cysts are often seen around blood vessels and in necrotic CNS tissue. Balamuthia like acanthamoeba secrete cytolytic enzymes such as that may cause CNS damage.

Pathophysiology of balamuthia amoebic encephalitis

Though, BAE may occur in healthy individuals, immunocompromised or weakened patients due to HIV infection, malnutrition, diabetes, those on immunosuppressive therapy, patients with malignancies, and alcoholism are predominantly at risk (Schuster and Visvesvara, 2004; Visvesvara *et al.*, 2007; Siddiqui and Khan, 2008). The clinical symptoms of the disease can be similar to viral or bacterial meningitis, leptomeningitis, and tuberculous meningitis and are characterized by headache, fever, nausea, skin lesions, stiff neck, sleepiness, mood swings, hemiparesis, aphasia, vomiting, acute confused state, increased intracranial pressure, cranial nerve palsies, seizures, brain edema and lastly lead to death (Martinez and Visvesvara, 1997; Jayasekera *et al*., 2004; Schuster and Visvesvara, 2004; White *et al.*, 2004).

According to Martinez and Visvesvara 1997, the amoebae attacks brain tissue and produce sub-acute necrotizing hemorrhagic encephalitis leading to brain dysfunction. Their cysts and trophozoites are found within the perivascular spaces and in the necrotic CNS parenchyma

Normally, the encephalitis caused by this organism is of the granulomatous type composed of CD_4 and CD_8 T-cells, B lymphocytes, macrophages, few plasma cells and multinucleate giant cells. But, in immunocompromised patients with an weakened cellular immune response, granuloma formation can be negligible or absent (Martinez *et al.*, 2001).

Clinical manifestations

Balamuthia mandrillaris may enter the body through the lower respiratory tract or through open wounds. The Balamuthia amebas can infect the skin, sinuses, brain and other organs of the body. Upon introduction, the amoebas may form a skin lesion, or migrate to the brain. The skin lesions may appear at the site of an abrasion of the skin surface of the patient, or lesions can appear as single or multiple plaques or nodules (Deetz *et al.*, 2003; Bravo and Seas, 2006).

Once in the brain, it causes “Granulomatous amoebic encephalitis” (GAE) also known as “Balamuthia amoebic encephalitis” (BAE) which is usually fatal. The time period of transition from the cutaneous form to the CNS ranges from 30 days to 2 years, with an average of 5–8 months (Bravo and Seas, 2006).

Right from 1998, the California Encephalitis Project (CEP) has been testing different encephalitis cases for both common and uncommon agents known to cause Encephalitis, together with Balamuthia. This report describes the 10 Balamuthiasis cases identified by CEP during 1999-2007. The preliminary diagnoses in these cases included neurotuberculosis, viral meningoencephalitis, neurocysticercosis, and acute disseminated encephalomyelitis. Amongst whom only one patient died.

These finding goes on to highlight the importance of increasing awareness among clinicians, epidemiologists, and public health personnel for timely recognition and potential treatment of Balamuthia encephalitis.

Signs and symptoms

Balamuthia infection is very rare, but can cause a wide range of symptoms. Disease can begin on the skin, wound on the face, trunk, or limbs and can then progress to the brain where it causes GAE or BAE, diagnosis of which can be difficult, but some early symptoms may include:

- Headaches
- Stiff neck or head and neck pain
- Nausea
- Vomiting
- Lethargy (tiredness)
- Low-grade fever
- Other signs of Balamuthia GAE may include:
- Behavioral changes
- Seizures
- Weight loss
- Partial paralysis
- Speech difficulties
- Difficulty walking

The disease might appear mild at first but can become more severe over weeks to several months (Perez and Bush 2007, Visvesvara *et al*., 2007). Often the disease is fatal, with a death rate of more than 95% and the overall outlook for people who get this disease is poor, although early diagnosis and treatment may increase the chances for survival (Siddiqui and Khan, 2008).

