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The Epidemiology and Clinical Features of *Balamuthia mandrillaris* Disease in the United States, 1974 – 2016

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Abstract

Background—*Balamuthia mandrillaris* is a free-living ameba that causes rare, nearly always fatal disease in humans and animals worldwide. *B. mandrillaris* has been isolated from soil, dust, and water. Initial entry of *Balamuthia* into the body is likely via the skin or lungs. To date, only individual case reports and small case series have been published.

Methods—The Centers for Disease Control and Prevention (CDC) maintains a free-living ameba (FLA) registry and laboratory. To be entered into the registry, a *Balamuthia* case must be laboratory-confirmed. Several sources were used to complete entries in the registry, including case report forms, CDC laboratory results, published case reports, and media information. SAS© version 9.3 software was used to calculate descriptive statistics and frequencies.

Results—We identified 109 case reports of *Balamuthia* disease between 1974 and 2016. Most (99%) had encephalitis. The median age was 36 years (range 4 months to 91 years). Males accounted for 68% of the case patients. California had the highest number of case reports followed by Texas and Arizona. Hispanics constituted 55% for those with documented ethnicity. Exposure to soil was commonly reported. Among those with a known outcome, 90% of patients died.

Conclusions—*Balamuthia* disease in the United States is characterized by a highly fatal encephalitis that affects patients of all ages. Hispanics were disproportionately affected. The southwest region of the U.S. reported the most cases. Clinician awareness of *Balamuthia* as a

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cause of encephalitis might lead to earlier diagnosis and initiation of treatment, resulting in better outcomes.

Summary—We describe 109 case reports of *Balamuthia* disease in the United States between 1974 and 2016. Most were male with encephalitis, had a median age of 36 years, and were reported from southwestern states. Ninety percent of patients died.

Keywords

Balamuthia mandrillaris; free-living ameba; granulomatous amebic encephalitis

INTRODUCTION

Balamuthia mandrillaris is a free-living ameba found in the environment that causes rare cases of human disease, including cutaneous and central nervous system (CNS) disease called granulomatous amebic encephalitis (GAE). Initially thought to be a nonpathogenic soil organism, it was first reported to cause disease in a pregnant mandrill that died of meningoencephalitis at the San Diego Zoo [1]. Since then, *Balamuthia* has also been reported to cause infection in other animals including dogs, horses, and primates [2–5]. Before the case in the mandrill, other GAE cases that appeared to be caused by *Acanthamoeba*, a similar free-living ameba, had been reported. However, the brain tissue from these cases did not react with *Acanthamoeba*-specific immunohistochemical tests [6, 7]. Previously known as a leptomyxid ameba, because of some similar morphologic characteristics, the organism causing the *Acanthamoeba*-like infections was established as a new genus and species, *Balamuthia mandrillaris*, based on fundamental differences in morphology, physiology, and antigens [8]. Ribosomal RNA sequencing and phylogenetic analyses showed it to be closely related to *Acanthamoeba*, while confirming the distinct genus and species [9, 10].

Although *Balamuthia* and *Acanthamoeba* are distinct organisms, they are generally unable to be distinguished in tissue sections by light microscopy only. The life cycle of *Balamuthia mandrillaris* has two stages: a trophozoite and cyst. The trophozoite ranges in size from 12–60 μm, is usually uninucleate (with occasional binucleate forms seen), and pleomorphic while the cyst is 12–30 μm, uninucleate, and spherical [11]. *Balamuthia* is also distinguished from *Acanthamoeba* in that it cannot be cultured on bacteria-coated agar plates but must have mammalian cell culture for cultivation in the laboratory.

While *Balamuthia* was thought to be an environmental organism like *Acanthamoeba*, at the time of its initial description, it had not been isolated from the environment [8, 12]. Since that time, there have been a few reports of isolation from soil, dust, and water [13–16]. Despite these findings, the exact ecologic niche of *Balamuthia mandrillaris* remains unknown.

