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### LASSA FEVER: ANOTHER INFECTIOUS MENACE

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#### Abstract

Nigeria is presently suffering from another Lassa fever epidemic. This was confirmed in the statement of the Minister of Health of the Federation in which he said, "There has been an upsurge in the reported cases of Lassa fever since the beginning of this year, especially in the Federal Capital Territory and its environs.

Within two weeks, 12 cases with five deaths due to the disease were recorded. 25 contacts are confirmed by laboratory investigations to have been infected, including 4 health staff working in the National Hospital, Abuja."<sup>1</sup>

Lassa fever is an acute viral haemorrhagic fever first described in 1969 in the town of Lassa in Borno state, Nigeria.<sup>2</sup> It is endemic in West African countries, and causes 300,000 cases annually with 5000 deaths.<sup>3</sup> Lassa fever epidemics occur in Nigeria, Liberia, Sierra Leone, Guinea and the Central African Republic.<sup>4</sup> Lassa virus, the agent of the disease is a member of the Arenaviridae family. The virus is pleomorphic with single-stranded and bisegmented RNA genome.<sup>3</sup> Its primary host is Natal Multimammate Mouse (*Mastomys natalensis*). Transmission to man occurs via exposure to the rat excrement through respiratory or gastrointestinal tracts<sup>5</sup>, exposure of broken skin or mucus membrane to infected material, direct contact, sexually and transplacentally.

The prevalence of antibodies to the virus is 8-22%<sup>9</sup> in Sierra Leone, 4-55% in Guinea,<sup>12</sup> and 21% in Nigeria.<sup>13</sup> The disease is mild or asymptomatic in 80% of infected people, but 20% have a severe multisystemic disease. Clinical features are difficult to differentiate from that of other viral haemorrhagic fevers and common febrile illness such as Malaria, Typhoid fever and so on. Definitive diagnosis is by viral isolation, Antigen and Antibody detection and Reverse Transcriptase PCR. Treatment is with Ribavirin, an antiviral agent. No vaccine is currently available. Prevention is by keeping rats away from homes.

**Key Words:** Lassa fever, Lassa Virus and Epidemic.

#### INTRODUCTION

Nigeria is presently suffering from another Lassa fever epidemic. The Minister Of Health of the country said in a statement on the recent Lassa fever outbreak that: " Since the beginning of this year, there has been an upsurge in the reported cases of Lassa fever especially in the Federal Capital Territory (FCT) and its environs. Within the last two weeks, we have recorded 12 cases with five deaths (41.7% case fatality). Much more worrisome is the danger that the outbreak poses to health workers. Four health staff working in the National Hospital, Abuja who were taking care of one of the Lassa fever

cases have also fallen ill and laboratory investigations have confirmed they are infected with the Lassa virus." "About 25 contacts in all were found to be positive with the Lassa virus from laboratory investigations but did not come down with the disease" (1).

Lassa fever is an acute viral haemorrhagic fever first described in 1969 in the town of Lassa in Borno state, Nigeria, located in the Yedseram river valley at the south end of Lake Chad (2). Clinical case of the disease had been known for

over a decade earlier but not connected with this viral

pathogen. The infection is endemic in West African countries, and causes 300,000-500,000 cases annually with approximately 5000 deaths (3). Outbreaks of the diseases occur in Nigeria, Liberia, Sierra Leone, Guinea and Central African Republic, but it is believed that human infections also exist in Democratic Republic of Congo, Mali and Senegal (4). Its primary animal host is the Natal Multimammate Mouse (*Mastomys Natalensis*), an animal indigenous to most of Sub-Saharan African (5). The virus is probably transmitted by the contact with the faeces and urine of animals accessing grain stores in residential areas (6).

#### **CAUSATIVE AGENT OF LASSA FEVER**

Lassa fever is caused by the Lassa virus, a member of the arena viridae; it is an enveloped, single-stranded, bisegmented RNA virus (3). The virions exhibit pleomorphic morphology when examined by cryoelectron microscopy. The surface of the virion envelope is studded with glycoprotein projections that consist of tetrameric complexes of the viral Glycoprotein GP1 and GP2 (6).

