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Case Report

Delayed-onset paraparesis in Lassa fever: A case report

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ABSTRACT

Lassa fever (LF) is an endemic viral hemorrhagic fever in West Africa. Among the serious complications of the disease are neurological manifestations whose spectrum is incompletely known. Here we report the case of a 61-year-old man who developed a delayed-onset paraparesis a few weeks after getting infected with Lassa virus, thereby suggesting a possible association between LF and spinal cord disorders.

Introduction

Lassa fever (LF) is an endemic viral hemorrhagic fever in West Africa. The Lassa virus is transmitted to humans from a rodent, *Mastomys natalensis,* by various direct or indirect routes. Human-to-human transmission is mainly reported in a nosocomial context (Houlihan and Behrens, 2017). Central nervous system (CNS) disorders associated with LF, including encephalitis and meningitis, have been described previously (Günther et al., 2001; Okokhere and Akpede, 2013; Okokhere et al., 2016, 2018b) and are associated with an increased number of deaths (Okokhere and Akpede, 2013; Okokhere et al., 2018a). Here we report a case of delayed-onset paraparesis in an LF survivor.

Case description

A 61-year-old shepherd with no significant medical history living in Nigeria's Ondo State (endemic area of LF) experienced fever, chills, severe headaches, anorexia, diarrhea and extreme fatigue as of July 1st, 2018. Five days later, he observed blood in his urine and feces, which led him to attend the Emergency Department of the Federal Medical Center Owo on July 5th, 2018. Upon admission, he had a fever of 39.5 °C, asthenia, conjunctival pallor, normal heart rate, normal blood pressure, macroscopic hematuria and melena (Figure 1). The diagnosis of malaria was ruled out by microscopic examination. He was therefore transferred to the LF isolation ward supported by the Alliance for International Medical Action, where his initial tests revealed mild anemia, slightly impaired renal function and

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moderate metabolic acidosis with increased anion gap, proteinuria and hematuria. Liver function tests were within normal range (Figure 1).

His clinical status rapidly deteriorated, with persistent fever above 40 °C, melena, worsening hematuria and apparition of cough, chest pain, abdominal pain, vomiting and watery diarrhea. As a consequence, ribavirin therapy (with doses in accordance to McCormick protocol (McCormick et al., 1986)) was commenced on July 6th without waiting for LF diagnostic confirmation. The result of Lassa RT-PCR came positive on July 8th (Figure 1).

On July 14th, he became oliguric, despite normal hemodynamic parameters. At the same time, he presented with worsening vomiting and hiccup, suggesting hyperuremia, as confirmed by a deteriorating kidney function with KDIGO stage 3 acute kidney failure (Figure 1). The patient was placed under intermittent hemodialysis because of symptomatic azotemia. Due to persistently detectable viremia after ten days of treatment, ribavirin was continued until July 22nd. At this point, Lassa RT-PCR was still positive and it was decided to stop ribavirin. His status progressively improved while daily urine output increased transiently up to 4 L before returning to normal values. Dialysis was discontinued on August 9th after the sixth session (Figure 1).

On August 13th, the patient became feverish again at 38.3 °C for two days. At the same time, he complained of not being able to step well. He subsequently developed headaches without neck stiffness, abdominal discomfort, vomiting and hiccup on August 19th, then lumbar pain on August 21st. Concomitantly, kidney parameters worsened again. On August 23rd, Lassa RT-PCR became negative in blood, allowing transfer of the patient to the nephrology unit. Kidney function progressively improved and symptoms suggestive of hyperuremia finally disappeared. Meanwhile, lumbar pain persisted and a paraparesis gradually settled, preventing the patient from going home (Figure 1). On September 10th, he was totally unable to walk. Neurological examination showed severe and symmetrical motor deficiency of lower limbs graded 1/5 to 2/5, no sensitive impairment, no sensitive level, depressed osteotendinous reflexes and plantar response in extension bilaterally. Taken together, these findings suggested a pyramidal syndrome of possible spinal origin. Medullar magnetic resonance imaging (MRI) ruled out extrinsic or intrinsic spinal cord compression but was otherwise inconclusive. In particular, it did not show signs of medullar inflammation. Lumbar puncture was unfortunately not performed because of a persistent melena causing fear of a clotting disorder. Due to the history of protracted Lassa viremia, it was decided not to administrate corticosteroids to the patient but only to propose physiotherapy.