Balamuthia is thought to enter the human body via the lungs by inhalation of cysts or direct contamination of a break in the skin[17]. Although animal-model evidence exists for infection of the brain via the olfactory nerve pathway, similar to *Naegleria fowleri* [18], this route is not considered relevant for human *Balamuthia* infection because histopathologic

findings from cases do not show olfactory lobe involvement of the type seen in *Naegleria fowleri* cases. In further support of hematogenous spread, the amebae frequently cluster around blood vessels and autopsies have shown multiple infected tissues [19, 20]. *Balamuthia mandrillaris* primarily affects two organ systems in humans: the skin and the CNS. Infection occurs in both immunocompetent and immunocompromised patients. Onset is described as subacute to chronic with nonspecific neurologic symptoms in GAE cases [11]. When the skin is involved, lesions are often singular and located on the central face but occasionally on the extremities or trunk. They have been described as painless plaques that may progress to central ulceration [21]. *Balamuthia* usually presents with manifestations in a single organ system, as with GAE or cutaneous balamuthiasis. However, autopsy specimens from patients with GAE have demonstrated amebae in other organs, such as the kidneys, lungs, and adrenal glands [6, 20]. Mortality is high for *Balamuthia* infections; few survivors have been reported [22–24]. Treatment of *Balamuthia* disease has been based on *in vitro* drug activity and the small number of survivor case reports. Drugs with known activity include pentamidine, fluconazole, flucytosine, sulfadiazine, azithromycin, clarithromycin, and miltefosine [25, 26].

What little is known about the epidemiology of *Balamuthia* infections has been derived from case reports and small case series. In the United States, these originated with the California Encephalitis Project (CEP), an enhanced surveillance program to test encephalitis cases for both common and uncommon pathogens that operated in California from 1998 to 2010; CEP reported 10 cases of *Balamuthia* from 1999–2007 [27]. The CEP's case series and others, and additional case series from Peru, show widely ranging patient ages and male predominance [27, 28]. There is also evidence that a high proportion of *Balamuthia* patients are of Hispanic ethnicity [29]. Soil exposures are reported frequently in *Balamuthia* cases [27]. In 2009, a new mode of transmission was documented when two kidney transplant recipients became ill simultaneously with encephalitis. It was later determined that the donor of the kidneys had died of *Balamuthia* GAE and had transmitted the infection to the kidney recipients via the transplanted organs [30]. Subsequently, two additional *Balamuthia* transplant-transmitted outbreaks were reported in 2010 and 2012 [30, 31]. As *Balamuthia* is an environmental organism, exposure is likely common; a serosurvey of healthy landscapers and blood donors reported seropositivity prevalence of 2.5–3.6% [32]. Another serosurvey showed high levels of seropositivity among a group of West Africans living in rural areas. The same study also showed the antibody assay to be specific for *Balamuthia* with little cross-reactivity with *Acanthamoeba* spp [33].

As one of the few centers in the United States with the ability to confirm *Balamuthia* infection in clinical specimens, the Centers for Disease Control and Prevention (CDC) has been in a unique position to collect data on a large number of *Balamuthia* infections. To shed light on this little known but devastating infection, we report a case series of *Balamuthia* infections confirmed at CDC.

METHODS

The CDC free-living ameba (FLA) registry was used as the primary data source for this study. Cases were classified on the basis of the state of exposure, if known, or by the state of

residence or diagnosis, if state of exposure was not known. SAS© version 9.3 software and Excel were used to calculate descriptive statistics and frequencies.

RESULTS

During 1974–2016, 109 case reports of *Balamuthia* disease (range 0–9 cases per year) were reported in the United States (Figure 1). The median age of patients was 36 years (n=109; range 4 months–91 years); 19% (n=20) were age less than 5 years). Of the 108 case patients with sex reported, 68% were male. For the 59 case patients where race was reported, 68% were white, 22% were black, 10% were Asian/Pacific Islander, and 3% were American Indian. Of the 58 case patients whose ethnicity was reported, 55% were Hispanic (Table 1). *Balamuthia* cases were reported from 27 states and the District of Columbia (Figure 2). State of exposure was documented in 30 cases and included California (12 cases), Arizona (4 cases), Texas (3 cases), Mississippi (3 cases),Hawaii (2 cases), and 1 case each from Georgia, Florida, New Mexico, Illinois, Virginia, and Washington. Of 41 case patients with a documented soil exposure history, 35 (85%) reported soil-related exposures, including those categorized as gardening/landscaping/yard work or play and farming/ranching/agricultural. A history of swimming or recreational water exposures was reported in 66% (21/32) of case patients with a documented water exposure history. Thirteen cases patients reported both water and soil exposure. Symptom onset occurred in all months of the year in those patients with a documented symptom onset date (n=65) with no apparent seasonality.