The genome of Lassa virus like other arena consists of two single-stranded RNA segments designated S (small) and L (large). In virions, the molar ratio of S to L RNAs is roughly 2:1. The 5' terminus of

each segment contains a tri-or diphosphate group and lacks a cap structure. The S RNA segment contains two genes that encode three final gene products- the nucleoprotein (NP or N) and the envelope glycoproteins GP1 and GP2 (also termed GP-1 and GP-2, or G1 and G2). GP1 and GP2 are first expressed as a precursor protein, GPC (or GP-C), which is cleaved post translationally (7). The L RNA segment contains two genes that encode two genes product, the viral polymerase (L protein) and Z protein, a small protein of undetermined function (7). On both segment, the genes are arranged in an ambisense orientation. The NP and polymerase genes reside at the 3' end of the S and L RNA segment, respectively, and are encoded in the conventional negative sense- that is, they are expressed through transcription of genome - complimentary mRNAs.

The genes located at the 5' end of the S and L RNA segment, GPC and Z, respectively, are encoded in mRNA sense but there is no evidence that they are translated directly from genomic RNA. These genes are expressed instead through transcription genomic-sense mRNAs from antigenomes, full length complimentary copies of genomic RNAs that function as replicative intermediates (6). Lassa virus will infect almost every tissue in the human body. It starts with the mucosa, intestine, lungs, and urinary system, and then progresses to the vascular system (4).

## EPIDEMIOLOGY OF LASSA FEVER

**Vectors:** Lassa virus is zoonotic. The natural hosts for the virus are multimammate rats (*Mastomys natalensis*), which breed frequently throughout west, central, and east Africa<sup>8</sup>. They are probably the most common rodent in tropical Africa and are found predominantly in rural areas and in dwelling more often in surrounding country side (9); members of the genus are infected persistently and shed the virus in their excreta. Humans are infected by contact with rats or by eating them. Rats found in houses of infected people are seropositive for the virus ten times more often than those in control houses (10). Virus antibodies occur after a febrile illness in twice as many people who eat rats as in those who do not, and deafness (an effect of Lassa fever) occurs four times more frequently (11). Infection in humans typically occurs via exposure to animal excrement through the respiratory or gastrointestinal tract. Inhalation of tiny particles of infective materials (aerosol) is believed to be the most significant means of exposure (6). It is possible to acquire the infection through broken skin or mucous membranes that are directly exposed to infective materials. Transmission from person to person has also been established, presenting a challenge for health care workers. Sexual transmission and transplacental transmission of the virus have also been established (4). Transmission through breast milk has been observed (4).

## PREVALENCE/INCIDENCE

Dissemination of the infection can be assessed by prevalence of antibodies to the virus in populations. The prevalence of antibodies to the virus is 8-52%<sup>9</sup> in Sierra Leone, 4-55% in Guinea (12), and in Nigeria (13). Seropositivity has also been found in the Central African Republic Democratic of the Congo, Mali and Senegal (14). Sporadic cases have occurred in travellers returning to Britain, the Netherlands, and Germany from the endemic areas.

## MORBIDITY AND MORTALITY

Lassa fever affects people of all ages. The disease is mild or has no observable symptoms in about 80% of people infected, but 20% have a severe multisystem disease. Incubation period is 6-21 days. The virus is excreted in urine for three to nine weeks from infection and in semen for three month (14). Sensorineural hearing deficit is a visual of the disease it was found in the 29% of confirmed cases compare with none of febrile controls in hospital in patients (15). In the general population, 81% of those who experienced sudden deafness had antibodies to Lassa virus as against 19% of matched controls (16). There is no apparent relationship between the severity of viral illness, initial hearing loss, or subsequent recovery(16).

Presentation of cases used to be highest during the dry season (January to March) and lowest during the wet season (May to November). However, recent data from Kenema, Sierra Leone show that admissions were highest during the change from the dry to the wet season (17).