Amoebic keratitis may arise due to Balamuthia lesions on the face, and generally produces facial swelling, which are mostly localized and very slow to heal, or fails to heal completely. In some cases, the lesion may be mistaken for some forms of skin cancer.

Balamuthia encephalitis is an extremely deadly disease, and as of 2008, only seven recoveries had been reported, all with lasting brain damage

Epidemiology and risk factors

Balamuthia amoebas being single-celled living organisms are thought to enter the body when soil containing the organism comes in contact with skin wounds and cuts, or when dust containing the organism is inhaled or gets into the mouth. Balamuthia ameobas live freely in soil around the world, thus gardening, playing with dirt, or breathing in soil carried by the wind might increase the risk for infection.

Balamuthia might also be present in fresh water. There have been reports of Balamuthia GAE infection in dogs that swam in ponds. However, there have been no reported human cases where the only potential exposure was swimming.

An open wound, such as a cut or scrape, may be a potential entry point for Balamuthia. The amoeba is able to infect anyone, including healthy people and those who are at bigger risk of contracting the infection include:

- People with HIV/AIDS, cancer, liver disease, or diabetes mellitus
- People taking immune system inhibiting drugs
- Alcoholics
- Young children or the elderly
- Pregnant women

In the United States, Balamuthia infection might be more common among Hispanic Americans. However, the reason for this trend is unknown, but might be due to differences in exposure, biology, data collection, or other causes. And so extra research is needed to understand those causes, which might be associated with increased reporting among persons of Hispanic ethnicity (Schuster *et al.,* 2004).

There's been no report of a Balamuthia infection spreading from one person to another except through organ donation/transplantation.

Potential risk factors

Five patients had preexisting medical conditions: diabetes, gout and heart disease, status post splenectomy, nephrotic syndrome with a prolonged course on steroid therapy, and a possible lymphoma. Patients in five of the 10 cases had a known exposure to soil: motorcycling in desert terrain, handling flowerpot soil, working in construction, or gardening as a hobby. No pertinent soil exposures were identified from the other five patients.

Laboratory diagnosis

Trophozoites of *B. mandrillaris* in brain tissue stain with Hematoxylin and Eosin (H&E). Currently, indirect immunofluorescence staining of formalin-fixed tissue specimens (e.g. brain tissue) is the definitive diagnostic test for balamuthiasis.

There are three types of tests that can help confirm the diagnosis of BAE.

- The indirect immunofluorescence assay (IFA) is a test used to detect antibodies attached to Balamuthia amebas in body tissues.
- Immunohistochemistry (IHC) which uses specific antibodies against Balamuthia to detect the amebas.
- Finally, a molecular assay which detects Balamuthia DNA being Polymerase chain reaction (PCR)

BAE or GAE a serious infection of the brain and spinal cord caused by Balamuthia and is often diagnosed only after death. However, it can be diagnosed by examining blood, cerebrospinal fluid, and tissue samples from a living patient as well. Diagnosis of GAE in a living patient is less common because the amebas are difficult to identify under the microscope, even with commonly used stains.

Balamuthiasis is difficult to diagnose because;

1) The clinical symptoms mimic those of several other types of encephalitis,
2) Few laboratories perform appropriate diagnostic testing, and
3) Many physicians are unaware of the disease.
The lack of recognition and subsequent delay in diagnosis might be a factor in its high mortality. Since 1998, the California Encephalitis Project (CEP) has been testing encephalitis cases for both common and

uncommon agents known to cause encephalitis, including Balamuthia.

Culture and identification

Balamuthia is most easily identifiable in a brain biopsy performed on an individual suffering from Balamuthia meningoencephalitis. The amoeba cannot be cultured on an agar plate coated with gram-negative bacteria because unlike most amoebae, *Balamuthia mandrillaris* does not feed on bacteria.

Instead the amoeba must be cultured on Primate hepatic cells or human brain microvascular endothelial cells (HBMECs) the cells that constitute the blood–brain barrier (Martínez and Visvesvara, 2001).

