FIELD MEDICINE

LASSA FEVER – UN PEACEKEEPERS' NIGHTMARE IN WEST AFRICA

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ABSTRACT

Lassa fever is a viral haemorrhagic fever caused by Lassa virus belonging to Arenaviridae family and is endemic in West African countries of Sierra Leone, Liberia, Guinea and Nigeria. The virus is present in a multi-mammate rat (Mastomys natalensis) found in tropical endemic areas. The clinical picture of disease in the initial stages can be confused with many other bacterial, viral and parasitic diseases prevalent in the area. The disease, if untreated, may lead to haemorrhagic manifestations and can prove fatal. The highly infectious nature of disease and lack of diagnostic facilities in the endemic areas add to the dilemma. The civil unrest in most of the West African countries and large population migration has increased the incidence of this disease in these areas. The UN peace keeping troops deployed in these areas are at risk of this disease. This review highlights the epidemiology, clinical course, diagnostic modalities and treatment options of Lassa fever. The latest situation of Lassa fever in Sierra Leone is also discussed.

Keywords: Lassa fever, viral haemorrhagic fevers, West Africa

INTRODUCTION

Lassa fever is a viral haemorrhagic fever transmitted by rats. It remains a potential threat to 160 – 200 million people in West Africa where it causes 100'000 to 300'000 new cases every year with approximately 5000 deaths [1]. The disease has been known for decades throughout West Africa but the virus was not identified until January 12th 1969 when a missionary nurse working in the small town of Lassa, Nigeria, began complaining of backache. Thinking she had merely pulled the muscle, she ignored the pain and went on about her business. After a week, however, the nurse had a throat so sore and filled with ulcers, she couldn't swallow. She was administered every antibiotic they had on store in the Town's Church of The Brethren Mission Hospital, but the antibiotics did nothing. Her fever escalated, she was severely dehydrated and haemorrhagic spots began to appear on her skin. She began to swell, became delirious, started to have convulsions and died. After a few days another nurse, who was attending her colleague, came down with same symptoms and died. The autopsy revealed significant damage to every organ in the body. The heart, arteries and veins were filled with blood cells and platelets. Fluids and blood filled the lungs. Dead cells and lipids clogged the liver and spleen. The kidneys were congested with red cells and proteins [2].

Two persons, working in US laboratory, with material from the original outbreak, subsequently became infected, one fatally. One person had worked with animals infected with the live virus, but it is uncertain how the other person acquired the infection [3, 4]. Naturally occurring infections, often associated with subsequent nosocomial outbreaks, have been recognized in Nigeria, Sierra Leone and Liberia [5].

The years of civil unrest in Sierra Leone in the past decade has forced the United Nations to send the peacekeeping troops in this area in year 2000. Pakistan has been a major contributor in this mission since 2001 with about 3800 peacekeeping troops who are rotated on yearly basis. Recently, a new Pakistani contingent has taken over the responsibilities of peacekeeping in the neighboring country of Liberia, as well. There have been cases of Lassa fever among the UN peacekeepers deployed in Sierra Leone in recent past [6]. The area thus recognized endemic for Lassa fever exposes the UN troops to the risk of this deadly disease.

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METHOD OF REVIEW

The sources of information were a literature review using Pub Med and Ovid Internet Search (search term Lassa fever) and relevant websites (such as those of World Health Organization and Centre for Disease Control). In addition, the record of cases was taken from Lassa Ward in Kenema general hospital (eastern city of Sierra Leone). The record of Lassa fever in UN personnel was taken from Force Medical Branch of United Nations Mission in Sierra Leone (UNAMSIL), Freetown.

EPIDEMIOLOGY

Lassa fever is a zoonotic viral haemorrhagic fever caused by a single stranded RNA virus belonging to family Arenaviridae and is a disseminated systemic primary viral infection [7]. The main feature of fatal illness is impaired or delayed cellular immunity leading to fulminant viraemia [8]. The prevalence of the antibodies to the virus in the population is 8 – 52 % in Sierra Leone [9], 4 – 55 % in Guinea [10] and 21% in Nigeria [11]. Sero-positivity has also been found in the Central African Republic, Democratic Republic of Congo, Mali and Senegal [12].