Lassa fever was responsible for 10-16% of all adult medical admissions in 1987 into hospitals studies in Sierra Leone and for about 30% of adult deaths (18). The case fatality rate varied from 12% -23% for the period of 1997 -2002 (19). During pregnancy, high rate of maternal death (29%) and fatal and neonatal loss (87%) have been recorded, with 20% of all maternal deaths in Sierra Leone being due to Lassa fever (20). An estimate of the case fatality rate in the general population is 1-2%, must lower than in hospitalized cases, possibly as a consequence of differences in severity.

Using the figures for rural populations (available from United Nations Development Programme) and the epidemiology of the disease we estimate that the 'at risk' seronegative population (in Sierra Leone, Guinea, and Nigeria) may be as high as 59 million, with an annual incidence of illness of three million, fatalities up to 67,000 and up to three million reinfections (19).

#### **CLINICAL FEATURES OF LASSA FEVER**

Infection with Lassa virus leads to the gradual onset of fever and malaise after an incubation period of about 10 days (range, 5-21days), as the process develops, there is an increase in fever and myalgia, with severe prostration. Gastrointestinal manifestations such as abdominal pain, nausea, and vomiting, diarrhoea, or constipation are common. Sore throat occurs in two thirds of cases and is usually accompanied

by objective inflammatory or exudative pharyngitis. Retrosternal pain and cough are frequent, and pleural effusions may develop. Bleeding manifestations are seen in less than a third of patients but signal an unfavourable prognosis. Signs of increase vascular permeability such as facial oedema or pleural effusion are present in a minority of patient and also suggest a poor prognosis. Mortality in hospital patients is 15-20% (6).

A careful case-control study comparing Lassa fever to other febrile diseases seen in a West African hospital found features significantly associated with Lassa fever, including bleeding, oedema, exudative pharyngitis, conjunctivitis, and pharyngitis, but positive predictive values ranged between 0.61 to 0.74 (18). The same study also found vomiting, sore throat, tachypnoea, or bleeding to predict a 2.5-fold or higher increased risk of death. In spite of the relative non-specificity of the clinical findings, more than three fourths of patients thought to have severe Lassa fever are confirmed through viral assays. Lassa fever is a major paediatric problem as well (21, 22). Disease is more difficult to diagnose clinically. Occassionally, cases of infants developing anasarca have been described.

The course of fatal Lassa fever is relentless, with progression of signs and symptoms culminating in the onset of shock and death. In

Survivors symptoms and viremia persist until, 2 to 3 weeks after onset, there is defervescence

accompanied by the disappearance of virus from the blood. Pericarditis may occur in early convalescence, particularly in male patients. A case of polyserositis and recurrent pericarditis with constriction has been reported, which suggest that such complications should be sought more carefully (23).

Neurologic disease is not usually a dominant clinical manifestation in Lassa fever, but aseptic meningitis, encephalitis, global encephalopathy with seizures, and more subtle neurologic problems are well described (24-26). Cerebellar ataxia in convalescence is an uncommon but interesting occurrence. In convalescence, deafness is common; this is an important feature of Lassa fever, as it provides an important diagnostic clue (27). Late in course of the disease or early in convalescence, unilateral or bilateral hearing loss was noted in 29% of prospectively studied patients (15). No treatment is available and the effects may be transitory or often permanent. The auditory patterns and clinical course resemble idiopathic nerve deafness (16).

The clinical laboratory provides few clues to the diagnosis. The leucocytes count can be low, normal, or modestly elevated. Platelet counts are generally normal but may be modestly decreased (28). Albuminuria is common. AST is usually at least mildly elevated and the degree of elevation, which parallels the viremia, is useful predictor of mortality<sup>29</sup>. Patients with AST values in the hundreds or thousands are at

considerable risk of dying even with ribavirin treatment. Chest radiography may show infiltrates, pleural effusions, or, more commonly, no abnormalities. Electrocardiographic findings are often non-specifically abnormal (30).

