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 XbaI 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 XbaI- and BlnI-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


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

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To the Editor: Balamuthia mandrillaris is a free-living ameba 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

1These first authors contributed equally to this article.
2These 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 antituberculosis 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 angitis of the meningeal vessels (arrow) (original magnification ×25). C) Medium-power microscopic scan (original magnification ×200) showing perivascular trophozoite cuffing (arrows) and granulomatous inflammation. D) High-power microscopic scan (original magnification ×630) showing encysted amebae (arrows) and free trophozoites (arrowhead). Hematoxylin and eosin stains.
Balamuthia mandrillaris is a free-living ameba naturally found in the environment. It 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 a serious infection, it was 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.

**etymologia**

Balamuthia mandrillaris [bal"-e-moo'-the-ə man"-dril-ə-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**


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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

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb 2013</td>
<td>Gambia visit</td>
<td>1-week visit</td>
</tr>
<tr>
<td>May 2013</td>
<td>Gambia visit</td>
<td>1-week visit</td>
</tr>
<tr>
<td>Aug 2013</td>
<td>Gambia visit</td>
<td>1-week visit</td>
</tr>
<tr>
<td>Sept 2013</td>
<td>First illness</td>
<td>Fatigue, diarrhea, fever, and pustular skin lesions on patient's back and lower extremities. Wound swab culture collected from lesion showed <em>Staphylococcus aureas</em>, for which patient was successfully treated with oral clarithromycin and topical fucidine ointment.</td>
</tr>
<tr>
<td>Nov 2013</td>
<td>Gambia visit</td>
<td>1-week visit during week 1 of November</td>
</tr>
<tr>
<td>Dec 2013</td>
<td>Second illness</td>
<td>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.</td>
</tr>
<tr>
<td>Spring 2014</td>
<td>Postmortem analysis</td>
<td>Pathologic and histologic examination of postmortem-collected brain, skin, and lung specimens. <em>B. mandrillaris</em> trophozoites and cysts were observed in brain tissue. PCR analysis showed presence of <em>B. mandrillaris</em> in postmortem brain biopsy specimens and in cerebrospinal fluid specimens collected on day 4 and 7 after admission.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Specimen</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Blood</td>
<td>ESR 33 mm/h; leukocytes 17.3 10⁹/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</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>Day 4: leukocytes 366 10⁶/L (345 monocytes); protein 721 mg/dL; glucose 1.2 mmol/L (serum 7.1 mmol/L) Day 7: leukocytes 262 10⁶/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</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Blood</td>
<td>Cultures: negative Tuberculosis*: negative Schistosoma*: negative</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>Malaria‡: negative Trypanosomiasis Gambiense¶: negative Cryptococcus antigen¶: negative Cultures: negative for aerobic and anaerobic bacteria and fungi Mycobacteria#: negative Amebae*: negative</td>
</tr>
<tr>
<td>Virology</td>
<td>Blood</td>
<td>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</td>
</tr>
</tbody>
</table>
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.