The median length of time from symptom onset until death was 24 days (range 4–450 days, n=43) and the median hospital stay was 21 days (range 4–372 days, n=52). *Balamuthia* disease manifested as encephalitis in 99% of patients. Seven of 109 case patients (6%) had a combination of GAE and cutaneous disease and one patient had cutaneous disease only. Five case patients who had GAE had evidence of amebae in other organs on post-mortem exam including lung, liver, kidney, pancreas, and adrenal glands. Among 82 case patients ≥10 years of age, 18% reported alcohol misuse and 22% reported illegal drug use. Among 94 patients with information on comorbid conditions, 39% had an immunocompromised condition, including diabetes (9), HIV/AIDS (9), solid organ transplant (6), and use of immunosuppressive drugs (5) (Table 2). Ten (10%) patients of 101 with a known outcome survived their *Balamuthia* infection (Table 2).

Data was available on 101 patients regarding clinical features at initial presentation with *Balamuthia* disease. The most common general clinical features on presentation were fever (39%), headache (39%), vomiting (30%), and lethargy (28%). The most common neurologic features on presentation were altered mental status (30%), seizures (21%), and weakness (19%).

When CSF data were available, the median white blood cell count was 106 cells/μL with a median of 57% lymphocytes, median protein of 105 mg/dL, and median glucose of 46 mg/dL (Table 3). One patient was reported to have had amebae visualized on a wet mount of the CSF. Sixty-six percent of patients had *Balamuthia* disease diagnosed by indirect immunofluorescence, followed by 47% by polymerase chain reaction (PCR), 45% by histopathology, and 3% by culture. Fifty-nine percent were diagnosed by a combination of

tests. This testing was primarily performed on brain tissue (96 had a brain biopsy) followed by skin tissue (10 had a skin biopsy). Six patients had *Balamuthia* detected in the CSF by PCR or culture. Eighty-eight percent of *Balamuthia* case patients required a brain biopsy to aid in making the diagnosis (Table 3).

Brain imaging data were available for 92 patients, all demonstrating abnormal findings. Typical *Balamuthia* GAE findings on brain imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) included enhancing lesions (29%), multifocal lesions (23%), and edema (27%). Lesions were located throughout the brain with no predilection for a particular region.

The most common medications given initially to *Balamuthia* case patients were acyclovir, amphotericin B, ceftriaxone, isoniazid, metronidazole, and rifampin. Overall, 9 *Balamuthia* survivors had treatment data reported and received at least one of the following drugs: azithromycin (7/9) or clarithromycin (6/9), fluconazole (7/9), flucytosine (7/9), and sulfadiazine (8/9). Over half of survivors received pentamidine (6/9) as part of their treatment. Three of 9 survivors received miltefosine (Table 4) [22, 23, 34–38].

Among 52 patients with a recorded initial admitting diagnosis, the most common diagnoses were neoplasm/metastases (12), tuberculous meningitis (5), brain abscess (4), toxoplasmosis (4), acute disseminated encephalomyelitis (3), and neurocysticercosis (3). Other initial diagnoses included stroke, septic emboli, and viral encephalitis.

Twenty-seven patients (including the 10 known survivors) received an antemortem diagnosis of *Balamuthia* disease, allowing for treatment initiation. The median time from symptom onset to initiation of treatment in this sub-group was 30 days (range 6–557 days). All but four of these antemortem-diagnosed cases occurred in the last 10 years.

DISCUSSION

As a rare and highly fatal infection, the large case series of *Balamuthia* disease presented here represents a unique opportunity to describe this infection and examine patterns that might help better diagnose, treat, and possibly prevent this devastating infection. This case series confirms that *Balamuthia* disease is highly fatal, with fewer than 10% of patients surviving.

