

International concern is growing regarding antimicrobial drug resistance in *Shigella* infections associated with India. Fluoroquinolone resistance emerged in *S. dysenteriae* in 2002, in *S. flexneri* in 2004, and in *S. sonnei* in 2007 (5). Studies from Japan have also reported an association between travel to India and infection with an *S. sonnei* clonal group that was multidrug resistant, including resistance to nalidixic acid (6). Furthermore, ciprofloxacin-resistant *S. sonnei* isolates from foodborne outbreaks in India in 2009 and 2010 (7) had *Xba*I- PFGE types and resistance profiles visually indistinguishable from those reported in our study. A study of *S. sonnei* isolates in Bhutan showed that this clonal group was also common there (8). Furthermore, a 2010 outbreak of ciprofloxacin-resistant *S. sonnei* in Canada associated with men who have sex with men showed *Xba*I- and *Bln*I-PFGE patterns that appear similar to the patterns for isolates in this study (9).

Antimicrobial drug resistance is a major global problem that is likely to be exacerbated in places with poor sanitation and intensive use of antimicrobial drugs in humans and animals. These factors have contributed to increased ciprofloxacin resistance in *Salmonella enterica* serovars Typhi and Paratyphi A (10).

A review of published literature and informal communication indicates that our observation of ciprofloxacin resistance in *S. sonnei* infections associated with travel to India is part of a general global trend. This increasing resistance suggests that ciprofloxacin may no longer be suitable for empiric therapy for *S. sonnei* infection, particularly for patients with a history of travel to the subcontinent of India.

## References

- Holt KE, Baker S, Weill FX, Holmes E, Kitchen A, Yu J, et al. *Shigella sonnei* genome sequencing and phylogenetic analysis indicate recent global dissemination from Europe. *Nat Genet*. 2012;44:1056–9. <http://dx.doi.org/10.1038/ng.2369>
- DeLappe N, O'Connor J, Morris D, Cormican M. Molecular detection of *Shigella* species impacts on apparent epidemiology and reference laboratory workload. In: Final Program of the 24th European Congress of Clinical Microbiology and Infectious Diseases; Barcelona, Spain; 2014 May 10–13; ePoster 091. Basel (Switzerland): European Society of Clinical Microbiology and Infectious Diseases; 2014.
- Ribot EM, Fair MA, Gautom R, Cameron DN, Hunter SB, Swaminathan B. Standardization of pulsed-field gel electrophoresis protocols for the subtyping of *Escherichia coli* O157:H7, *Salmonella* and *Shigella* for PulseNet. *Foodborne Pathog Dis*. 2006;3:59–67. <http://dx.doi.org/10.1089/fpd.2006.3.59>
- World Health Organization. Guidelines for the control of shigellosis, including epidemics of *Shigella dysenteriae* type 1. 2005 [cited 2015 Mar 4]. <http://whqlibdoc.who.int/publications/2005/9241592330.pdf>
- Nandy S, Mitra U, Rajendran K, Dutta P, Dutta S. Subtype prevalence, plasmid profiles and growing fluoroquinolone resistance in *Shigella* from Kolkata, India (2001–2007): a hospital-based study. *Trop Med Int Health*. 2010;15:1499–507. <http://dx.doi.org/10.1111/j.1365-3156.2010.02656.x>
- Izumiya H, Tada Y, Ito K, Morita-Ishihara T, Ohnishi M, Terajima J, et al. Characterization of *Shigella sonnei* isolates from travel-associated cases in Japan. *J Med Microbiol*. 2009;58:1486–91. <http://dx.doi.org/10.1099/jmm.0.011809-0>
- Nandy S, Dutta S, Ghosh S, Ganai A, Jyothi R, Ramani Bai JT, et al. Foodborne-associated *Shigella sonnei*, India, 2009 and 2010. *Emerg Infect Dis*. 2011;17:2072–4. <http://dx.doi.org/10.3201/eid1711.110403>
- Ruekit S, Wangchuk S, Dorji T, Tshering KP, Pootong P, Nobthai P, et al. Molecular characterization and PCR-based replicon typing of multidrug resistant *Shigella sonnei* isolates from an outbreak in Thimphu, Bhutan. *BMC Res Notes*. 2014;7:95.
- Gaudreau C, Ratnayake R, Pilon PA, Gagnon S, Roger M, Lévesque S. Ciprofloxacin-resistant *Shigella sonnei* among men who have sex with men, Canada, 2010. *Emerg Infect Dis*. 2011;17:1747–50. <http://dx.doi.org/10.3201/eid1709.102034>
- Dutta S, Das S, Mitra U, Jain P, Roy I, Ganguly S, et al. Antimicrobial resistance, virulence profiles and molecular subtypes of *Salmonella enterica* serovars Typhi and Paratyphi A blood isolates from Kolkata, India during 2009–2013. *PLoS ONE*. 2014;9:e101347. <http://dx.doi.org/10.1371/journal.pone.0101347>

