



LASSA FEVER UPDATE

by

Dr J. B. McCormick¹



INDEXED

I. INTRODUCTION

Lassa fever is a febrile illness caused by infection with Lassa virus. Lassa virus is a member of a group of viruses called arenaviruses, many of whose members cause haemorrhagic fever in various parts of the world.

Lassa virus was first discovered in 1969 when it was isolated from a stricken missionary from Northern Nigeria. The virus was isolated at Yale University following which two laboratory workers at the University became infected with the virus. This experience then severely restricted the number of laboratories working on this, and similar viruses, to those with special containment facilities.

The disease continued to crop up sporadically in West Africa. It occurred again in Nigeria, as well as Sierra Leone and Liberia. Field investigations in Sierra Leone in 1972 established that the disease has probably been endemic in the Eastern Province. In addition it was found in 1972 that a rodent, Mastomys natalensis, was the reservoir of the virus. This rodent is one of the most common in Africa, and is often the predominant rodent infester of houses in parts of Africa.

After cases continued to occur in the Eastern Province of Sierra Leone, it was decided to establish a long-term study of the disease and its ecology in that area. Most of the data in this update are from this long-term study which is still in progress.

A. Clinical features

Lassa fever usually has its onset from six to 15 days after infection. It begins with a fever, malaise and headache during the first 24-48 hours. By the second to fourth day of illness frequent symptoms are abdominal pain, retrosternal or epigastric pain, sore throat and often vomiting or diarrhoea. Physical examination often shows some conjunctivitis, pharyngeal exudate, and abdominal tenderness. Laboratory findings are non-specific and may include a normal to low white blood cell count, proteinuria and granular urinary casts.

The fever is usually rather high, up to 40°C in severe cases, and may last for 10-14 days, and sometimes longer, before settling to normal. In the typical hospitalized case prolonged weakness, malaise and postural hypotension are the rule. The sore throat, epigastric pain and back pain generally subside about the same time as does the fever. In severe cases an encephalopathic or meningitic picture may occur and in fact the virus has been isolated on several occasions from spinal fluid. Lassa cases who die frequently display bleeding symptoms (50%) usually from the bowel, vagina or oral mucosa. Certainly not all of those who have bleeding manifestations will die. A harbinger of death is usually a sudden and profound drop in blood pressure. Death usually ensues within 12-24 hours after such a drop despite vigorous efforts in stabilizing intravascular volume with intravenous fluids including protein. The cause of this sudden hypotension is not known.

¹ Medical Officer, Special Viral Pathogens, Center for Disease Control, Atlanta, Georgia 30333, United States of America.

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The differential diagnoses of Lassa fever are numerous. They include: typhoid fever, malaria and non-specific viral illness in the absence of sore throat, influenza and other respiratory viral infections, streptococcal sore throat, non-icteric yellow fever, various other arboviral illnesses and finally other haemorrhagic fevers such as Congo virus, Ebola and Marburg disease.

B. Treatment

There is no proven effective therapy for Lassa fever. There are some reports of patients recovering from Lassa fever following administration of immune plasma. However, there are an equal number of reports where the immune plasma failed to cause recovery.

We are now systematically studying the therapy of Lassa fever with immune plasma and with an antiviral drug called Ribavirin. Thus far neither form of therapy has produced a survival result better than non-specific supportive therapy. Nor does either therapy produce a reduction in viraemia compared to no therapy. Our studies will continue, however at this point no specific therapeutic measures can be recommended.

II. EPIDEMIOLOGY OF LASSA

Lassa virus is found in nature in the blood, urine and tissues of the rodent Mastomys natalensis. This rodent is one of the most common found in sub-Saharan Africa. It is found both in villages and in the bush depending on the subspecies of the rodent and the terrain. Thus far, evidence of Lassa virus has been found in many countries of West Africa as well as the Central African Republic. In addition a new strain of Lassa has been isolated from Mastomys in Mozambique and in Rhodesia. Antibody to this new strain has been found in humans but it is not known whether it causes illness.

Although it is believed that most human Lassa infections occur as a result of virus transmission from infected Mastomys, it is also known that some infection occurs as a result of transmission from man to man. This fact is based on the hospital transmission which occurred during Lassa epidemics in Nigeria and Liberia.