In this case series, some epidemiologic patterns can be discerned. As seen in Figure 1, there were an increasing number of cases reported in the last decade, which likely reflects increasing recognition of *Balamuthia* disease in more recent years once it became known as a human pathogen and not necessarily a true increase in cases. While patient age ranged from 4 months to 91 years, it is notable that the median age was 36 years. This median age differs from that reported for encephalitis hospitalization and death, which are highest at the extremes of life: < 1 year and >65 years of age [39, 40]. The predominance of male patients in this case series also differs from the female predominance reported for encephalitis hospitalization and death of all causes [39]. The reasons for these differences are not clear but might be a result of different data sources and more recent years of data that were used for the referenced analyses. It might also represent how *Balamuthia* has the ability to infect

people of all ages and immune status, rather than just the extremes of age. Another notable demographic pattern is that of those with a reported ethnicity, more than 50% were Hispanic, which has been previously reported [29]. The findings of male predominance as well as Hispanic ethnicity might reflect higher exposure to occupations with heavy soil exposure such as agriculture and landscaping [41].

The western and southern regions of the United States reported the most *Balamuthia* cases. While the western and southern regions of the United States might provide an environment that is conducive to the growth of *Balamuthia*, reporting bias might have contributed to this finding. The California Encephalitis Project that operated in California during the time period of this study represents a form of active surveillance that likely promoted the identification of *Balamuthia* cases that might not have otherwise been identified. As other states did not have this kind of surveillance and relied on passive identification of cases, the western region might appear to have more cases than the rest of the country. However, it is worth exploring the possibility that the hot, dry environment of the U.S. Southwest might be the type of environment in which *Balamuthia* thrives. This geographic predilection for the southwest United States might also explain why we found a higher number of cases with Hispanic ethnicity, since people of Hispanic ethnicity comprise a higher percentage of the southwest U.S. population [42]. Not surprisingly, given what is known about where *Balamuthia* is found in the environment, soil exposures were reported in 85% of patients with a documented soil exposure history while water exposures were only reported in 66% of patients with a documented water exposure history. Unfortunately, given how common soil exposure is and the lack of knowledge about what the incubation period is for *Balamuthia* infection, for most cases it is difficult to pinpoint exactly what exposure led to infection.

Unlike patients with disease caused by *Acanthamoeba,* a closely-related free-living ameba that causes CNS, cutaneous, and disseminated disease in primarily immunocompromised people [11], fewer than 40% of the patients with *Balamuthia* disease in this case series were immunocompromised. However, alcohol or drug use was reported as a co-morbidity in 18% and 22% of *Balamuthia* patients, which is higher than reported in the general population (10% and 6.5%) in the National Survey on Drug Use and Health https://www.cdc.gov/nchs/data/hus/hus16.pdf#050).

As a rarely reported infection, *Balamuthia* disease is known to few clinicians. Although the infection has been reported from most parts of the world, only one other group in Peru has reported on multiple cases of *Balamuthia* disease [24, 28]. The Peruvian experience is largely similar to ours, with one notable exception: the Peruvian case series reported that a majority of their patients presented initially with a cutaneous lesion, whereas in this series only 5% of patients were reported to have a cutaneous form of the disease [28]. This is an important distinction as the finding of a skin lesion presents an opportunity for an easier and earlier diagnosis and treatment to prevent progression to neurologic disease. Although it seems to be a rare finding in U.S. *Balamuthia* patients, when *Balamuthia* is suspected, a careful skin exam should be conducted, as detection of a lesion consistent with cutaneous balamuthiasis might allow for early diagnosis on easily accessible tissue. Additionally, *Balamuthia* should be considered as an infectious etiology for one or more chronic skin

lesions and as an etiology for meningitis/encephalitis in the presence of a skin lesion, particularly in the presence of other epidemiologic clues, such as Hispanic ethnicity, soil or water exposure, residence in or travel to the Southwest United States, and male sex although such factors need not be present for *Balamuthia* to be in the differential diagnosis.

The presenting clinical features in this series were not specific to *Balamuthia* disease. Neuroimaging can be helpful in that almost all patients have abnormal brain imaging, often with parenchymal lesions. The CSF profile does not distinguish *Balamuthia* disease from other more common causes of encephalitis [43]. It shows that most *Balamuthia* patients have a mildly elevated white blood cell (WBC) count with a lymphocytic predominance, elevated protein, and low normal glucose. By comparison, the CSF profile that is generally seen in patients with primary amebic meningoencephalitis caused by *Naegleria fowleri* has a greatly elevated WBC count with a neutrophilic predominance, elevated protein, and low glucose [44]. The nonspecific presenting clinical features and CSF profile of *Balamuthia* GAE are likely a factor in the delayed diagnosis in most patients. Only 27 patients in this case series received an antemortem diagnosis of *Balamuthia* disease. Among this group, the median time from onset of symptoms to initiation of *Balamuthia*-specific treatment was 30 days.