Two months after hospital discharge, the patient was still suffering of stable lower limb weakness. Seven months after discharge, motor deficiency had dramatically improved and the patient was able to walk. Muscular power of lower limbs was almost normal at the proximal level but a moderate deficiency graded 3/5 persisted at the distal level.

Discussion

The incubation period of LF ranges from 2 to 21 days. Most Lassa virus infections in humans are mild or asymptomatic. When symptomatic, it is marked at early stage by aspecific manifestations such as headaches, myalgia, sore throat, thoracic or abdominal pain, cough, vomiting and diarrhea. At a later stage,

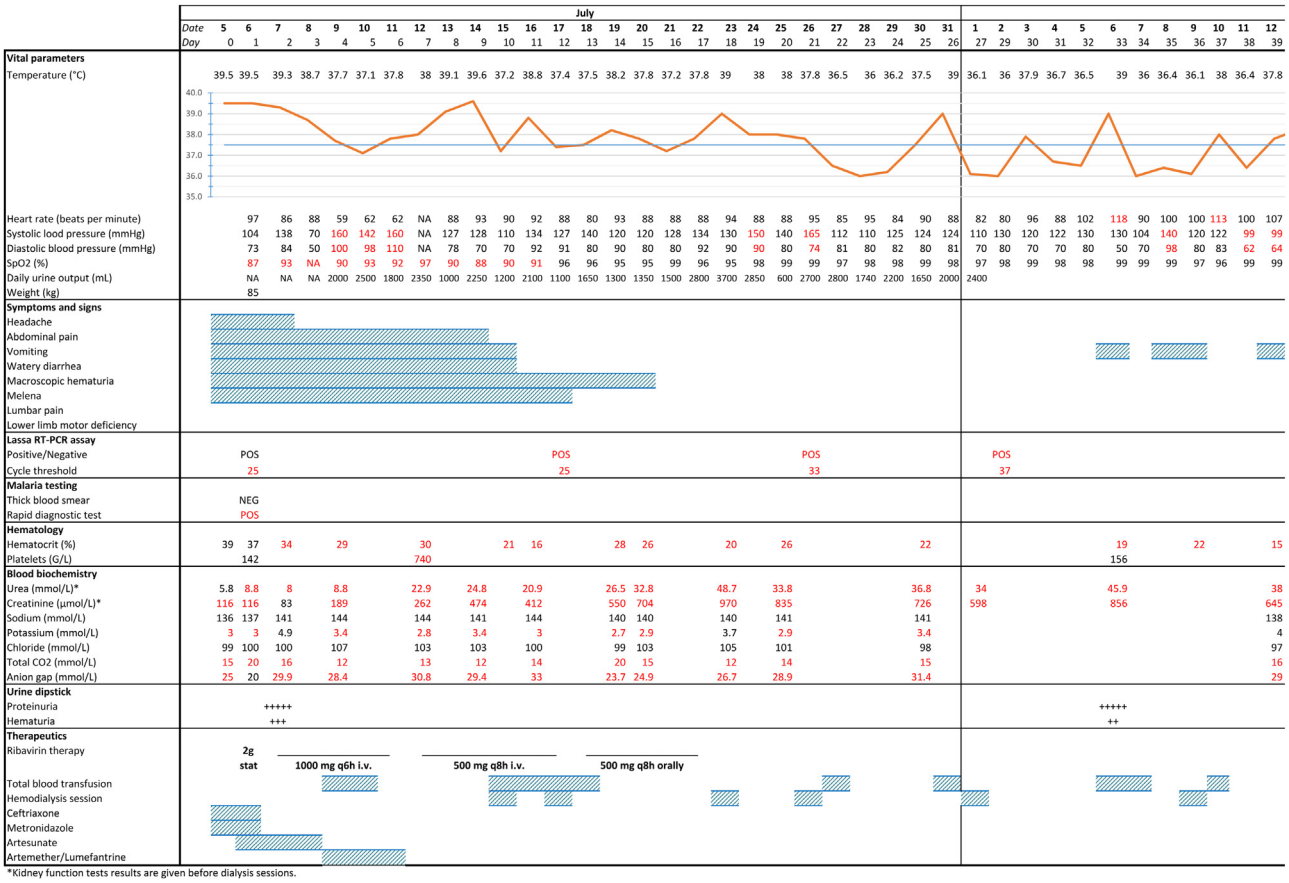

Figure 1. Clinical and biological evolution and medical management from admission to discharge in a 61-year-old man hospitalized for acute symptomatic Lassa fever who developed delayed-onset paraparesis, Owo, Ondo State, Nigeria, July to September 2018. Figures in black refer to normal values and those in red to abnormal values.