Among village Mastomys populations in Sierra Leone we have found as high as 15% with Lassa virus in the blood, and another 15-20% with Lassa antibody, meaning they were at one time infected with the virus.

From our village trapping surveys we have found that Mastomys tend to cluster in some houses, but not others, and that they can and often do exist in a house with other rodent species such as the house mouse and the roof rat. In areas where we have worked the Mastomys were often caught, prepared and eaten by the people.

We have also confirmed that there are two probable subspecies of Mastomys in Sierra Leone. One has been found predominantly in the Eastern Province, has 32 chromosome pairs and tends to dwell in and around houses. The other is found predominantly in the Northern Savanna areas both in the bush and in houses and has 38 chromosome pairs. It is very difficult to differentiate between the two by any physical characteristics. Both can and do carry Lassa virus.

As a disease Lassa fever varies in frequency from area to area. In the Eastern Province of Sierra Leone, where our studies have been most concentrated, we have found that Lassa fever makes up from 5% to 15% of adult medical admissions and up to 50% of adult medical deaths. We have seen more than 500 active cases of Lassa fever admitted to our two study hospitals. The overall death rate of hospitalized patients is about 18%.

Serosurveys carried out in various parts of Sierra Leone have shown Lassa antibody prevalences ranging from less than 10% in the coastal area to as high as 30-40% in some Eastern Province villages to 10-20% in the villages of the Northern Savanna.

We have carried out long-term village surveillance in two villages in Sierra Leone. In the first village we found an initial antibody prevalence of 24% (106 of 433 persons tested). Three hundred and twenty-seven persons were found to have no antibody at initial bleeding, and were followed for seven months. At the end of seven months 14 were found to have seroconverted, which is an overall infection rate of 7.2/100 susceptible per year.

In another village surveillance study 621 persons were bled initially of whom 98 or 16% had antibody titres considered positive against Lassa virus. The incidence of seroconversion to the virus was 8.8 per 100 persons per year.

In each of the above villages the proportion of febrile illnesses caused by Lassa fever was about 10%. The illness to infection ratio may be from 1:3 to 1:5.

III. LABORATORY FEATURES

The laboratory diagnosis of Lassa fever is most frequently made by means of an indirect fluorescent antibody test performed on acute and convalescent sera taken from patients suspected of having Lassa fever. The test is rapid and reliable and can be performed in the field by an experienced person with a fluorescent microscope.

The diagnosis can also be made by isolating the virus from clinical specimens, usually from serum or whole blood, in tissue culture. This method is not practical in the field because of the relatively sophisticated laboratory which is required.

A third method of diagnosis, though not completely specific, is by a formalin fixed post-mortem liver biopsy. Such a specimen can be taken within one or two hours of death, put into 10% formalin and shipped in the mail without fear of communication of the virus. The typical finding of non-inflammatory focal liver necrosis associated with a compatible clinical illness would lead to a presumptive diagnosis of Lassa fever. This method cannot reliably separate Lassa fever from Ebola or Marburg disease.

IV. LASSA CASE DETECTION AND SURVEILLANCE

In Sierra Leone we have used three methods for detecting Lassa virus transmission:

- (1) hospital-based surveillance of febrile admissions;
- (2) village-based surveillance of febrile disease;
- (3) repeat village serosurveys.

A. Hospital-based surveillance of febrile admissions

This is the most efficient method of finding acute cases of Lassa fever in areas where medical facilities are available and used. It does require the interest and training of selected hospital personnel or the placement of a surveillance officer at the hospital.

Adults admitted with illnesses associated with high fever, headache, malaise and vomiting or diarrhoea with sore throat and/or epigastric pain are considered suspect Lassa patients. Clearly any patient with haemorrhagic manifestations is even more suspect. Admission and discharge blood specimens are taken for antibody examination in order to establish the diagnosis. Such specimens can be allowed to clot and be separated carefully with the serum put into a screw-cap plastic vial, marked with a number, name and date and placed at 4°C or at -20°C if a freezer is available.