Further complicating the diagnosis of *Balamuthia* disease is the frequent need for brain tissue on which to perform confirmatory testing. Unlike *Naegleria fowleri*, *Balamuthia* is rarely detected in the CSF of infected patients, either visually by microscope or by PCR. In this case series, 88% (96/109) of patients had a brain biopsy performed and only 6% (6/109) had *Balamuthia* detected in CSF. While CDC is usually willing to perform *Balamuthia* PCR on CSF since a positive result would be helpful and facilitate earlier initiation of treatment, clinicians should be aware that a negative result on CSF does not rule out the diagnosis of *Balamuthia* disease and often brain tissue must be obtained.

The initial treatment received by many *Balamuthia* case patients included acyclovir, ceftriaxone, isoniazid, and rifampin. These medications are not effective against *Balamuthia* and reflect empiric treatment that is used for more common causes of meningoencephalitis such as herpes simplex virus, *Neisseria meningitides*, *Streptococcus pneumoniae*, and tuberculosis. The drugs used to treat survivors are drugs that are commonly available in U.S. hospital inpatient pharmacies and have been shown to have activity against *Balamuthia*. Based on their *in vitro* activity and successful use in survivor cases, the following drug combination is recommended for treatment of *Balamuthia* infection: pentamidine, sulfadiazine, flucytosine, fluconazole, azithromycin or clarithromycin, and miltefosine (which is now available commercially in the United States).

Encephalitis of any cause remains a significant cause of morbidity and mortality in the United States and fewer than half of cases have an etiology identified [39, 40]. While *Balamuthia* is likely one of the rarer causes of encephalitis, it should be considered in the differential diagnosis, early in the patient's evaluation if possible, but certainly if other more common causes have been ruled out or if there are epidemiologic and clinical suggestions in favor of GAE. Clinician awareness of *Balamuthia* as a cause of encephalitis (as well as chronic skin lesions) might lead to more antemortem diagnoses and earlier initiation of treatment, possibly resulting in better outcomes for these patients.

Experts at CDC are available 24/7 for diagnostic and clinical assistance for clinicians who suspect *Balamuthia* disease in a patient they are evaluating. Clinicians should call the CDC Emergency Operations Center at 770–488-7100 to obtain a consultation.

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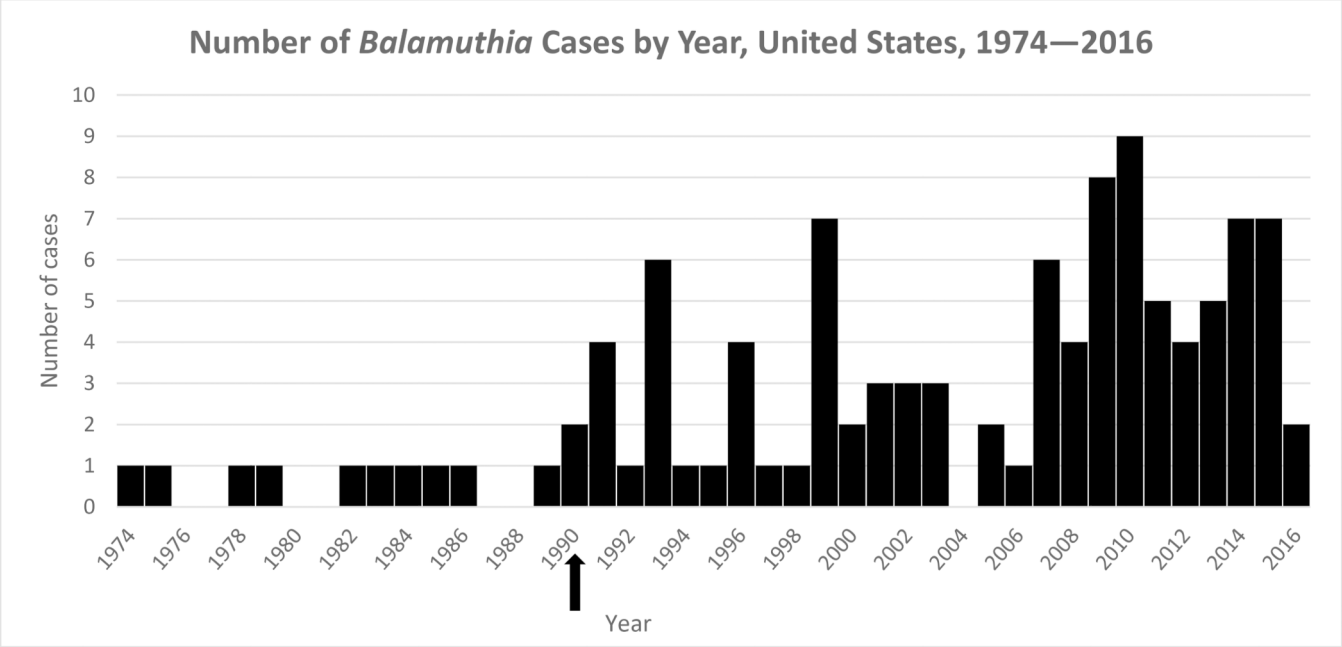

