A curse of Lassa fever: An update

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Abstract

This planet has seen a great number of terrible pandemics and epidemics that have wreaked havoc on mankind. The most impacted species among all living things by these epidemics and pandemics are humans. There have been many instances of pandemic like covid in the 19th and 20th centuries; the first plague pandemic (6th–8th century); the second plague pandemic (14th–19th century); etc. Lassa fever is also one of the deadliest of all the species that have wreaked havoc on humanity. In the town of Lassa in Nigeria's Borno state, the acute viral hemorrhagic fever known as Lassa fever was initially identified in 1969. Epidemics of Lassa fever have been reported in Guinea, Liberia, Sierra Leone, Nigeria, and the Central African Republic. The disease's cause, the Lassa virus, is a member of the Arena viridae family. The RNA genome of the pleomorphic virus is single-stranded and bi-segmented. By coming into contact with the excretions of infected Mastomysnatalensis rats and other rodent species, LASV, an endemic disease of West Africa, is spread. LASV is one of the high-priority infections included in the WHO R&D Blueprint due to its high fatality rate, lack of effective treatments, and challenges with prevention and control. In 80% of cases, the illness is minor or asymptomatic. Clinical characteristics can be hard to distinguish from those of other viral hemorrhagic fevers and common febrile disorders including malaria, typhoid fever, and other similar conditions. Reverse transcriptase PCR, viral isolation, and antigen and antibody detection are used to provide a final diagnosis. Antiviral medication ribavirin is used for treatment. There is presently no available vaccination. Rats can be avoided by keeping them out of residences.

Key words: Pandemic, Epidemics, Fever, Rats, Fatality, cases.

Introduction

Lassa fever outbreaks have shook the world, particularly the Federal Capital Territory (FCT) and its surroundings. In the two weeks prior, 12 instances were reported with 5 fatalities (41.7 percent). The threat the outbreak offers to medical professionals is even more horrifying. Four medical personnel were treating a patient with Lassa fever at the National Hospital in Abuja when they all experienced symptoms and were subsequently identified as carrying the virus. A total of 25 contacts tested positive for the Lassa virus, but they were not infected, according to pathological examinations [(1)]. Over five thousand people each year die from the disease, which is endemic in many African countries like Nigeria, Guinea, Sierra

Leone, Liberia, the Central African Republic (CAR), and, more recently, Senegal and Mali [2]. Though, most Lassa virus infections are without any symptoms, moderate, or self-limiting, and up to 70% to 80% of cases may go undiagnosed. However, serious sickness progresses in 20–30% of patients, with a 50% or greater fatality rate [3,4,5].

Causative agent

Lassa fever is brought on by the Lassa virus, an enveloped, single-stranded, bisegmented RNA virus that belongs to the family Arena viridae. Cryoelectron microscopy assessment of the virions reveals poorly differentiated morphology. Tetrameric complexes of the viral glycoproteins GP1 and GP2, which are composed of glycoprotein projections, cover the surface of the virion sheath [6]. The genome of the Lassa virus is composed of two single-stranded RNAs known as S (small) and L. (large). S to L RNAs typically have a molar ratio of 2:1 in virions. The 5' terminal of each fragment has a tri- or di-phosphate group and no cap structure. Two genes located in the sRNA segment encode the nucleoprotein (NP or N) and the envelope glycoprotein GP1 and GP2 (also termed GP-1 and GP-2, or G1 and G2). The initial form in which GP1 and GP2 are expressed is in the post-translationally cleaved precursor protein GPC (or GP-C) [7].

Epidemiology of Lassa fever

Lassa virus infections are spread globally. Multi-mammate rats (Mastomysnatalenses), which regularly proliferate in almost whole African continent, are the virus' natural hosts. They are most commonly encountered in rural locations, and are most usually spotted in around nearby rural areas. Most of the rodents are found in these rural areas in tropical Africa. The Lassa fever zone is the name given to a large West African region where the disease most routinely breaks out [8]. LASV is a single-stranded RNA virus that belongs to the family Arenaviridae. The first cases of Lassa Fever infection were initially reported in Nigeria in 1969 [9].The first reports of LF and the isolation of LASV were made possible in 1969 by the deaths of two missionary nurses in the Nigerian town of Lassa. Following that, it was discovered that LF was widespread in several West African nations, including Benin, Guinea, Liberia, Côte d'Ivoire, Mali, Nigeria, and Sierra Leone. However, there are differences in the seroprevalence of LF within these endemic locations, with the reported frequency being highest in West African forested areas [10]. In Sierra Leone, for instance, the proportion of seropositive people varies from 8% in coastal areas to 52% in the Eastern Province (CDC, 2017). From 4 to 55% of Guineans have been reported to have antibodies. Since its first discovery in Nigeria, the Lassa virus has spread throughout Central and West Africa, mostly affecting 300,000–500,000 individuals in Nigeria, Guinea, Sierra Leone, and Liberia, where it is responsible for over 5,000 annual fatalities [11]. The overall case fatality rate (CFR) of Lassa fever in an endemic setting is predicted to be between 1 and 10%. The CFR of Lassa virus, however, can increase to 50% during an epidemic outbreak, with a greater incidence in severe cases. The main routes of transmission for LF are contact with infected rodents and, to a lesser extent, person-to-person contact (see the section below on LASV maintenance and transmission). As a result, people who live in rural regions are typically at the greatest risk, particularly in neighborhoods with

bad sanitation and/or congested living circumstances. Healthcare professionals who care for LF patients without the required personal protective equipment are also at danger, and modelling has suggested that nosocomial transmission may account for up to 20% of infections during some LF outbreaks [12].