VECTOR

The natural hosts for the virus are multi-mammate rats (Mastomys natalensis) that breed frequently and are distributed widely throughout west, central and east Africa [13]. They are the most common rodents in Tropical Africa and are found predominantly in rural areas [9]. Members of the genus are infected persistently and shed the virus in their excreta. Humans are infected by contact with the rats or by eating them (they are considered a delicacy and are eaten by up to 90% of people in some areas) [14].

MORBIDITY AND MORTALITY

The record of admissions in Lassa ward in Kenema General Hospital Sierra Leone, which is the World's only Lassa fever isolation ward [15], reveals that there have been 1794 serologically confirmed cases of Lassa fever amongst the local population from January 1999 to April 2004 with 409 (22.7%) deaths (table-1). The serum samples of all these cases were collected by WHO Collaborating Centre and detection of IgM antibodies by ELISA (Enzyme Linked Immunosorbent Assay) was performed in National Institute for Communicable Diseases in South Africa.

On 17th March 2004, a paediatric nurse in Kenema General Hospital, Sierra Leone died of suspected Lassa fever. During her emergency treatment Dr. Aniru Conteh, medical officer in charge of Lassa ward and the world's greatest expert on Lassa fever (15), received a needle stick injury in the hand while trying to recap the needle he had used on the patient. About 2 weeks later he contracted a laboratory-confirmed Lassa fever. Despite intensive efforts to save his life, he died on 6th April 2004 [15, 16]. Concord Times, the Sierra Leonean local newspaper wrote: "News of his death spread in Kenema and its environs like a bush fire. Most people were devastated to learn that the only Lassa fever specialist in Sierra Leone was gone, gone for ever. Nurses cried, patients wept. Kenema was thrown into a state of shock and mourning."

There have also been 27 serologically positive cases of Lassa fever from June 2001 to April 2004 amongst the UN peacekeepers deployed in or around the Kenema district of Sierra Leone. Out of 27 Lassa fever cases, 5 (18.5%) eventually died. Zambian peacekeepers bore the maximum brunt of this disease with 23 cases (4 deaths) followed by Pakistan 3 cases (1 death) and Ukraine 1 case (table-2).

People of all ages and sexes are susceptible. The disease is mild or has no observable symptoms in about 80% of people infected, but 20% have a severe multi-system disease. The incubation period is 6 to 21 days. The virus is excreted in urine for three to nine weeks from infection and in semen for three months [12].

Sensorineural hearing deficit is a feature of the disease. It was found in (29%) confirmed cases compared with none of febrile controls in hospital in-patients [17]. During pregnancy, high rates of maternal death (29%) and fetal and neonatal loss (87%) have been recorded in Sierra Leone due to Lassa fever [18].

CLINICAL COURSE

Lassa fever presents with symptoms and signs that are largely indistinguishable from other febrile illnesses. The onset is gradual with fever, malaise, headache, sore throat, cough, nausea, vomiting, diarrhea, myalgia and chest and abdominal pain [12]. The fever may be either constant or intermittent with spikes. Inflammation of the throat and eyes is commonly observed, with white tonsillar patches being a consistent clinical feature. In severe cases, hypotension or shock, pleural effusion, mucosal haemorrhages, seizures, encephalopathy and swelling of face and neck are frequent [19, 20]. The clinical stages of Lassa fever are shown in (table-3) [21].

No one clinical picture is diagnostic of Lassa fever. However Hosp based case definition for Lassa fever has been developed by Merlin (Medical Emergency Relief International) to facilitate clinicians in early diagnosis and treatment of the patients pending laboratory results (table -4). Based on a case series of 2001 (Collected by Merlin) the course can vary considerably in progression. The gap between onset and death may vary between 2 and 43 days with an average 12, whilst the interval between onset and discharge may vary between 6 and 43 days with an average of 19 days. Signs associated with poor prognosis are convulsions, bleeding and pregnancy [19].

The complications include mucosal bleeding (17%), sensorineural deafness (4%), pleural effusion (3%) and pericardial effusion (2%) [20]. The outcome is related to the degree of viraemia, not the antibody response and is worse with high levels of aspartate aminotransferase [22].

