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Imported cases of Lassa fever in South Africa: clinical and public health aspects

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Summary

Lassa fever (LF), caused by the Lassa virus, is a rodent-borne viral haemorrhagic fever (VHF) endemic to certain West African countries. The disease poses a significant public health concern, particularly due to its potential to cause severe disease and high mortality rates in cases reported from non-endemic regions. LF is the most frequently reported VHF in travellers returning from endemic countries. This report summarises the clinical findings and public health response to two cases of LF in South Africa. Lessons learned from the diagnosis and response to these cases are provided.

Introduction

Lassa fever (LF) is an acute viral haemorrhagic illness caused by the Lassa virus (LASV), a member of the *Arenaviridae* family.[1] The disease is endemic in several West African countries, namely Benin, Ghana, Guinea, Liberia, Mali, Nigeria, and Sierra Leone. In these countries, an estimated 100 000 to 300 000 cases of LF are reported annually, corresponding to approximately 5 000 deaths.[2] The virus is primarily transmitted to humans via exposure to the infected excreta and secreta (i.e., urine, faeces, and saliva) of infected *Mastomys natalensis* rodents, with human-to-human transmission through direct contact with infected bodily fluid well-documented, but considered rare.[3] Following an incubation period of two to 21 days, the disease exhibits a wide spectrum of clinical manifestations in humans, ranging from mild, nonspecific symptoms to severe conditions, i.e., viral haemorrhagic fever (VHF) with multi-organ failure and death.[3]

LF is one of the most prevalent causes, if not the primary cause, of imported VHF in non-endemic countries.[4,5] While the overall case fatality rate (CFR) for LF is below 1%, it increases substantially to an estimated 15–25% among hospitalised patients; in addition, LF is distinguished by a disproportionately high maternal CFR – particularly in late pregnancy.[5] In cases of LF diagnosed in returning travellers, the CFR may be as high as 35%, which could be attributed to delays in the clinical diagnosis of the disease in non-endemic areas.[5]

In South Africa (SA), LF (and other VHF) are regulated as Category 1 Notifiable Medical Conditions (NMCs), requiring an immediate public health response following clinical suspicion (and confirmation) of cases. SA, a non-endemic country, reported its first imported case in 2007, followed by a second case in 2022. Both cases involved travellers with exposure histories in Nigeria where LF is endemic. This report consolidates these case reports to provide insights into the clinical presentations, diagnostic challenges, management protocols, and public health responses, aiming to enhance preparedness and response to LF in non-endemic settings.

Materials and methods

A retrospective document review was conducted using data collected during routine investigations of VHF in SA.

The National Institute for Communicable Diseases (NICD), a division of the National Health Laboratory Service, serves as the national reference laboratory for VHF in SA. The NICD curates a database for confirmed VHF cases, which was compiled through data collection from test request and submission forms, case investigation forms, field investigation reports by provincial Department of Health (DoH) Communicable Disease Clusters, emails and electronic messaging from referring hospitals, and the NICD hotline phone calls received for medical advice, as available for each case. Confirmed LF cases were defined as cases for which clinical samples tested positive by reverse transcription Polymerase Chain Reaction (RT-PCR)[6] and/or anti-LASV IgM positive and/or a fourfold increase in anti-LASV IgG in serially collected blood samples. Descriptive epidemiology was used to describe the confirmed LF cases.

Case descriptions

Case 1

A 46-year-old male was evacuated to SA for medical attention on 19 February 2007. The patient was a medical practitioner residing in Abuja, Federal Capital Territory, Nigeria, but also had a home in the village of Jalingo, Taraba State, Nigeria. The patient visited Jalingo in January 2007 and, for a 10-day period, participated in the rollout of a polio vaccination campaign in the area. According to the patient's wife, prior to hospital admission in Nigeria, the patient presented with fever, diarrhoea, abdominal pains, and anorexia. The patient self-medicated with antimalarials and antibiotics. He was admitted to a hospital in Nigeria on 10 February 2007 after being unwell for about seven days. On admission, the patient was found to have a fever (38.5°C), mild generalised abdominal tenderness, mildly elevated liver transaminases (AST 149 IU/L), leukopenia (white blood cell count 2.4 x 10^9/L with neutrophils 51% and lymphocytes 49%), and thrombocytopenia (74 x 10^9/L). HIV and malaria tests were negative, and there were no remarkable findings on abdominal x-rays or ultrasounds. The patient was treated for possible typhoid fever with intravenous fluids, ciprofloxacin, and metronidazole. The patient became afebrile after four days of treatment. On 15 February, the patient was vomiting and had tonic-clonic convulsions, which were aborted with 10 mg intravenous diazepam, followed by nuchal rigidity (neck stiffness) and confusion. General petechial haemorrhages were noted on the upper trunk, and oozing from venipuncture sites was observed. By 17 February, the patient had progressive uraemia, persistent oliguria, and waning consciousness; he was treated with emergency haemodialysis. On 20 February 2007, the patient was evacuated by air ambulance to SA for medical treatment. On admission, the patient was found to be in renal failure and had a very depressed level of consciousness (only responding to pain stimuli). Based on the epidemiological history of the patient and the clinical features and progression, VHF was suspected. Blood samples were submitted to the NICD on 20 February, which tested positive for LASV on RT-PCR and for anti-LASV IgG and IgM antibodies. The patient was treated with antibiotics for possible secondary bacterial infections and received ribavirin therapy orally (2g first dose, 1g every six hours for five days). However, the patient succumbed to his illness.