Over the past 20 years, Lassa fever outbreaks have frequently occurred in Nigeria. Out of 36 states and the Federal Capital Territory of Abuja, approximately 200 people in 18 states in Nigeria were infected by the disease's most recent outbreak, which occurred between August 2015 and March 2016 [13].

Clinical Lassa fever disease

A wide range of clinical symptoms are linked to LF, which affects people of all ages and genders. Following LASV infection, the incubation period typically lasts 7 to 10 days with a 21-day maximum. In the majority of infections (80%), LF has a mild or asymptomatic clinical manifestation [14]. The most common way that humans become infected is by being exposed to animal faeces through their digestive or respiratory systems. The most major method of exposure is thought to be inhaling microscopic particles of infectious materials (aerosol) [15]. Normally, the incubation phase lasts between six to twenty-one days. Fever, headache, sore throat, cough, chest discomfort, nausea, vomiting, malaise, myalgia, stomach pain, and diarrhoea are some of the non-specific initial symptoms of lassa fever. Since the clinical course of LASV infection is highly varied and symptoms might appear anywhere between two and twenty-one days after infection, early detection is challenging. The symptoms of lassa fever can resemble those of other endemic illnesses such malaria, typhoid fever, and other VHFs [16]. 15%–20% of severe cases result in death within 14 days of the disease's beginning. LASV has a disproportionately negative effect on children and pregnant women; during the third trimester, maternal and foetal mortality rates can reach 80% and 95%, respectively [17,18].

Lab diagnosis of Lassa fever

In order to identify the disease and determine its progress and complications, a variety of laboratory examinations are carried out. Even after the development of IFA antibodies, Lassa virus is still easily isolated from blood or serum during the feverish stage of the illness for up to 14 days or more after the commencement. Additionally, virus can be found in necropsy tissues. The presence of the virus (through culture), LASV RNA, an IgG or IgM antibody response, or LASV antigens generated during replication can all be used to identify LASV infection in a laboratory setting. LASV RNA can be found using nucleic acid amplification techniques such as polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP), and strand displacement tests. The formats of the western blot (WB), ELISA, and rapid diagnostic test (RDT) can all be used to identify antibodies and antigens. By using virus isolation, PCR, LASV antigen positive, IgM, and clinical signs resembling Lassa fever, active infections can be identified. There are various diagnostic test kinds, each with a different level of infrastructure needs, complexity, and suitability for quick action. A summary of the implementation specifications for the various LASV diagnostics accessible. Most worldwide laboratories employ internal LASV assays, and reports indicate that there are roughly

equal numbers of published and unpublished procedures [19]. Given the significant genetic variety among LASV isolates, RT-PCR, the "gold standard" for viral identification, may not be sufficient as the only detection method. For secondary confirmation, ELISA and/or tissue culture studies are advised. According to studies' findings, there is a high degree of certainty in the diagnosis of LF when using RT-PCR, antigen ELISA, and viral culture alone or in combination. There is evidence that IgG and IgM detection can occur at various periods, from the early stages of an infection to after the acute illness has gone, hence studies that accept IgM and/or IgG ELISA testing equally with these procedures have a lower degree of confidence [20]. Although the detection of the virus in urine and throat swabs is inconsistent among patients with serum viremia, Lassa virus can be cultivated from patient blood, cerebrospinal fluid, urine, and swabs [21]. At autopsy, viral cultures from organ samples (liver, spleen, lung, kidney, heart, and placenta) may be positive in cases of fatal infections [22].