Address for correspondence: Niall De Lappe, National *Salmonella*, *Shigella* and *Listeria* Reference Laboratory, Department of Medical Microbiology, University Hospital Galway, Galway, Ireland; email: niall.delappe@hse.ie

## Fatal *Balamuthia mandrillaris* Meningoencephalitis in the Netherlands after Travel to The Gambia

Nadine A.M.E. van der Beek,<sup>1</sup> Carla van Tienen,<sup>1</sup> Jubi E. de Haan, Jeroen Roelfsema, Pieter J. Wismans, Perry J.J. van Genderen, Herve L. Tanghe, Rob M. Verdijk, Maarten J. Titulaer,<sup>2</sup> Jaap J. van Hellemond<sup>2</sup>

Author affiliations: Erasmus University Medical Centre, Rotterdam, the Netherlands (N.A.M.E. van der Beek, C. van Tienen, J.E. de Haan, H.L. Tanghe, R.M. Verdijk, M.J. Titulaer, J.J. van Hellemond); National Institute for Public Health and the Environment, Bilthoven, the Netherlands (J. Roelfsema); Harbor Hospital, Rotterdam (P.J. Wismans, P.J.J. van Genderen, J.J. van Hellemond)

DOI: <http://dx.doi.org/10.3201/eid2105.141325>

**To the Editor:** *Balamuthia mandrillaris* is a free-living amoeba that has a worldwide distribution in soil and was first reported in 1990 (1). Approximately 200 *B. mandrillaris* meningoencephalitis cases have been described, mostly from warm climate areas in South America. Its prevalence in the United States is estimated to be 1 case/year (2). However, *B. mandrillaris* meningoencephalitis

<sup>1</sup>These first authors contributed equally to this article.

<sup>2</sup>These senior authors contributed equally to this article.

has not been reported in Africa, and only 4 cases have been reported in Europe (3–6). Transmission occurs through the respiratory tract or the skin or by organ transplant, and the incubation period varies from weeks to months after primary infection (7). After an indolent, subacute phase with aspecific symptoms, the amebae invade the central nervous system, and illness rapidly progresses, leading almost invariably to death (7). Because *B. mandrillaris* is difficult to detect in soil, its specific geographic distribution around the world is unknown and is estimated on the basis of where illnesses have been reported (7). This report addresses fatal *B. mandrillaris* meningoencephalitis in a woman from the Netherlands who had visited The Gambia.

In December 2013, a previously healthy 61-year-old white woman in the Netherlands sought care for fever, headaches, and muscle pains she had experienced for 1 week. That year, she had traveled 4 times to The Gambia, the last visit being 1 month before her hospitalization (online Technical Appendix Table 1, <http://wwwnc.cdc.gov/EID/article/21/5/14-1325-Techapp1.pdf>). After she returned from her visit in September 2013, fatigue, diarrhea, fever, and pustular skin lesions on her back and lower extremities developed. A wound swab culture showed *Staphylococcus aureus*, for which she was treated successfully with oral clarithromycin and topical fucidin ointment.