California encephalitis project surveillance

CEP was initiated to better understand the etiologies, risk factors, and clinical features of human encephalitis. The project was started in 1998 in collaboration with the California Department of Public Health Viral and Rickettsial Disease Laboratory and CDC's Emerging Infections Program. Specimen referrals to CEP are received statewide from clinicians seeking diagnostic testing for immunocompetent patients aged >6 months who meet the CEP case definition for encephalitis. CEP defines encephalitis as illness in a patient hospitalized with encephalopathy and one or more of the following: fever, seizures, focal neurologic findings, cerebrospinal fluid (CSF) pleocytosis, and electroencephalogram or neuroimaging results consistent with encephalitis.

Specimens from approximately 3,000 encephalitis patients were referred to CEP during 1999-2007. The majority of submissions included acute serum (2,652), Cerebrospinal fluid CSF (4,016), and respiratory samples (1,759). Five hundred cases were selected for Balamuthia serology based on at least one of the following:

1) Clinical symptoms (e.g. cranial nerve palsies, seizures, and coma);
2) Elevated CSF levels of protein and leukocytes, with normal or low glucose;
3) Abnormal neuroimaging findings (e.g. hydrocephalus, ring-enhancing lesions, or space-occupying lesions); or
4) Occupational or recreational contact with soil (e.g. work in agriculture or construction or dirt biking).

A titer >1:128 was considered a presumptive positive and selected for further testing of brain tissue, if available. From the 500 patient specimens tested, 10 cases of Balamuthia encephalitis were identified, first by serology and then definitively by additional methods. For two additional cases with elevated titers for Balamuthia antibodies by indirect immunofluorescence antibody (IFA) staining, brain tissue was not available, so the significance of positive titers was unknown. The median age of the 10 patients was 15.5 years (range: 1.5-72.0 years); nine of the patients were male. Seven of the 10 CEP cases occurred in southern California, and three occurred in central and northern California. Neurologic symptoms indicative of CNS involvement were the initial manifestations in nine of the 10 cases. In one case, the patient developed a cutaneous lesion on his upper arm several months before development of CNS symptoms. Development of the lesion was temporally associated with cleaning a backyard pond. Postmortem, the skin lesion was found to be positive for Balamuthia amebae by indirect immunofluorescence staining and polymerase chain reaction (PCR), and might have been the portal of entry preceding development of CNS disease.

CSF analysis in nine(9) of the 10 cases showed elevated protein with a median value of 188 mg/dL (range: 64-674 mg/dL), elevated white blood cell count with a median value of 170.5 cells/mm3 (range: 11-540 cells/mm3) and a lymphocytic predominance, and normal or low glucose with a median value of 40 mg/dL (range: 15-74 mg/dL). Abnormal neuroimaging results were observed in all 10 cases, headache was reported in six cases, altered mental status was reported in four cases, and manifestations of cranial nerve palsies were reported in four cases.
The median interval from onset of symptoms to hospital admission was 8.5 days (range: 1-30 days) with a median hospital stay of 16.5 days (range: 3-20 days). Nine of the 10 balamuthiasis patients died; one was living at the time of last follow-up

Therapy/Treatment

In the absence of data to the contrary, recommendations for treatment of Acanthamoeba infection also apply to infections due to *B. mandrillaris*

CDC has now an investigational drug called "Miltefosine" available for treatment of Free-living ameba (FLA) infections caused by *Naegleria fowleri*, *Balamuthia mandrillaris*, and Acanthamoeba species. Drugs used in treating Granulomatous Amebic Encephalitis (GAE) caused by Balamuthia have included a combination of flucytosine, pentamidine, fluconazole, sulfadiazine and either azithromycin or clarithromycin. Recently, miltefosine in combination with some of these other drugs has shown some promise.