LABORATORY INVESTIGATIONS

Clinical diagnosis is complicated by the fact that the initial symptoms of the disease are indistinguishable from a number of other infections endemic in the area including malaria, typhoid fever, yellow fever and septicemia. Early laboratory confirmation of infection is therefore , most important, both for therapeutic intervention and prevention of nosocomial spread.

The 'gold standard' for the diagnosis of acute Lassa fever infection is isolation of the virus from the patient. The procedure is quite slow (culture of the virus may take 7-10 days). Lassa fever virus is internationally classified as a hazard group 4 pathogen, the group of infectious agents considered to pose the greatest risk to the life of an individual and community. Isolation of virus is undertaken in bio-safety level 4 laboratories, the most sophisticated and most expensive of all biological laboratories [7,19,23,24].

Tab-1: Lassa fever cases in kenema hospital sierra leone

Year	Total Cases	Deaths	Case Fatality Ratio
1999	200	50	25%
2000	500	100	20%
2001	280	60	21.4%
2002	310	70	22.5%
2003	330	85	25.7%
2004 (April)	174	44	25.2%
Total	1794	409	22.7%

Tab-2: Lassa fever in UN peacekeepers

Year	Unit	No. Lassa Cases	Deaths
2002	Zambia Battalion III	3	1
2002	Zambia Battalion IV	14	2
2002	Zambia Battalion V	5	1
2003	Zambia Battalion VII	1	-
2003	Pakistan Battalion VI	1	-
2004	Pakistan Battalion IX	2	1
2004	Ukraine Battalion	1	-
	Total	27	5

Tab-3: Clinical stages of disease

Stage	Symptoms
1 (1-3 days)	Generalized weakness and malaise, high fever (> 39°C continuous with peaks of 40-41°C).
2 (4-7 days)	Sore throat (with white exudative patches) very common; headache; back, side, chest or abdominal pain; conjunctivitis; nausea and vomiting; diarrhea; productive cough; proteinuria; low blood pressure (systolic <100mmHg); anemia.
3 (After 7 days)	Facial oedema; convulsions; mucosal bleeding (mouth, nose or eyes); internal bleeding; confusion or disorientation.
4 (After 14 days)	Coma and death.

Adopted from McCarthy, 2002 [21]

Tab–4: Case definition of lassa fever in hospital setting

A patient with fever > 38°C not responding to effective anti-malarial and broad spectrum antibiotics, with no obvious localizing signs of infection and at least two major or one major and at least two minor criteria.

Major Criteria	Minor Criteria
• Abnormal bleeding (including mouth, nose, haematemesis, or from the vagina) • Swollen neck or face • Conjunctivitis or subconjunctival haemorrhage • Spontaneous abortion • Unexplained tinnitus or altered hearing during a febrile illness • Persistent low systolic blood pressure • Known exposure to a confirmed Lassa patient	• Headache • Sore throat • Persistent vomiting • Diffuse abdominal pain/tenderness • Retrosternal pain • Diarrhoea • Generalised myalgia and arthralgia • Profuse weakness • Proteinuria • WBC count < 4000μL • Markedly elevated liver enzymes

If a patient satisfies the hospital definition, isolate patient and inform the Lassa Ward. Take full contact precautions (i.e. gloves, masks and protective clothing) when administering care to the patient and maintain a strict hand washing protocol with 1% chlorine solution or chlorine-containing blue soap.

Adapted from Merlin [19]

Serological diagnosis involving the detection of IgM and IgG antibodies by enzyme linked immunosorbent assay (ELISA) is quick and highly sensitive and specific tool available [24]. At hospital admissions, most patients have antibodies to the virus 67% IgM and 53% with IgG [22].

Other effects of illness include lymphocytopenia and a moderate thrombocytopenia occurring maximally 10 to 11 days after the onset [25]. The depressed platelet activity is associated with the presence of serum inhibitor that is strongly associated with the occurrence of hemorrhage, depression of platelet aggregation and severity of Lassa fever [26].