On admission in December, her physical and neurologic examination results were unremarkable. Malaria was excluded; because of persisting headaches, a cerebral computed tomography scan without contrast was performed but showed no abnormalities. In the following days, high fevers, altered mental status, and nuchal rigidity without focal neurologic deficits developed. Cerebrospinal fluid (CSF) examination showed mononuclear pleocytosis, highly elevated protein levels, and low glucose levels (online Technical Appendix Table 2). Serial cerebral computed tomography and magnetic resonance imaging scans showed development of an asymmetric hydrocephalus and diffuse leptomeningeal and subependymal contrast enhancement,

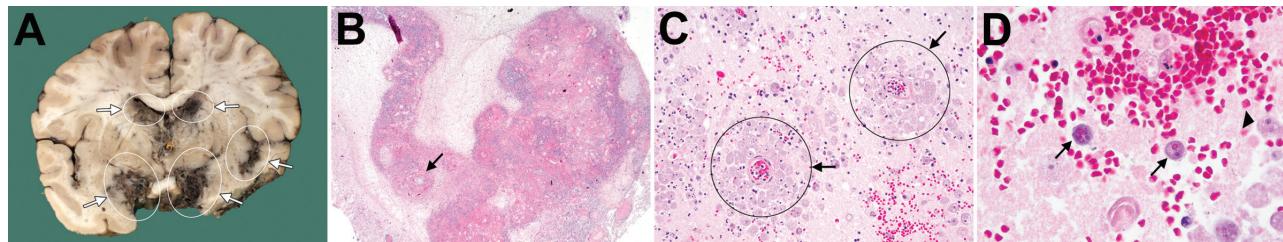
especially around the brainstem, without signs of intracerebral mass lesions (online Technical Appendix Figure).

Presumed diagnosis was tuberculous meningitis, and she was treated with tuberculostatic drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) combined with intravenous acyclovir, ceftriaxone, and co-trimoxazole for other infectious causes of meningoencephalitis. Despite external lumbar and ventricular (both lateral ventricles and fourth ventricle) CSF drainage, her neurologic condition deteriorated. Multiple cranial nerve palsies developed, and she became comatose and died 11 days after admission.

Informed consent for postmortem examination was obtained, and macroscopic pathologic examination showed uncal and cerebellar herniation caused by increased intracranial pressure. Microscopic brain tissue examination showed signs of acute granulomatous inflammation, multiple hemorrhagic infarctions, and angiitis in the presence of numerous amebic trophozoites and cysts (Figure), which showed granulomatous hemorrhagic necrotic amebic meningoencephalitis. Real-time PCR and subsequent sequencing on brain biopsy and CSF specimens showed *B. mandrillaris* to be the causative ameba (8,9).

The infection could have been acquired in The Gambia or the Netherlands because the patient had intensive soil contact in The Gambia, where she frequently cultivated land, and in the Netherlands, where she worked in glass horticulture. She may have been infected through the skin after contact with contaminated soil, but her skin lesions were atypical for *B. mandrillaris*, and postmortem examinations failed to identify *B. mandrillaris* except in the central nervous system.

The lack of reported *B. mandrillaris* cases from Africa might indicate a low number of postmortem examinations and little access to advanced diagnostics, rather than a low environmental prevalence of *B. mandrillaris*. The few reported cases in Europe might be related to lack of awareness and to clinical signs and symptoms that mimic tuberculous meningitis: a lymphocytic pleocytosis with an elevated protein level and a low glucose level in CSF, together with a hydrocephalus and subependymal and



