BRIEF REPORT

Imported Case of Lassa Fever in Sweden With Encephalopathy andSensorineural Hearing Deficit

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We describe an imported case of Lassa fever with both encephalopathy and bilateral sensorineural hearing deficit. Absence of fever during hospitalization, initially nonspecific symptoms, and onset of hearing deficit in a late stage of disease probably contributed to delayed diagnosis (14 days after admittance to hospital). The pathogenesis of neurological manifestations of Lassa fever is poorly understood and no specific treatment has been given. A total of 118 personnel had close contact with the patient, but no secondary cases occurred. This case highlights the importance of considering Lassa fever as a differential diagnosis in patients with recent travel to endemic areas.

Keywords. encephalitis; encephalopathy; hearing deficit; Lassa fever; viral hemorrhagic fever

Lassa fever is a potentially severe viral hemorrhagic illness caused by Lassa virus ([LASV] family Arenaviridae). The reported mortality rate is 1% overall and 15%–20% among hospitalized patients [1–3]. The primary animal host is the multimammate rodent, and the virus is transmitted to humans by exposure to rodent excreta or urine [3]. Person-to-person transmission can occur via contact with infected body fluids [3]. Lassa fever is endemic in West Africa, with most cases reported from Nigeria, Liberia, Sierra Leone, and Guinea. The incubation time is reported to be 3 to 21 days [1, 3, 4]. Primary symptoms are often nonspecific, including fever, sore throat, chest pain, arthralgia, headache, nausea, vomiting, and diarrhea [1, 5], although approximately 80% of cases are asymptomatic [2, 3]. However, the disease may progress with more severe symptoms including mucosal bleeding, respiratory distress, and circulatory shock [1, 3]. Neurological complications such as hearing deficits, encephalopathy, encephalitis, seizures, and cerebellar syndromes have been reported [1, 6, 7] and have been hypothesized to result from immunological responses or direct viral cytotoxicity [6, 8].

This imported case of Lassa fever presenting with both encephalopathy and bilateral sensorineural hearing deficit highlights the importance of considering Lassa fever as a differential diagnosis in patients with recent travel to endemic areas.

CASE PRESENTATION

A 72-year-old woman with a prior medical history of hypertension and hypothyroidism was admitted to Sahlgrenska University Hospital in Gothenburg, Sweden on March 17, 2016, 10 days after onset of fever, nausea, arthralgia, loose stools, and headache, and 2 days after the debut of personality changes including bradyphrenia, motivational anhedonia, and anorexia. The initial fever had resolved after 3 days, and 7 days before hospitalization, the patient had consulted a general practitioner who suspected a nonspecific viral infection. The patient and her husband had visited Liberia for 6 weeks and returned to Sweden 5 days before the onset of primary symptoms. While in Liberia, they had resided with local people under primitive, rural conditions in 4 different villages in the northern part of the country.

The physical examination upon admittance (Day 10) was unremarkable aside from general fatigue that hindered walking, slow speech, and an irregular pulse with 112 beats/minute (electrocardiogram showed probable atrial fibrillation). The patient was fully conscious and afebrile, with blood pressure of 110/80 mmHg and oxygen saturation of 92%. Her husband described one occasion of minor nasal bleeding (which she had previously been occasionally affected by), but otherwise no bleeding from any site was noted, nor any skin rash or sore throat. The initial laboratory data showed moderate elevations of C-reactive protein, creatinine, and liver transaminases, with the elevation of aspartate aminotransferase (AST) more pronounced than that of alanine aminotransferase (Table 1), and urine analyses showed slight proteinuria. A chest x-ray showed right-sided pleuritis. No malaria parasites were detectable by microscopy. Analysis of cerebrospinal fluid (CSF) revealed no signs of inflammation, and computer tomography of the brain was normal. Further analyses of the CSF including polymerase
chain reaction (PCR) for herpesviruses, enteroviruses, and bacteria and culture for bacteria and fungi were all negative, as were analyses for human immunodeficiency virus in serum.

An electroencephalogram performed on Day 11 revealed irregular low-frequency activity left temporally, consistent with encephalopathy. Magnetic resonance tomography of the brain performed on Day 14 showed a subcortical high signal intensity lesion in the anterior part of the left insula and in the anterior part of the external capsule/lateral putamen on fluid-attenuated inversion recovery images.