Case 2

A 60-year-old male technical manager, with a recent history of extensive travel in Nigeria, was admitted to a hospital in the KwaZulu-Natal (KZN) province, SA, on 01 May 2022. The patient had been treated for malaria in Nigeria (28 April 2022) after reporting symptoms of body ache, fever, nausea, joint pain, oliguria, and diarrhoea for about a week (since 21 April 2022). On presentation in SA, the patient had a fever (38.2°C) and was vomiting persistently. Blood tests revealed that he was in renal failure with elevated urea (9.7 mmol/l) and creatinine (138 µmol/l) levels and a low glomerular filtration rate (48 ml/min). He also had thrombocytopenia with a platelet count of 64 x 109/L and a high C-reactive protein (59 mg/L). Comprehensive differential testing, including for malaria, acute renal infection, hepatitis, thrombocytopenia, acute liver failure, and bacterial gastroenteritis, was done, and the patient tested positive for enteroaggregative *Escherichia coli* and *Shigella*/enteroinvasive *Escherichia coli* (EIEC) on day three of hospital admission. However, his condition continued to deteriorate, and he succumbed to his illness on 06 May 2022. Prior to his death, further considerations of differential diagnoses included dengue virus, leptospirosis, yellow fever, Rift Valley fever, and rickettsial infection. Upon receipt of the request for yellow fever testing at the NICD (09 May 2022), the epidemiological and clinical history prompted the testing for LF, and a diagnosis of LF was confirmed by RT-PCR posthumously on 12 May 2022. The delay in diagnosis stemmed from nonspecific symptoms and the absence of an early clinical suspicion. While 59 contacts were identified, including healthcare workers and family, no secondary infections were reported, as infection control measures aligned with standard protocols.

Discussion

Clinical challenges and diagnostic delays

LF's non-specific presentation – including fever, gastrointestinal symptoms, and haematological abnormalities, combined with the low index of suspicion in non-endemic areas complicates early diagnosis.[3] Both South African cases underscored this difficulty, with delays in recognition resulting from overlapping symptoms with other endemic diseases such as malaria and typhoid fever, and highlighted similar diagnostic delays in a global review of imported cases.[5]

Early detection is critical for effective management, as ribavirin therapy within six days of symptom onset significantly reduces mortality.[7] In the 2007 case (Case 1), although intervention was facilitated, it was likely administered outside of the window of maximum efficacy, whereas in 2022 (Case 2), the absence of early suspicion precluded administration of any therapeutic intervention.

Public health responses

Contact tracing and monitoring of exposed individuals were pivotal in preventing secondary transmission. In both cases, healthcare workers adhered to infection prevention measures, including personal protective equipment

(PPE) and isolation protocols. The 2022 case underscored the importance of vigilance even posthumously, as LF was diagnosed after the patient's death. Risk communication and education were integral to mitigating public concern and ensuring adherence to monitoring protocols.[8]

Management and infection control

Standard precautions and isolation practices were critical in limiting nosocomial transmission. The 2007 case benefitted from the proactive application of VHF protocols. In contrast, initial management in 2022 reflected challenges in distinguishing LF from other febrile illnesses. This underscores the need for heightened clinical awareness and the importance of a good travel history in non-endemic regions as well as the need for appropriate diagnostic tools. Delayed recognition also increases the risk of healthcare worker exposure in the absence of appropriate PPE.

Epidemiological implications

Both cases reinforce the potential for LF importation through global travel and the necessity for clinicians to consider it in differential diagnoses of febrile illnesses among travellers from endemic regions. Seasonal trends in West Africa (November to May) and outbreaks in Nigeria, such as the 1 055 confirmed cases reported in 2022, further underscore this risk.[9]

Conclusion

The imported LF cases in SA demonstrate recurring challenges in the diagnosis and management of this and other VHF outside endemic regions. Enhanced clinical awareness, rapid diagnostic capabilities, and adherence to infection control measures are essential in mitigating VHF public health impact. The integration of LF in travel medicine protocols and broader infectious disease surveillance systems will bolster preparedness and response in non-endemic countries.

Recommendations

- **Operationalise provincial and national VHF preparedness and response planning**

Although VHF is a rare occurrence in SA, preparedness and response plans for VHF should be available at provincial and national levels. These plans should be updated and routinely tested at provincial and national levels and include clear roles for all pillars of response, including surveillance, laboratory testing, case management, infection prevention and control (IPC), contact tracing and monitoring, risk communication, and inter-provincial co-ordination. Testing of response plans can be achieved through

tabletop drill or simulation exercises which are scheduled at an agreed frequency. Testing is particularly important given the low frequency of VHF in the country and to ensure that systems and protocols are in place for when such cases occur. The preparedness and response plans should leverage the existing NMC surveillance platform, NICD technical support, and established outbreak response structures in SA.

- **Strengthen early clinical suspicion through targeted clinician training**

Both cases involved delayed clinical recognition due to a low index of suspicion. Provincial and national VHF preparedness plans should include training for all pillars of response (as highlighted above), including case management (including clinical diagnosis) and laboratory investigation. Given anticipated healthcare worker staff turnover and the low frequency of VHF cases in SA, training should be provided on a predetermined schedule and not only to support outbreak responses. Training may be delivered via existing continued professional development platforms and the NICD, NHLS, and DoH webinar platforms to ensure reach to a wider healthcare worker audience.

- **Reinforce infection prevention and healthcare worker protection**

Given the high risk associated with VHF and healthcare workers, all healthcare facilities (as VHF cases may present at any facility) should have IPC protocols to support the management of suspected or confirmed cases of VHF. These protocols should align with national IPC guidance. Regular IPC drills and audits should be performed at designated facilities.

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Ethical considerations

This report is presented under the ethical approval provided by the Human Research Ethics Committee of the University of the Witwatersrand (Reference: M210752). This protocol allows for the reporting of infectious diseases of public health importance without patient consent. Patient anonymity and confidentiality were maintained throughout the study.

Conflicts of interest

The authors declare no conflict of interest.

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