Figure 1.

Arrow denotes the year *Balamuthia mandrillaris* was first described as a human pathogen. Cases reported prior to 1990 were retrospectively diagnosed.

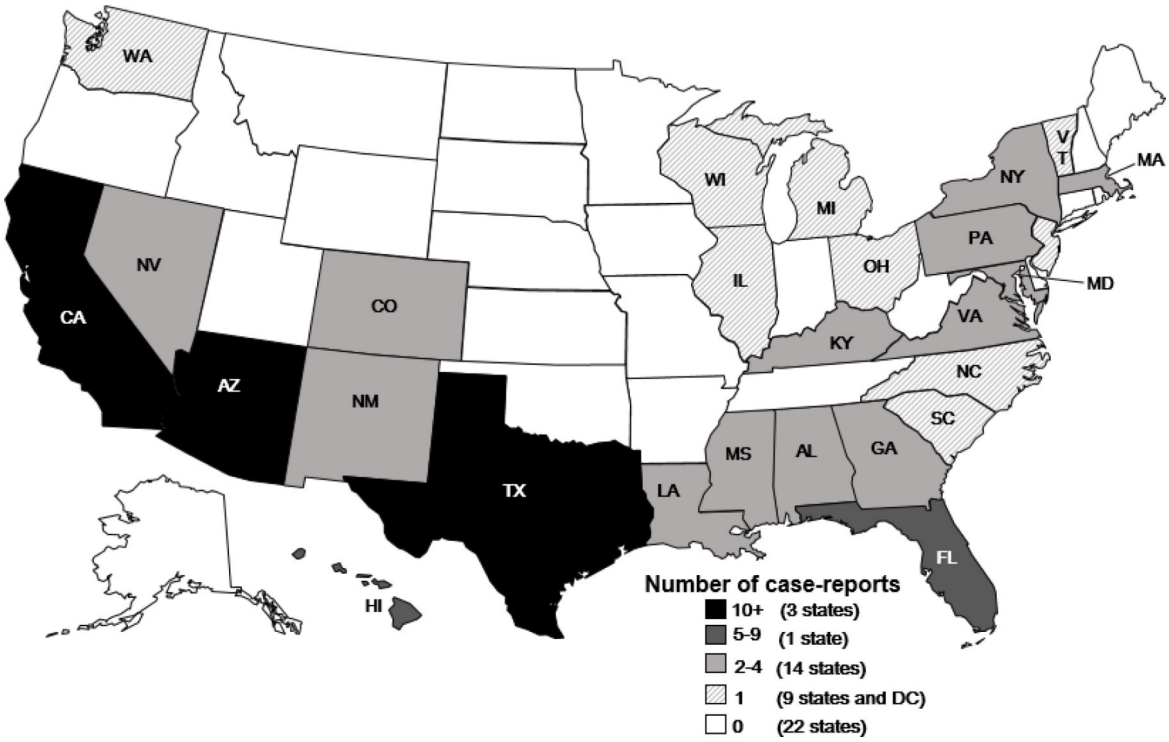

Figure 2.

Balamuthia Cases by State, United States, 1974–2016*

*Cases were classified on the basis of the state of exposure, if known, or by the state of residence or diagnosis, if state of exposure was not known.