**Figure.** Postmortem pathologic findings for woman in the Netherlands who died of *Balamuthia mandrillaris* meningoencephalitis after returning from travel to The Gambia. A) Macroscopic coronal central section scan showing hemorrhagic necrotizing lesions of the subependymal, meningeal, and parenchymal areas of the parietotemporal lobes (circles and arrows). B) Low-power microscopic scan showing hemorrhagic necrotizing angiitis of the meningeal vessels (arrow) (original magnification  $\times 25$ ). C) Medium-power microscopic scan (original magnification  $\times 200$ ) showing perivascular trophozoite cuffing (arrows) and granulomatous inflammation. D) High-power microscopic scan (original magnification  $\times 630$ ) showing encysted amebae (arrows) and free trophozoites (arrowhead). Hematoxylin and eosin stains.

leptomeningeal contrast enhancement on magnetic resonance imaging (10). Also, *B. mandrillaris* meningoencephalitis imaging findings are often nonspecific, including cerebral edema, hydrocephalus, multiple space-occupying and ring-enhancing lesions, leptomeningeal enhancement, or formation of mycotic aneurysms (2). Furthermore, amebic trophozoites are seldom detected in CSF by microscopy (2,3). Consequently, *B. mandrillaris* meningoencephalitis could be underdiagnosed, especially where this infection has no or only sporadic reports.

*B. mandrillaris* should be considered in refractory or unexplained cases of meningoencephalitis, even outside the Americas and in immunocompetent patients. Detecting *B. mandrillaris* by PCR in CSF seems most likely to enable early diagnosis and timely treatment. However, appropriate therapy is not well defined; success has been sparsely reported with the simultaneous use of azoles, flucytosine, pentamidine, sulfazidine, macrolide antimicrobial drugs, phenothiazines, and miltefosine (2,7,10).

## References

1. Visvesvara GS, Martinez AJ, Schuster FL, Leitch GJ, Wallace SV, Sawyer TK, et al. Leptomyxid ameba, a new agent of amebic meningoencephalitis in humans and animals. *J Clin Microbiol*. 1990;28:2750–6.
2. Diaz JH. The public health threat from *Balamuthia mandrillaris* in the southern United States. *J La State Med Soc*. 2011;163:197–204.
3. Jayasekera S, Sissons J, Tucker J, Rogers C, Nolder D, Warhurst D, et al. Post-mortem culture of *Balamuthia mandrillaris* from the brain and cerebrospinal fluid of a case of granulomatous amoebic meningoencephalitis, using human brain microvascular endothelial cells. *J Med Microbiol*. 2004;53:1007–12. <http://dx.doi.org/10.1099/jmm.0.45721-0>
4. Kodet R, Nohynkova E, Tichy M, Soukup J, Visvesvara GS. Amebic encephalitis caused by *Balamuthia mandrillaris* in a Czech child: description of the first case from Europe. *Pathol Res Pract*. 1998;194:423–9. [http://dx.doi.org/10.1016/S0344-0338\(98\)80033-2](http://dx.doi.org/10.1016/S0344-0338(98)80033-2)
5. Tavares M, Correia da Costa JM, Carpenter SS, Santos LA, Afonso C, Aguiar A, et al. Diagnosis of first case of *Balamuthia* amoebic encephalitis in Portugal by immunofluorescence and PCR. *J Clin Microbiol*. 2006;44:2660–3. <http://dx.doi.org/10.1128/JCM.00479-06>
6. White JM, Barker RD, Salisbury JR, Fife AJ, Lucas SB, Warhurst DC, et al. Granulomatous amoebic encephalitis. *Lancet*. 2004;364:220. [http://dx.doi.org/10.1016/S0140-6736\(04\)16640-3](http://dx.doi.org/10.1016/S0140-6736(04)16640-3)
7. Matin A, Siddiqui R, Jayasekera S, Khan NA. Increasing importance of *Balamuthia mandrillaris*. *Clin Microbiol Rev*. 2008;21:435–48. <http://dx.doi.org/10.1128/CMR.00056-07>
8. Qvarnstrom Y, Visvesvara GS, Sriram R, da Silva AJ. Multiplex real-time PCR assay for simultaneous detection of *Acanthamoeba* spp., *Balamuthia mandrillaris*, and *Naegleria fowleri*. *J Clin Microbiol*. 2006;44:3589–95. <http://dx.doi.org/10.1128/JCM.00875-06>
9. Kiderlen AF, Radam E, Lewin A. Detection of *Balamuthia mandrillaris* DNA by real-time PCR targeting the RNase P gene. *BMC Microbiol*. 2008;8:210. <http://dx.doi.org/10.1186/1471-2180-8-210>
10. Visvesvara GS, Moura H, Schuster FL. Pathogenic and opportunistic free-living amoebae: *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia diploidea*. *FEMS Immunol Med Microbiol*. 2007;50:1–26. <http://dx.doi.org/10.1111/j.1574-695X.2007.00232.x>