Lassa virus also causes unusually high fetal mortality. Gravid women have been recognized to have an increased risk of death from Lassa fever, and prospective studies have shown that this is particularly pronounced 30% in the third trimester, compared to a 13% mortality in non pregnant women<sup>20</sup>. Fetal loss was 87%, all infants infected in the last trimester died in-utero or during the neonatal period. Viremia, which is correlated with the risk of dying in Lassa fever patients, was higher in pregnant than non pregnant women. High concentrations of virus were found in fetal tissue as well as placenta (31). The biologic basis for these findings is unknown, but it seems likely that, once infected, the immature fetus is unable to mount an effective T-cell response to control the virus infection, maternal T cells would not be able to attack the placental infection because of the lack of MHC class I or II antigen expression on placental cells (32). Thus, the fetus and its supporting tissues would be a source of high level virus production.

#### **LABORATORY DIAGNOSIS**

There are a range of laboratory investigations that are performed to diagnose the disease and

assess its course and complications. Lassa virus is easily isolated from the blood or serum during the febrile phase of the disease up to 14 or more days after onset, even after the appearance of IFA antibody. Virus can also be detected in necropsy tissues (33, 24). Vero cell cultures examined by fluorescent antibody allow a diagnosis in 5 to 7 days or sooner. Lassa virus antigen can be detected by ELISA capture in serum within 4 hours of beginning testing and as it becomes negative, IgM antibodies appear (35). Antigen detection by ELISA is robust and reliable in rapidly fatal cases, even if the specimens are not handled properly for virus isolation (35). ELISA test for antigen and IgM antibodies give 88% sensitivity and 90% specificity for the presence of the infection (4). Reverse transcriptase (RT-PCR) is also a sensitive test for virus RNA, being positive in the blood of 23 of 29 patients on admission and 29 of 29 patients by the third day of hospitalization (36, 37).

Antibody can be detected by CF, IFA, or ELISA. IFA using lassa-infected vero cells as substrate is widely used (38) interpretation is subjective and discrepancies between laboratories are common IFA IgG seroreversion has been reported and thought to represent loss of antibody by previously sero-positive individuals (9). Lassa IgG and IgM can also be detected by ELISA (35, 39, 40). ELISA IgM titres appear earlier and persist longer than IFA IgM titres. IgG ELISA antibody persists for long period, whereas IFA

antibody appears to wane below detectable limits within several years (6).

Other effects of illness include lymphocytopenia and a moderate thrombocytopenia, which are maximal 10-11 days after the onset of symptoms (19) the thrombocytopenia is associated with a serum inhibitor and with the occurrence of haemorrhage, depression of platelet aggregation, and the severity of Lassa fever (19).

### TREATMENT

All persons suspected of Lassa fever infection should be admitted to isolation facilities and their body fluids and excrete properly disposed.

### ANTIVIRAL DRUGS

Although several compounds have shown in vitro efficacy, only the guanosine analogue ribavirin has had practical application. The drug is efficacious in lassa fever and is the therapeutic agent of choice in the disease (6). Early and aggressive treatment of Lassa fever using ribavirin was pioneered by Joe McCormick in 1979. After extensive testing, it was determined that early administration is critical to success. Additionally,

ribavirin is almost twice as effective when given intravenously as when taken by mouth (41). ribavirin is a prodrug which appears to interfere with viral replication by inhibiting RNA dependent nucleic acid synthesis, although the precise mechanism of action is disputed (42). the drug is relatively inexpensive, but the cost of the drug is still very high for many of those in poverty stricken west African states.

When Lassa fever infects pregnant women late in their third trimester, it is necessary to abort the pregnancy for the mother to have a good chance of survival (20). This is because the virus has an affinity for the placenta and other highly vascular tissues. The fetus has only one in ten chance of survival no matter what course of action is taken, hence focus is always on saving the life of the mother (19). Following abortion, women should receive the same treatment as other Lassa fever patients.

Siga Technologies is developing an antiviral drug that has been shown to be effective in treating experimentally infected pigs. In a study conducted at the U.S Army research institute of infectious Disease (USAMRIID), treatment with ST-193 once a day for 14 days resulted in significant reduction in mortality (71% of the animals survived at the low dose), whereas all untreated animals and those treated with ribavirin died within 20 days of the infection (4). Intravenous interferon therapy has also been used in the management of Lassa fever infection (4).