Susceptibility *in vitro* and *in vivo*

Schuster and Visvesvara (1996)examined the in vitro susceptibility of three strains of *B. mandrillaris* in axenic culture. When examined after 6 days of incubation, pentamidine isethionate and propamidine inhibited amoebal growth by approximately 80% when tested at 1 µg/ ml and 93% at 10 µg/ ml. At those concentrations, however, propamidine was toxic to monkey kidney cells. Polymyxin B and gramicidin S were each more than 95% inhibitory at 10 µg/ml; the former was 49% inhibitory at 1µg/ ml. Amphotericin B was only modestly inhibitory, as were the azoles tested. Trimethoprim-sulfamethoxazole had no inhibitory effect. Thus, these studies suggest that pentamidine is the most active among the drugs tested against this organism; it is, however, only amoebistatic rather than amoebicidal. Azithromycin was amoebastatic in tissue culture (rat glioma cells) monolayers at a concentrations > 0.1 µg/mL, but was ineffective in the absence of the monolayer. Complete inhibition of growth of the organism in tissue monolayer was obtained by exposure to various phenothiazines at a concentration of 5µg/mL, but lesser activity was found in the absence of the monolayer

Adjunctive therapy

Surgical excision of cerebral mass lesions due to granulomatous amebic encephalitis, should be considered if possible.

Endpoints of monitoring therapy

Clinical endpoints for treating GAE have not yet been determined. Patients may need therapy for many months after clinical response.

Identification and diagnostic challenges of balamuthiasis

Since Balamuthia was first discovered in 1986, about 200 cases of infection have been reported worldwide. This number includes at least 70 confirmed cases in the United States. Balamuthia infection is very rare but often causes fatal disease.

The infection is worldwide and few patients are known to have survived as a result of successful drug treatment. Because the disease is so uncommon, it is possible that there have been additional cases that were misdiagnosed, but early diagnosis and treatment might increase the chances for survival (Siddiqui and Khan, 2008).

Even with the improvements in the diagnosis of Balamuthia which manifest in its only commonest way as BAE or GAE, enormous challenges remain in the identification of this organisms, due to;

1. Clinical symptoms mimicking those of several other types of encephalitis,
2. Few laboratories perform appropriate diagnostic testing, and
3. Many physicians are unaware of the disease.

Thus the lack of recognition and subsequent delay in diagnosis might be a factor in its high mortality. Also, there is not a single report of GAE or BAE in Africa, despite millions of HIV-infected individuals, who are susceptible hosts to opportunistic pathogens, as well as the warm climate, probable frequent environmental exposure and subordinate sanitation. Therefore BAE or GAE cases should be deliberated as possible causes of encephalitis when patients exhibit general nonspecific encephalitis symptoms.

Vaccines, prevention and control

There are no vaccines for Balamuthia species and currently there are no known ways to prevent infection with Balamuthia, since it is unclear how and why some people become infected while others donot. But a lot can be achieved in terms of early diagnosis, increased awareness on the disease especially on the part of medical health personnel and the setting up of diagnostic centers**.**

Conclusion and Recommendation

While the number of infections due to *B. mandrillaris* is fairly low, the difficulty in diagnosis, lack of awareness, problematic treatment of GAE or BAE, and the resulting fatal consequences highlights that this infection is of great concern, not just for humans but also for animals

Current methods of treatment require increased awareness of physicians and pathologists of GAE or BAE and strong suspicion based on clinical findings. Early diagnosis followed by aggressive treatment using a mixture of drugs is crucial, and even then the prognosis remains extremely poor.

Accordingly, there is an imperative need for the understanding of the pathogenesis and pathophysiology of GAE both at the molecular, cellular, and clinical levels. As well as the ability of *B. mandrillaris* to transmit to susceptible hosts, adapt to diverse host and environmental conditions, their ability to overcome host defense barriers and emerge as infective trophozoites to produce CNS infection, provide targets for therapeutic interventions and to help design strategies for preventive measures.

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Quick Response Code

DOI:10.22192/ijarbs.2020.07.08.003

How to cite this article:
Pam Martin Zang. (2020). A Review of Balamuthiasis. Int. J. Adv. Res. Biol. Sci. 7(8): 15-24.
DOI: http://dx.doi.org/10.22192/ijarbs.2020.07.08.003