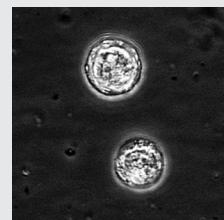
Address for correspondence: Jaap J. van Hellemond, Medical Microbiology and Infectious Diseases, Erasmus Medical Centre and Harbour Hospital, PO Box 2040, NL-3000 CA Rotterdam, the Netherlands; email: [j.vanhellemond@erasmusmc.nl](mailto:j.vanhellemond@erasmusmc.nl)

# etymologia

## *Balamuthia mandrillaris* [bal"ə-moo'the-ə man"dril-a'ris]

A free-living ameba naturally found in the environment, *Balamuthia mandrillaris* can cause a serious infection of the brain, other organs (skin, liver, kidneys), and rarely, spinal cord. Originally isolated from the brain of a mandrill that died of meningoencephalitis at the San Diego Zoo, *Balamuthia mandrillaris* is named for the late professor

William Balamuth of the University of California at Berkeley, for his contributions to the study of amebae. More recently, *B. mandrillaris* has been shown to be transmissible through organ transplantation.



## Sources

1. Centers for Disease Control and Prevention. *Balamuthia mandrillaris*—granulomatous amebic encephalitis (GAE) [cited 2015 Feb 10]. <http://www.cdc.gov/parasites/balamuthia/>
2. Centers for Disease Control and Prevention. *Balamuthia mandrillaris* transmitted through organ transplantation—Mississippi, 2009. *MMWR Morb Mortal Wkly Rep*. 2010;59:1165–70.
3. Schuster FL. In memoriam: William Balamuth (1914–1981). *J Protozool*. 1982;29:1–2. <http://dx.doi.org/10.1111/j.1550-7408.1982.tb02872.x>
4. Visvesvara GS, Schuster FL, Martinez AJ. *Balamuthia mandrillaris*, n. g., n. sp., agent of amebic meningoencephalitis in humans and other animals. *J Eukaryot Microbiol*. 1993;40:504–14. <http://dx.doi.org/10.1111/j.1550-7408.1993.tb04943.x>

Address for correspondence: Ronnie Henry, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop E03, Atlanta, GA 30329-4027, USA; email: [boq3@cdc.gov](mailto:boq3@cdc.gov)

DOI: <http://dx.doi.org/10.3201/eid2105.ET2105>

# Fatal *Balamuthia mandrillaris* Meningoencephalitis after Travel to The Gambia, the Netherlands

## Technical Appendix

**Technical Appendix Table 1.** Timeline of relevant events, *Balamuthia mandrillaris* meningoencephalitis patient, the Netherlands