A second lumbar puncture was performed on Day 16, showing mild lymphocytosis with 10 cells \( \times 10^6 \) cells/L. Analyses of fractioned proteins showed 2 different immunoglobulin G (IgG) bands in CSF and a modestly increased IgG index indicating discrete damage to the blood-brain barrier in addition to intrathecal production of IgG. However, no specific LASV intrathecal antibody production could be confirmed when retrospectively comparing LASV IgG detected in serum and CSF (Table 1). Because of pronounced fatigue and continued anorexia, total parenteral nutrition was initiated on Day 17. Hearing loss was initially noted on Day 22. The medical history was further explored, and the husband reported that acquaintances had contracted Lassa fever in proximity to where the couple had resided and that the patient had probably been exposed to rodent excreta. Lassa virus was suspected, and by Day 24 analyses of serum obtained on Day 15 were reactive for LASV IgG antibodies and low titers of LASV IgM antibodies, and LASV ribonucleic acid (RNA) was detectable by PCR. The same day,

### Table 1. Laboratory Test Results in Patient With Lassa Virus Encephalopathy

| Day of Sampling After Onset of Primary Symptoms | Day 10 | Day 11 | Day 14 | Day 16 | Day 21 | Day 28 | Day 30 | Day 35 | Day 42 | Day 58 | Day 72 | Day 78 |
|-----------------------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| **Serum Analyses**                            |       |       |       |       |       |       |       |       |       |       |       |       |
| C-reactive protein (mg/L)                     | 77    | 42    | 12    | NA    | 3     | <5    | <5    |       |       |       |       |       |
| Leukocytes (\( \times 10^9 \)/L)              | 11.4  | 10.9  | 16.4  | NA    | 7.8   | 74    | 74    |       |       |       |       |       |
| Hemoglobin (g/L)                              | 166   | NA    | 145   | NA    | NA    | 121   | 129   |       |       |       |       |       |
| Platelets (\( \times 10^9 \)/L)               | 211   | NA    | 328   | NA    | NA    | 187   | 399   |       |       |       |       |       |
| Sodium (mmol/L)                               | 124   | 133   | 147   | 145   | 137   | 134   | 135   |       |       |       |       |       |
| Creatinine (mmol/L)                           | 139   | 110   | 75    | 67    | 53    | 61    | 60    |       |       |       |       |       |
| AST (\( \mu \text{kat/L} \)) (ref 0.25–0.60) | 13    | 8.5   | 1.7   | 1.1   | 0.66  | NA    | NA    |       |       |       |       |       |
| ALT (\( \mu \text{kat/L} \)) (ref 0.15–0.75) | 6.8   | 5.4   | 2.3   | 1.5   | 0.75  | 0.53  | 0.24  |       |       |       |       |       |
| ALP (\( \mu \text{kat/L} \)) (ref 0.60–1.80) | 1.1   | 1.1   | 1.2   | 1.0   | 0.98  | NA    | NA    |       |       |       |       |       |
| Total bilirubin (\( \mu \text{mol/L} \))     | 6.1   | 5.5   | 6.2   | 6.5   | 5.8   | 5.0   | 6     |       |       |       |       |       |
| INR                                           | 0.9   |       |       |       | 1.0   |       |       |       |       |       |       |       |
| Albumin (g/L)                                 | NA    | NA    | 21    | NA    | NA    | NA    | NA    |       |       |       |       |       |
| Glucose (mmol/L) (random sample)              | 9.9   | NA    | NA    | 9.5   | NA    | NA    | NA    |       |       |       |       |       |
| Fractioned proteins                           |       |       |       |       |       |       |       |       |       |       |       |       |
| **CSF Analyses**                              |       |       |       |       |       |       |       |       |       |       |       |       |
| Lymphocytes (\( \times 10^9 \)/L)             | 3     |       | 10    |       |       |       |       |       |       |       |       |       |
| Monocytes (\( \times 10^9 \)/L)               | <3    | <3    | <3    | <3    | <3    | <3    | <3    |       |       |       |       |       |
| Neutrophils (\( \times 10^9 \)/L)             | <3    | <3    | <3    | <3    | <3    | <3    | <3    |       |       |       |       |       |
| Erythrocytes (\( \times 10^9 \)/L)            | 9     |       | <5    | <5    | <5    | <5    | <5    |       |       |       |       |       |
| Lactate (mmol/L)                              | 2.5   | 2.5   | 2.8   | 2.8   | 2.8   | 2.8   | 2.8   |       |       |       |       |       |
| Albumin (mg/L)                                | 87    |       | 243   |       |       |       |       |       |       |       |       |       |
| Glucose (mmol/L)                              | 4.0   |       | 5.2   |       |       |       |       |       |       |       |       |       |
| Fractioned proteins                           |       |       |       |       |       |       |       |       |       |       |       |       |
| **Lassa Virus Diagnostic Analyses**           |       |       |       |       |       |       |       |       |       |       |       |       |
| Serology (IF) serum                           |       |       |       |       |       |       |       |       |       |       |       |       |
| IgM                                           | Neg   |       | 160   |       |       |       |       |       |       |       |       |       |
| IgG                                           | Neg   |       | 1280  |       |       |       |       |       |       |       |       |       |
| Virus culture (serum)                         | Pos   | Pos   |       |       |       |       |       |       |       |       |       |       |
| Serology (IF) CSF I(gG)                       |       |       |       |       |       |       |       |       |       |       |       |       |
| PCR serum (copies/mL)                         | 1.2 \( \times 10^4 \) | 7.5 \( \times 10^4 \) | 5.1 \( \times 10^4 \) | NA | <300 | <300 | <300 | <300 | <300 | Neg | Neg | Neg |
| PCR blood-EDTA                                | NA    | NA    | NA    | 6.7 \( \times 10^2 \) | 3.2 \( \times 10^2 \) | <300 | <300 | <300 | <300 | <300 | Neg | Neg |
| PCR CSF (copies/mL)                           | NA    | <300  | NA    | NA    | NA    | NA    | NA    | NA    | NA    | NA    | NA    | NA    |
| PCR urine                                     | NA    | NA    | NA    | 5.7 \( \times 10^7 \) | NA    | 1.7 \( \times 10^7 \) | 4.6 \( \times 10^7 \) | Neg | Neg | Neg | Neg | Neg |
| PCR feces                                     | 4.4 \( \times 10^4 \) | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Maximum temperature (°C)                     | 36.6  | 370   | 36.5  | 370   | 36.2  | 36.6  | 36.5  | 37.2  | 36.9  | 36.9  |       |       |