#### **SUPPORTIVE THERAPY**

Supportive therapy is important in the management of patient with lassa fever (43, 44). Avoidance of travel and general trauma, gentle sedation and pain relief with conservative doses of opiates, the usual precautions of such patients with bleeding diatheses (such as avoiding intramuscular injections and acetylsalicylic acid), and careful maintenance of hydration are indicated. Bleeding should be managed by

platelet transfusions and factor replacement as indicated by clinical judgment and laboratory studies.

Management of shock is difficult. Vigorous infusion of crystalloid carries a high risk of pulmonary edema. Cautious administration of fluids and early use of pressors is indicated, but careful monitoring is important.

#### **CONTAINMENT**

The most dangerous exposure is parenteral and must be avoided through staff training. Thus, patients with these lassa fever should be treated in mask, gown, and glove isolation. Protection to care givers and other patients should be enhanced by the addition of reparatory protection against small-particle aerosol (43, 45, 46). Close personal contacts should be monitored for fever for a period of 3 weeks. The patient may continue to excrete virus in urine or semen for weeks after recovery, so body fluids should be monitored for infectivity before the patient is released, meanwhile, a program of counselling emphasizing addition of disinfectant to toilets before use and protection of sexual partners should be followed. Special precautions are indicated when blood and other body fluids are handled in the clinical laboratory

#### **PASSIVE ANTIBODY**

Lassa virus infections are more difficult prospects for antibody therapy than other arenaviruses, because the volumes of plasma needed based on animal studies are large:

experimental studies of IgG for intravenous administration indicate that this could be a useful means of treatment only if selected, highly active preparations were available (48, 49). The future of antibody therapy in any of these diseases lies in development of standardized monoclonal antibody preparations of proven efficacy (50, 51).

### PREVENTION AND CONTROL

Of all the arenaviridae, the Lassa fever virus has the greatest public health implication and control of the *Mastomys* rodent population is impractical, so measures are limited to keeping the rodent out of homes and food supplies, as well as maintaining effective personal hygiene. Gloves, face masks, laboratory coats, and goggles are advised while in contact with an infected person.

Vaccine against Lassa fever is currently unavailable, though development is underway. The Mozambique virus closely resembles Lassa fever virus but lacks its deadly effects. This virus is being considered for possible use as vaccine.

Researchers at the USAMRIID facility have a promising vaccine against Lassa virus based on recombinant vesicular stomatitis virus vectors expressing the Lassa virus glycoprotein. After a single intramuscular injection, test primates have survived lethal challenges, while showing no clinical symptoms (53).

### CONCLUSION

Of all the Arenavirus diseases, Lassa fever has the greatest health impact and prospect for its

prevention through rodent control is least. No vaccine against the disease is currently available. The development of vaccines for Lassa fever carries several inherent problems. Clinically, Lassa fever infections are difficult to distinguish from other viral hemorrhagic fever and from more common febrile illness such as malaria, typhoid fever, shigellosis, leptospirosis, rickettsial disease and relapsing fever. Clinical laboratory provides little or no clue. RT-PCR tests which provide definitive diagnosis are not readily available in West African countries. Where, it is available it is too expensive and out of reach of the poor people living in the endemic areas. When the diagnosis is made, cost of Ribavirin and of barrier/isolated care is unaffordable. Furthermore, Lassa virus also causes usually high fetal mortality. Gravid women have been recognized to have an increased risk of death from Lassa fever, particularly pronounced in the third trimester. All infants infected in the last trimester died in utero or during the neonatal period. The disease is thus contributing in no small way to the high maternal, neonatal, infant and under five mortality rates in West Africa. Failure to effectively control the disease makes the attainment of the millennium development goals of reducing maternal and infant mortality rates impossible.

The disease also has the potential of being used as biological weapon. It therefore constitutes an infectious menace that must be curbed.

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