Date	Event	Details
Feb 2013	Gambia visit	1-week visit
May 2013	Gambia visit	1-week visit
Aug 2013	Gambia visit	1-week visit
Sept 2013	First illness	Fatigue, diarrhea, fever, and pustular skin lesions on patient's back and lower extremities. Wound swab culture collected from lesion showed <i>Staphylococcus aureas</i> , for which patient was successfully treated with oral clarithromycin and topical fucidine ointment.
Nov 2013	Gambia visit	1-week visit during week 1 of November
Dec 2013	Second illness	Fever and persisting headaches for 6 days; local hospital admittance in week 2 of December. On day 4 after admission, patient was referred to the Rotterdam Harbour Hospital because of progressive disease. First cerebrospinal fluid sample collected. On day 6 after admission, patient was referred to the Erasmus University Medical Center in Rotterdam because of progressive disease and increasing cranial pressure. On day 11 after admission, patient died.
Spring 2014	Postmortem analysis	Pathologic and histologic examination of postmortem-collected brain, skin, and lung specimens. <i>B. mandrillaris</i> trophozoites and cysts were observed in brain tissue. PCR analysis showed presence of <i>B. mandrillaris</i> in postmortem brain biopsy specimens and in cerebrospinal fluid specimens collected on day 4 and 7 after admission.

**Technical Appendix Table 2.** Laboratory investigations during hospitalization of *Balamuthia mandrillaris* meningoencephalitis patient, the Netherlands\*

Investigation	Specimen	Findings
General	Blood	ESR 33 mm/h; leukocytes 17.3 10 <sup>9</sup> /L; other blood cell counts, electrolytes, liver enzymes, and kidney function tests were normal B2-microglobulin, IgG1–IgG4, and paraprotein levels were within reference ranges
	CSF	Day 4: leukocytes 366 10 <sup>6</sup> /L (345 monocytes); protein 721 mg/dL; glucose 1.2 mmol/L (serum 7.1 mmol/L) Day 7: leukocytes 262 10 <sup>6</sup> /L (256 monocytes); protein 1,320 mg/dL; glucose 2.0 mmol/L No evidence for monoclonal B-cell population or abnormal T-cell population
	Microbiology	Blood Cultures: negative Tuberculosis†: negative Schistosoma‡: negative CSF Malaria§: negative Trypanosomiasis Gambiense¶: negative Cryptococcus antigen‡: negative Cultures: negative for aerobic and anaerobic bacteria and fungi Mycobacteria#: negative Amebae**: negative
Virology	Blood	West Nile virus, HIV, HTLV-1/2, CMV, mumps, Rift Valley fever virus†: negative Rickettsia (Spotted fever group and typhoid fever group) ††: negative EBV IgG VCA and NA: positive; IgM VCA†: negative EBV, West Nile virus‡‡: negative

Investigation	Specimen CSF	Findings HSV types 1 and 2, VZV, CMV, human herpesvirus type 6, enterovirus, West Nile virus††: negative EBV††: positive
Pathology	CSF	No malignant cells

\*ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; CSF, cerebrospinal fluid; HTLV, human T-cell lymphotropic virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; VCA, viral capsid antigen; NA, nuclear antigen; HSV, herpes simplex virus; VZV, varicella zoster virus.

†Interferon Gamma Release Assay (Quantiferon; QIAGEN, Valencia, CA, USA).

‡Serology.

§Thick blood film and PCR.