Successful attempts have been made to diagnose Lassa fever by use of the polymerase chain reaction (PCR) and hybridization procedures. As a surrogate for virus isolation (the most accurate method for diagnosis), rapid and sensitive coupled reverse transcriptase–PCR (RT-PCR) assays have been developed recently. These techniques have already proved of considerable value in the rapid diagnosis and molecular characterization of Lassa fever virus strains [27].

CLINICAL MANAGEMENT

All suspected cases should be admitted to hospital where adequate isolation facilities must be provided. The primary aim is to manage the patient with Lassa fever and to prevent its transmission. Hospital transmission has occurred when inadequate infection control measures were practiced [28]. Therefore, strict isolation of cases in a hospital and barrier nursing techniques for handling body fluids and excreta should be maintained [29].

TREATMENT

Ribavirin is the drug of choice. It is administered intravenously 30mg/Kg initially as a loading dose (maximum 2g) once, followed by 16mg/Kg intravenously (maximum 1g per dose) every 6 hours for 4 days, followed by 8mg/Kg intravenously (maximum 500mg per dose) every 8 hours for 6 days [30]. It is considered to be twice as effective when given intravenously as orally, and if administered within the six days of start of illness, reduces death by 90%. A serum aspartate aminotransferase level greater than or equal to 150 I.U. per liter at the time of admission is associated with high probability of death, a case fatality ratio of 55% has been recorded. Whereas patients with the same risk factor who were treated for 10 days with intravenous ribavirin, begun within first 6 days of the onset of fever had a case fatality rate of 5% [19].

Patients should also receive supportive care consisting of maintenance of appropriate fluid and electrolyte balance, oxygenation and blood pressure, as well as treatment of any other complicating infections [20, 30].

SURVEILLANCE AND DISEASE CONTROL

Surveillance of all close contacts including people living with, giving nursing care, testing laboratory specimen of patient is carried out for three weeks from the date of last contact. Close surveillance of the contacts should be done by conducting body temperatures twice daily. The person with body temperature greater than 38.3oC (101^{o}F) should be immediately hospitalized in isolation facilities. The place of residence of the patient during the three weeks prior to onset should be determined and a search initiated for unreported or undiagnosed cases [12, 19]. Two areas of risk deserve special consideration because of their potential to propagate the disease. One relates to the burial of infected corpses with the possible risk of spread to large number of people involved in traditional burial ceremonies. The grave has to be at least 2 meters deep with concrete on all sides to prevent access to rodents. The other relates to the treatment of undiagnosed cases in hospitals where conditions of over crowding and poor hygiene can spread the disease in many other patients, staff or visiting relatives and attendants [19,20].

Isolation and treatment of suspected and confirmed cases requires intense support to staff through training supervision and logistics. Health professionals, cleaners, burial teams, laundry and ambulance staff who come in direct contact with suspected or confirmed cases or their body fluids should be protected by work clothes, coverall or theatre style gowns together with double gloves, water proof aprons, gum boots, biosafety masks, caps and goggles. Further protection is given by constantly reducing viral contamination on the isolation unit using copious amounts of 1% bleach (hypochlorite) solution to which these viruses are sensitive [30].

VACCINE

Development of a vaccine against Lassa fever is one of the main goals of molecular research currently being undertaken on the virus. Work is needed to determine whether a recombinant vaccine based on a single strain specific Lassa proteins cross protects against heterologous Lassa strain but there are data that suggest that such cross protection may occur. Fisher, Hock and McCormick [31] put forward the attractive idea of using 17D strain of yellow fever as a vehicle and producing a Yellow fever / Lassa chimera able to vaccinate the recipients effectively against both diseases with a single dose. The cost and logistical problems of delivering would be huge, particularly since fewer than 20% of districts in the countries studied, achieve 80% uptake of childhood vaccination [19].

African continent, particularly West Africa has been lately devastated by political turmoil and armed conflicts. UN peace keeping troops are thus likely to stay in these areas for some time. Pakistan Army is playing a key role in most of the UN missions in West Africa. The dreadful nature of Lassa fever demands that troops in general and commanders in particular coming to this area are educated as regards the disease and rodent control measures to avoid the risk of contracting the disease. Implementation of strict anti-rodent measures thus at unit level is key in avoiding a catastrophic nightmare.

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