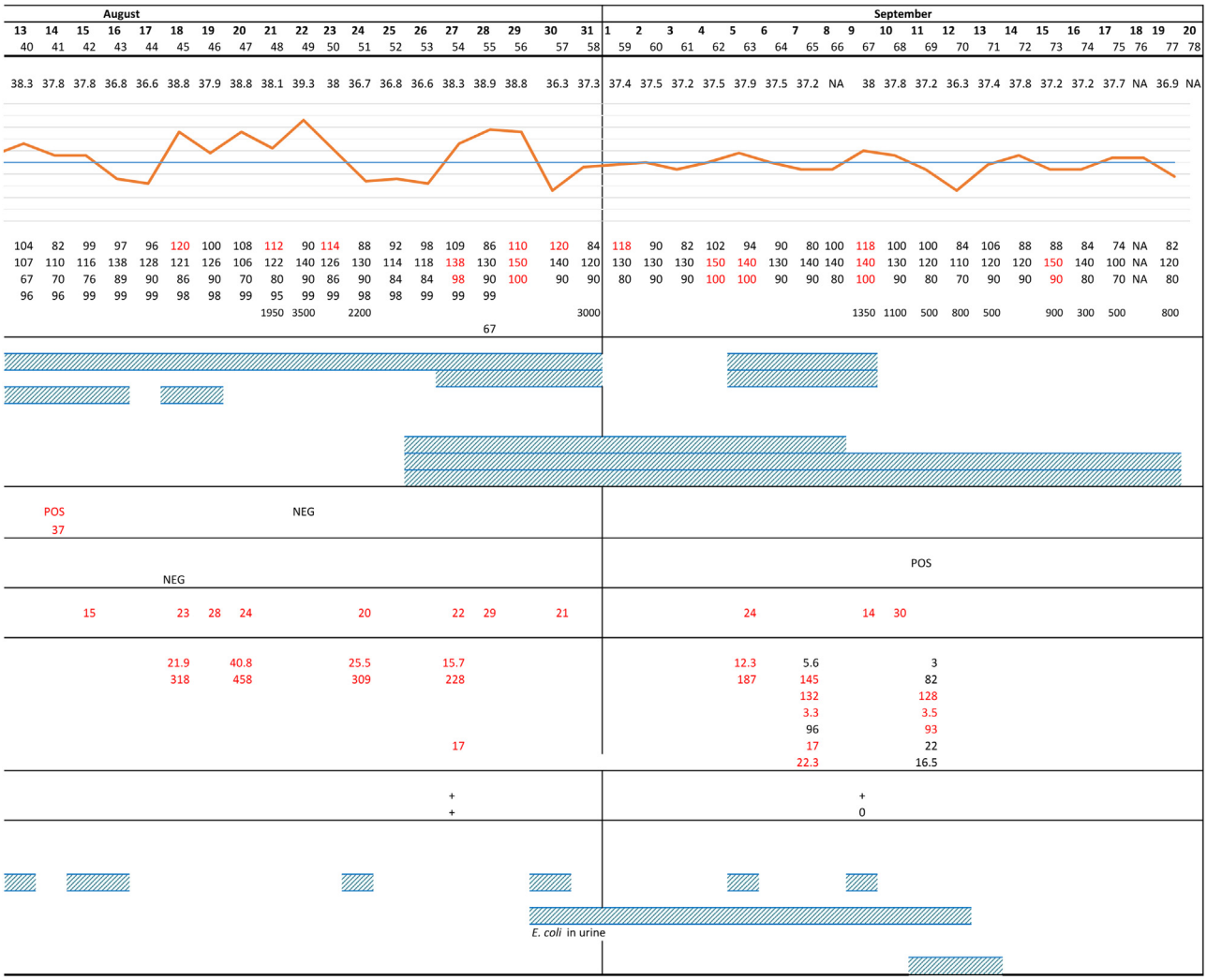

Figure 1. (Continued)

patients can present more severe and evocative features such as facial edema, shock, bleeding or neurological disorders. Death can occur during this late phase in 15 to 70% of hospitalized patients (Nigeria Centre for Disease Control; Houlihan and Behrens, 2017). In the case presented here, bleeding was present when the patient first presented to hospital, *i.e.* five days after symptom onset, and contributed to a high index of LF suspicion.