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSF, cerebrospinal fluid; EDTA, ethylenediaminetetraacetic acid; GFA-p, glial fibrillary acidic protein; IF, immunofluorescence; Ig, immunoglobulin; INR, international normalized ratio; NA, not analyzed; Neg, negative; PCR, polymerase chain reaction; Pos, positive.
Leptospirosis and West Nile serologies obtained on Day 15 were reported nonreactive. On Day 25, the patient was transferred by means of a custom-built isolation ambulance to the High Level Isolation Unit (HLIU) at the Department of Infectious Diseases in Linköping for continued isolation and care.

On arrival at Linköping, the patient’s medical condition was stable and her cognitive function had improved. No specific treatment for Lassa fever was initiated. On Day 51, the patient was discharged from the HLIU to her home. On discharge, the patient was ambulant and had normal cognitive function; however, the pronounced hearing deficit remained unchanged. Because small amounts of LASV RNA were still detectable by PCR analysis of blood and urine, she was discharged with restrictions, including instructions to stay in her home, to use a separate toilet, and to be mindful of hand hygiene.

The patient was sampled repeatedly from urine and blood after discharge. On Day 80, she was declared noncontagious, because LASV RNA was undetectable by PCR from urine and blood obtained on Days 72 and 78, and thus all restrictions were discontinued. The sensorineural hearing deficit was diagnosed as bilateral but more pronounced in the left ear, by audiometric investigation 2 months after discharge.

Virological Analyses
The diagnosis was confirmed using 2 different reverse-transcription (RT)-PCR assays [9] followed by Sanger sequencing of the amplicons. Sequencing of the PCR amplicon (partial glycoprotein precursor) showed 98% sequence similarity to LASV strain LiB07-444 (GenBank accession no. GU830834). A quantitative real-time PCR (qRT-PCR) was developed on the basis of the acquired sequence. The qRT-PCR primers and probe used were as follows: F: 5'-AAATGGTGTCCTGCAGACCTTC-3', R: 5'-ACCTGAGTCAAGAGCTATGTAACTACCAC-3', and FAM-ATGAGRATGGCTTGGG-MGB, respectively. The limit of quantitation was set to 300 copies/mL, and detectable but not quantifiable levels of LASV were defined as <300 copies/mL. Serological analysis was performed by means of immunofluorescence, using LASV (strain Nig08)-infected confluent Vero cells. The virological analyses of LASV were performed at the biosafety level 4 laboratory at the Public Health Agency of Sweden. All samples collected before Day 25 were analyzed retrospectively (Table 1).

Management of Contacts
During the first 14 days of hospitalization before the confirmatory laboratory diagnosis and transfer to the HLIU, the patient was isolated in a single-bed room with a toilet and cared for following basic hygiene principles [10]; that is, personnel wore protective gloves and a plastic apron when at risk of direct contact with body fluids from the patient. Risk assessment and management of contacts were performed as reported previously [11]. Contacts at possible risk (low or high risk), defined as having nursed the patient with basic hygiene principles or having had any unprotected contacts with body fluids, were monitored 21 days postexposure including check of body temperature twice daily and awareness of any new symptoms. In total, 4 family members and 73 personnel at Sahlgrenska Hospital, Gothenburg were monitored (Table 2). The 45 personnel at the HLIU in Linköping who used enhanced protective equipment were also monitored as a safety routine. Five of the 118 personnel reported symptoms possibly suggestive of Lassa fever, and they had blood samples drawn for analysis of LASV IgG. All analyzed samples were nonreactive, and no clinical secondary cases occurred.