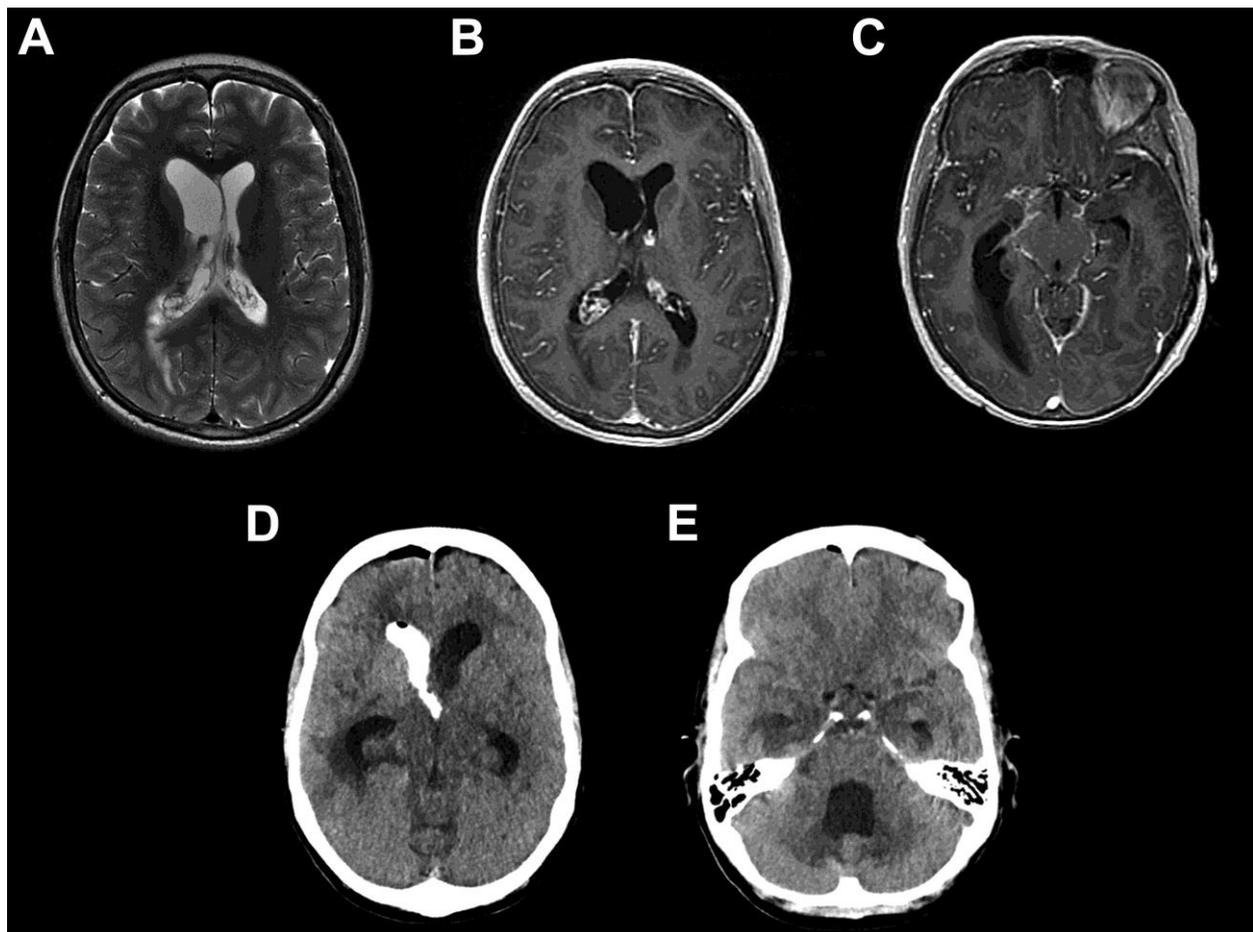
¶Quantitative buffy coat.

#PCR, auramine staining, culture.

\*\*No trophozoites by extensive microscopic inspection.

††Immunofluorescence.

‡‡PCR.



**Technical Appendix Figure.** Imaging findings for woman from the Netherlands who died of *Balamuthia mandrillaris* meningoencephalitis after returning from The Gambia. A) Axial MRI T2. B, C) T1 + intravenous Gadolinium. D, E) Computed tomography imaging sequences obtained from patient. A) Asymmetric hydrocephalus, which suggests compartmentalization within the ventricles because of high protein levels in the cerebrospinal fluid; enlarged plexus choroideus is also shown. B, C) Diffuse leptomeningeal and subependymal contrast enhancement without solid intracerebral mass lesions. D, E) Two hours after injection of intraventricular Visipaque contrast (GE HealthCare, Piscataway, NJ, USA), no diffusion of contrast occurred except in the right frontal horn and the third ventricle because of compartmentalization.