Neurological manifestations in patients with LF were reported in several works (Okokhere and Akpede, 2013; Okokhere et al., 2016, 2018b). However, to our knowledge, we report here the first case of LF-associated paraparesis. In our patient, medullar MRI excluded medullar compression and ischemic myelopathy but, due to movement induced artefacts and to the lack of short tau inversion recovery (STIR) sequences, it was not possible to rule out properly medullar inflammation. Even if no abnormality evocative of transverse myelitis was seen on MRI and if sensitive deficiency and sensitive level were lacking, the hypothesis of transverse myelitis is consistent both with the delayed and progressive onset of paraparesis accompanied by an inaugural transient feverish episode (Transverse Myelitis Consortium Working Group*, 2002). In this context, concomitant headache, vomiting and hiccup might raise the hypothesis of an associated area postrema syndrome (Shosha et al., 2018). Interestingly, area postrema syndrome and transverse myelitis constitute classic features of and are often associated in neuromyelitis optica spectrum disorders (NMOSD) (Bruscolini et al., 2018), a set of auto-immune CNS disorders. The delayed syndromic association seen in our patient, six weeks after the first symptoms of LF, suggests an immunologically driven CNS disorder, which calls for a para- or post-infectious condition. The fact that area postrema related symptoms disappeared while azotemia was improving and the lack of further evidence for brainstem inflammation (no brain MRI was performed) do not allow us to go further in this hypothesis. Furthermore, the unusually protracted Lassa viremia renders plausible persistent viral replication in cerebrospinal fluid at the time delayed CNS symptoms developed, as previously reported in cases of LF related encephalitis with detectable Lassa virus in cerebrospinal fluid despite negative RT-PCR in blood (Günther et al., 2001; Okokhere et al., 2018b). In the absence of lumbar puncture, it is not possible to rule out this hypothesis in our patient. The potential causes of myelopathy in this setting are numerous (Román, 2014). Of note, HIV serology was negative but the other classical infectious causes of paraparesis such as HTLV-1 and syphilis were not excluded. A medullar manifestation of schistosomiasis seems unlikely since no freshwater exposure was reported by the patient within the months before the start of symptoms. As he was receiving the same food coming from hospital's kitchen as other patients admitted at the same time, a toxic myelopathy consecutive to the consumption of bitter cassava (konzo) can be reasonably excluded. In the same way, neurolathyrism has never been reported in this area. Lastly,

due to the extended half-life of ribavirin and to its broad spectrum of adverse effects on both the central and peripheral nervous system, a delayed side effect more than four weeks after its discontinuation is not totally excluded. However, the presentation was not consistent with a peripheral neuropathy as previously reported in patients co-infected with HIV and HCV receiving antiretroviral plus ribavirin and experiencing mitochondrial toxicity (Lafeuillade et al., 2001). Beyond neurological toxicity, the benefit-risk ratio of this drug for the treatment of LF is currently being called into question as the available evidence of its efficacy is weak and some recently released data even suggest that its use could be associated to poorer outcomes when used to treat mild LF (Eberhardt et al., 2019).

In conclusion, if CNS manifestations are known complications of LF, their causative mechanisms are still poorly understood and their spectrum remains incompletely known. The case described here suggests that besides hemispheric encephalitis (Günther et al., 2001; Okokhere and Akpede, 2013; Okokhere et al., 2018b) and meningitis (Okokhere et al., 2016), delayed myelitis and brainstem encephalitis could be possible features of CNS involvement in patients with LF and might be immunologically driven. Further investigations are necessary to substantiate these hypotheses, to better understand their pathophysiology and to refine the syndromic categorization of LF related CNS disorders.

Conflict of interest

The authors have no competing interest to declare.

Ethical Approval

Written informed consent for participation in the LASCOPE cohort study (NCT03655561) and further publication of anonymous results has been obtained from the source patient. The LASCOPE study received approval from the Nigerian National Health Research Ethics Committee as well as the Federal Medical Centre Owo Research Ethics Committee. It is conducted in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

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