Table 1.

Demographic Characteristics of *Balamuthia* Disease Patients, United States, 1974–2016

Median age (range) (N=106)	36 years (0.33–91 years)
Age less than 5 years (n, %)	20 (19)
Sex (n, %) (N=108)	
Male	75 (68)
Female	33 (32)
Race (n, %) (N=59)	
White	40 (68)[a]
Black	13 (22)
Asian/Pacific Islander	6 (10)
American Indian	2 (3)
Ethnicity (n, %) (N=58)	
Hispanic	32 (55)
Non-Hispanic	26 (45)

[a]Percents sum to >100% due to some cases reporting more than one race.

Table 2.

Clinical Characteristics of *Balamuthia* Disease Patients, United States, 1974–2016

Median time from symptom onset–death (range), in days (N=43)	24 (4–450)
Median hospital stay (range), in days (N=52)	21 (4–372)
Type of *Balamuthia* disease, n (%) (N=109)	
Encephalitis only	101 (93)
Cutaneous only	1 (<1)
Encephalitis + cutaneous	7 (6)
Co-morbid conditions	
Alcohol misuse (% among cases ≥ 10 yrs) (N=82)	15 (18)
Illegal drug use (% among cases ≥ 10 yrs) (N=82)	18 (22)
Immunocompromised (N=94)	37 (39)
Diabetes	9 (10)
HIV/AIDS	9 (10)
Solid organ transplant	6 (6)
Immunosuppressive drug	5 (5)
Liver cirrhosis	3 (3)
Renal failure	3 (3)
Other hematologic condition	2 (2)
Other autoimmune condition	2 (2)
Cancer	1(1)
Glucose-6-phosphate dehydrogenase deficiency	1(1)
Survived (N=101)	10 (10)
General clinical features on presentation, n (%) (N= 101)	
Fever	39 (39)
Headache	39 (39)
Vomiting	30 (30)
Lethargy	28 (28)
Nausea	19 (19)
Stiff neck	7 (7)
Anorexia	7 (7)
Weight loss	3 (3)
Cough	2 (2)
Diarrhea	2 (2)
Neurologic clinical features on presentation, n (%) (N=101)	
Mental status changes	30 (30)
Seizures	21 (21)
Weakness	19 (19)
Confusion	15 (15)
Ataxia	14 (14)

Hemiparesis	13 (13)
Behavior changes	10 (10)
Aphasia	7 (7)
Cranial nerve VI palsy	5 (5)
Cranial nerve XII palsy	4 (4)
Admitting diagnosis (N=52)	
Neoplasm/metastases	12 (23)
Tuberculous meningitis	5 (10)
Brain abscess	4 (8)
Toxoplasmosis	4 (8)
Acute disseminated encephalomyelitis	3 (6)
Neurocysticercosis	3 (6)
Stroke	2 (4)
Septic emboli	2 (4)
Viral encephalitis	2 (4)

Table 3.

Laboratory and Radiologic Findings in *Balamuthia* Disease Patients, United States, 1974–2016

Cerebrospinal fluid values	**Median (Range)**
WBC (cells/μL) (N=64)	106 (0–4100)
% Neutrophil (N=38)	0 (0–90)
% Lymphocyte (N=38)	57 (0–100)
% Monocyte (N=38)	9.5 (0–100)
RBC (cells/ μL) (N=54)	2 (0–44,500)
Protein (mg/dL) (N=62)	105 (0–1042)
Glucose (mg/dL) (N=62)	46 (0–240)
Balamuthia diagnostic testing	N (%)
Indirect Immunofluorescence	61/92 (66)
PCR	43/92 (47)
Histopathology	41/92 (45)
Culture	3/92 (3)
Combination	54/92 (59)
Brain biopsy performed	96/109 (88)

Table 4.