DISCUSSION
The patient described in this report had LASV encephalopathy with magnetic resonance imaging changes, and she later developed sensorineural hearing deficit confirmed by LASV

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**Table 2. Categorization of Contacts in Sweden, Lassa Fever Importation, March 2016**

| Contacts Classification | Total | Sex | Age | Sex | Low Risk | High Risk |
|------------------------|-------|-----|-----|-----|----------|-----------|
|                        |       |     | Mean (Range) | F/M |          |           |
| Sahlgrenska University Hospital, Gothenburg | 73    | 2/2 | 36 (28–49)  | 4   | 0        |
| Doctors                | 4     | 2/2 | 36 (28–49)  | 4   | 0        |
| Nursing/AHP           | 37    | 32/5| 35 (22–59)  | 37  | 0        |
| Laboratory staff      | 27    | 42/3| 45 (22–61)  | 27  | 0        |
| Radiology             | 2     | 2/0 | NA<sup>b</sup> | 2   | 0        |
| Medical students      | 3     | 2/1 | NA<sup>b</sup> | 3   | 0        |
| High Level Isolation Unit, Linköping | 40    |     |              |     |          |
| Doctors                | 2     | 0/2 | 39 (35–43)  | NA<sup>c</sup> | NA|
| Nursing               | 38    | 35/3| 38 (23–61)  | NA<sup>c</sup> | NA|
| Laboratory staff      | 5     | 5/0 | 39 (27–35)  | NA<sup>c</sup> | NA|
| Family                | 4     | 2/2 | NA<sup>b</sup> | 4   | 0        |
| Totals                | 122   |     | 40 (22–61)  | 82  | 0        |

Abbreviations: AHP, Allied Health Professionals; NA, not analyzed.
<sup>a</sup>Allied Health Professionals such as physiotherapist and occupational therapist.
<sup>b</sup>No data given because of confidentiality reasons.
<sup>c</sup>All personnel used enhanced protective equipment and were categorized as no risk.
RNA detected by PCR in serum. The neurological symptoms are reported as characteristic for LASV [6, 7], including occurrence of hearing loss at 10–15 days after onset [1]. However, despite typically elevated AST levels, the initial nonspecific symptoms and the absence of fever during hospitalization probably contributed to a delay in diagnosis, which is not uncommon in imported cases [12]. Neurological complications are reported in 40% and hearing deficits in 30% of hospitalized patients [7]; this is in contrast to imported cases, among which reports of neurological symptoms are rare. It is possible that neurological symptoms in imported cases are underreported or underdiagnosed.

The underlying neuropathogenesis remains unknown, and both immunological and direct viral cytotoxic mechanisms have been proposed [6, 8, 13]. Lassa virus RNA detected in CSF but not in serum has been documented in 1 previous case of Lassa fever encephalopathy from Nigeria, and persistence of virus in the central nervous system (CNS) was suggested [8]. In the present case, unfortunately, an insufficient amount of CSF was available from the first lumbar puncture for PCR analysis, and only low levels of LASV RNA were detected from the second lumbar puncture. Moreover, no specific intrathecal IgG-antibody production against LASV could be confirmed. These findings, in addition to modestly increased concentrations of lymphocytes in CSF and the absence of fever during the hospitalization, may indicate that the neurological complications of Lassa fever in our patient primarily resulted from indirect immunological mechanisms.

No antiviral treatment (ie, ribavirin) was initiated. Ribavirin treatment in Lassa fever has been studied in a single trial in Sierra Leone, and it showed efficacy in reducing mortality when administered within 6 days after onset of fever [14]. This therapy might have been potentially favorable against the neurological symptoms, given that viral replication within the CNS is ongoing late in the course of the disease. However, spontaneous improvement of the neurological symptoms including speech and bradyphrenia occurred, and the most pronounced symptom when the diagnosis was made was the loss of hearing. Auditory nerve damage may develop even during ribavirin treatment [14], supporting an immunological mechanism [15], and the decision to refrain from antiviral therapy was made after a detailed discussion.

During the hospital stay before diagnosis, the patient was cared for with basic hygiene routines. No secondary cases occurred, consistent with prior reports of a low risk of secondary cases where a high level of hospital hygiene can be maintained [3, 16].

CONCLUSIONS

The pathogenesis of Lassa fever encephalopathy might include viral replication within CNS accompanied by immunological responses, and the optimal treatment for this manifestation is unknown. Lassa fever should be suspected in the presence of neurological and/or other nonspecific symptoms, even in the absence of fever, among patients recently returned from endemic areas. In this study, the exposed hospital staff members followed basic hygiene principles and no clinical secondary cases occurred.

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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