Serological and antigen detection assays

Antibody-based assays

ELISA is a reliable and straightforward technique that can be used in laboratories with few resources in nations where LF is widespread. The clinical value of antigen or LASV-specific IgM antibody detection for patient diagnosis is obvious. Because IgG is produced later in the infection, the value of detecting LASV-specific IgG in patient diagnosis is restricted. However, illness surveillance frequently makes use of this assay. Typically, a sandwich or capture ELISA is used for antigen detection. LASV is bound in a sample by a "capture" antibody linked to a solid support. A primary antibody "sandwiches" the captured antigen after removing non-binding substances. A measurable signal is produced by the addition of a secondary (anti-species-specific) antibody conjugated to a reporter molecule. Sandwich ELISA can also be used to find IgM, the first and most clinically important antibody generated following infection. In this instance, a serum sample containing LASV-specific IgM is exposed to the LASV antigen bound by the capture antibody. An anti-IgM antibody that is unique to that species and is attached to a reporter molecule detects the complex after the IgM binds the captured LASV. The positive control in the antigen capture ELISA or the IgM target in the capture IgM ELISA is typically entire inactivated viruses or virus-infected cell lysate. Due to the need for BSL-4 bio containment to generate, inactivate, and safety test antigen, these assays are challenging to maintain without LASV inactivated material. Recombinant antigens are now a viable alternative to viral preparations. se recombinants don't require biocontainment and can be produced in huge quantities with ease. However, it is always wise to compare recombinant-based assays to live and/or inactivated virus-based assays. A rabbit polyclonal antibody created by immunizing with a recombinant NP was affinity purified and used by Boisen and colleagues to create a LASV antigen capture ELISA (ReLASV). They discovered a sensitivity of 94% and a specificity of 84% against the gold-standard PCR-based assay when compared to RT-PCR [23]. To help in diagnosis and therapy, other laboratory tests like complete blood counts, urinalyses, liver function tests, urine and blood cultures,

and microscopy for malaria parasites are also performed. A verified case is any suspected case that has undergone laboratory confirmation by the use of a positive IgM antibody, molecular detection, and virus isolation. The suspected individuals that died or eluded capture for laboratory testing were the probable instances [24].

Treatment

Ribavirin, a broad range guanosine analogue, is the usual course of therapy for LF and for post-exposure prophylaxis using both oral and intravenous injection. To increase the survival percentage, early therapy commencement is crucial. Contrary to intravenous dosing, which begins with a loading dose of 2.4 g and then continues to 1 g every 6 h for 10 days based on an adult's average weight, oral ribavirin is advised at a dose of 500 to 600 mg every 6 h for 7 to 10 days [25].

Therapeutics

Both in NHP animal models and in a human experiment including LF patients in Sierra Leone, ribavirin has been shown to enhance outcomes. When combined with palliative care, which includes managing blood pressure, maintaining healthy levels of blood oxygen saturation, and correctly prioritizing secondary complications, ribavirin has been shown to reduce viral load when administered early in the course of infection and improve patient outcomes. Ribavirin is given in a 2 g loading dose, followed by 1 g every 6 hours for 4 days, and then 0.5 g every 8 hours for an additional 6 days [26].

Containment

The most dangerous type of exposure is parenteral; as a result, staff training is required to prevent it. Therefore, lassa fever patients should be treated in isolation while wearing a mask, gown, and gloves. The protection of carers and other patients should have increased with the availability of reparatory protection against small-particle aerosols [27].

Vaccine development

INOVIO Pharmaceuticals, Plymouth developed INO-4500, a DNA vaccine candidate for LF. In February 2021, the first trial subject received a dosage in Ghana for the phase 1B human research. In the clinical trial, about 220 participants between the ages of 18 and 50 will receive a two-dose injectable regimen on days 0 and 28 while having their immunogenicity and safety in an African population evaluated [28].

Prevention and control

Since the lassa fever virus poses the greatest threat to public health among the arenaviridae since it is impractical to suppress the mastomys rat population, interventions are limited to keeping rodents away from people's houses and food supplies and practicing good personal hygiene. Gloves, face masks, lab coats, and safety glasses are indicated while interacting with an infected person. Although research is ongoing, there is presently no vaccine available to prevent Lassa fever. The Lassa fever virus and the Mozambique virus are quite similar, but the Lassa fever virus is more dangerous. This virus is being considered for prospective use as a vaccine. Based on the recombination of vesicular stomatitis virus vectors expressing the Lassa virus glycoprotein, researchers at the USAMRIID facility have developed a promising vaccine against the Lassa virus. While exhibiting no clinical symptoms, test primates have survived single intramuscular doses and deadly alterations [29]. The development of an efficient Lassa fever vaccine should result in the

establishment of more diagnostic and treatment facilities for Lassa fever in the various areas of each country where it is endemic (which has reached an advanced stage with positive results in animal trials).

Conclusion

In order to minimise the spread of Lassa fever, effective management requires the application of preventative measures, quick laboratory diagnosis, fast treatment, supply of personal protective equipment, cross-border surveillance, contact tracing, community awareness, and vector control. In addition to identifying test resources for Lassa molecular diagnostics and serology, this review also documented numerous in-house LASV assays that are widely utilized around the world. However, there are still several holes that the 2016 WHO R&D Blueprint identified. Future directions for research in Lassa fever diagnostics include assay development to improve detection across the genetically diverse spectrum of Lassa virus strains, assay validation to demonstrate efficacy across geographical regions and viral lineages, point-of-care diagnostic development and field validation, and content expansion of multiplex assays to distinguish Lassa fever from other diseases with comparable clinical presentations.

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