Drug Combinations Received by *Balamuthia* Disease Patients with an Antemortem Diagnosis by Outcome, United States, 1974–2016

Year	Age (yrs)	Treatment	Outcome	Comment
1996	64	Amphotericin B, azithromycin, ceftriaxone, clarithromycin, ethambutol, fluconazole, flucytosine, isoniazid, pentamidine, rifampin, steroid (prednisone and dexamethasone), sulfadizine, pyrazinamide, doxycycline, trifluoperazine	Survived	Case described in Deetz et al.
2000	5	Acyclovir, azithromycin, clarithromycin, fluconazole, flucytosine, ketoconazole, metronidazole, pentamidine, thioridizine	Survived	Case described in Deetz et al.
2002	72	Clarithromycin, fluconazole, pentamidine, sulfadiazine	Survived	Case described in Jung et al.
2007	43	Albendazole, ciprofloxacin, clarithromycin, fluconazole, pentamidine, sulfadiazine, vancomycin, meropenem, posaconazole	Died	
2007	2	Clarithromycin, fluconazole, flucytosine, pentamidine, sulfadiazine, thioridizine	Survived	Case described in Cary et al.
2009	31	Azithromycin, fluconazole, flucytosine, miltefosine, pentamidine, sulfadiazine	Died	Case described in MMWR 2010
2009	27	Azithromycin, fluconazole, flucytosine, miltefosine, pentamidine, sulfadiazine,	Survived	Case described in MMWR 2010
2010	24	Albendazole, amphotericin B, azithromycin, miltefosine, sulfadiazine, linezolid	Died	Received only a few days of treatment prior to death
2010	11	Amphotericin B liposomal, azithromycin, fluconazole, flucytosine, metronidazole, miltefosine, pentamidine, dexamethasone, thioridazine, meropenem	Died	Treated with varying combinations of these drugs for 1–2 months
2010	84	Azithromycin, flucytosine, sulfadiazine, minocycline, clobetasol propionate spray	Survived	Had cutaneous disease + encephalitis
2010	27	Albendazole, amphotericin B liposomal, azithromycin, clarithromycin, fluconazole, flucytosine, metronidazole, miltefosine, pentamidine, dexamethasone, sulfadiazine, trimethoprim/sulfa, voriconazole	Survived	
2011	67	Metronidazole, miltefosine, pentamidine, steroid (unspecified)	Died	
2012	82	Acyclovir, amphotericin B liposomal, azithromycin, ceftriaxone, flucytosine, pentamidine, pyrimethamine, hydrocortisone, sulfadiazine, trimethoprim/sulfa, voriconazole, doxycycline, vancomycin	Died	Case described in Schafer et al.
2012	16	Acyclovir, ceftriaxone, clarithromycin, fluconazole, flucytosine, miltefosine, pentamidine, rifampin, sulfadiazine, meropenem	Died	Received ~2 weeks of treatment prior to death
2012	39	Albendazole, azithromycin, clarithromycin, fluconazole, flucytosine, miltefosine, pentamidine, sulfadiazine	Died	Received ~ 1 month of treatment prior to death
2013	13	Amphotericin B liposomal, azithromycin, fluconazole, rifampin, dexamethasone, sulfadiazine, caspofungin, meropenem	Died	Received only a few days of treatment prior to death
2014	63	Albendazole, amphotericin B liposomal, azithromycin, clarithromycin, fluconazole, flucytosine, sulfadiazine, miltefosine	Survived	
2014	20	Azithromycin, fluconazole, flucytosine, miltefosine, pentamidine, sulfadiazine	Died	Received ~ 10 days of treatment prior to death
2014	91	Azithromycin, sulfadiazine	Survived	Cutaneous disease only; case described in Chang et al.

Year	Age (yrs)	Treatment	Outcome	Comment
2014	32	Albendazole, azithromycin, fluconazole, flucytosine, miltefosine, pentamidine, sulfadiazine	Died	Received ~ 6 weeks of treatment prior to death
2014	50	Azithromycin, fluconazole, flucytosine, miltefosine, pentamidine, sulfadiazine	Died	Received ~ 1 week of treatment prior to death
2015	15	Acyclovir, amphotericin B liposomal, azithromycin, flucytosine, metronidazole, pentamidine, methylprednisolone, sulfadiazine, voriconazole, cefotaxime, vancomycin	Died	Received only a few days of treatment prior to death
2015	6	Azithromycin, fluconazole, flucytosine, miltefosine, pentamidine, sulfadiazine	Died	Only received 3 days of treatment prior to death; case described in Joo et al.
2015	63	Acyclovir, amphotericin B, azithromycin, ceftriaxone, fluconazole, flucytosine, miltefosine, pentamidine, methylprednisolone, vancomycin	Died	Received ~ 2 weeks of treatment prior to death