In the event of a fulminant illness with rapid death a post-mortem needle autopsy specimen is obtained and placed in formalin and glutaraldehyde for examination by light and electronic microscope techniques.

Routine clinical data are collected on standardized forms (see attached). Regular collections of paired sera, biopsies and accompanying data are made from participating hospitals. Feedback of results is crucial to maintaining interest and cooperation, and regular summaries of laboratory findings are furnished to the hospitals.

B. Village-based febrile illness surveillance

A second method of detecting active Lassa cases is to establish village-based surveillance of febrile illness. Such a scheme requires that the village population, or at least a cohort, be bled prior to beginning surveillance. People are encouraged to report, when they have febrile illness, to the surveillance officer placed in the village, or to the local dispenser if he is responsible for the surveillance. The persons reporting have their body temperatures taken and recorded, and are given antimalarial tablets and aspirin. If seriously ill they are referred to a hospital. Two weeks later the person is followed up and a blood sample taken. This is compared to the initial specimen for antibody to Lassa fever. At the time the follow-up specimen is taken the patients are given vitamin tablets with iron.

C. Repeat village serosurveys

Lastly in some villages the population, or a cohort of the population, is bled periodically to see the rate of seroconversion to Lassa. This method does not require the continued presence of a surveillance officer. Such studies are often carried out in conjunction with rodent trapping studies in the same village.

V. OUTBREAK INVESTIGATION

We do not normally carry out special investigations of individual cases of Lassa fever in Sierra Leone. Exceptions have been in areas where we normally do not expect Lassa fever to occur. Investigation of such cases, however, may be helpful in determining the source of the virus such as contact with an active case versus travelling in a highly endemic area.

Outbreaks of Lassa as such are somewhat unusual in an endemic area, but do occasionally occur. Specimens collected during such an investigation usually consist of serum taken either for antibody studies or for virus isolation. Data collected during the investigation consist of questions relating to person-to-person contact, or a history of direct contact with rats (see attached form).

Specimens are collected by vacutainer and allowed to clot before separation of serum. The serum is stored at -20°C . For some small children filter-papers are used to collect finger-prick blood. The filter-papers are dried in a dryer or incubator overnight and processed the following day. After the antibody is eluted from the filter-paper the material is stored at -20°C . Unprocessed filter-papers are stored in sealed plastic bags containing a desiccant. The bags are then kept at -20°C .

Blood or serum for virus isolation is placed either in dry ice or liquid nitrogen, or in a cold box for transportation back to the laboratory where it is placed in a -70°C freezer.

VI. CONTROL METHODS AND INDIVIDUAL PROTECTION

At present there are no proven methods of controlling Lassa fever in an endemic area. We are presently studying the effect of village-wide elimination of rodents, by kill trapping, on the transmission of Lassa virus. These studies are in progress so it is too early to know if an effect can be shown.

The prevention of disease spread in a non-endemic situation involves the observation of strict isolation methods in caring for the patient suspected of having Lassa fever. The patient must be put in an isolation room. All persons entering the room must wear gowns, gloves and masks which are then decontaminated immediately upon leaving the room. An alternative is to place the patient in an isolator with negative air pressure, a technique not available in many areas of the world.

Regardless of the isolation method used all excreta and any article coming in contact with the patient must be decontaminated prior to disposal. A 0.5% calcium or sodium hypochlorite or a 1% formalin solution can be used.

All close contacts, family or others with physical contact, of a suspected case should be put under active surveillance. Casual contacts may be put under a passive, voluntary surveillance system for a period of 14 days from the last date of contact.

Form 01

LASSA FEVER RESEARCH PROJECT

GENERAL INFORMATION

OP No. or ANC No. _____

IP No. _____

Name _____
(1-20) Last First

Province 21 (name _____)

District 22 23 (name _____)

Chiefdom 24 25 (name _____) Location _____

Village 26 27 28 (name _____)

Husband or father's name _____

Accession No. _____
(29-36)

Age _____
(37-40)

Sex 41

Onset date _____
(42-47)

Admission date _____
(48-53)

Discharge date _____
(54-59)

Outcome 60

Final diagnosis 61 62 (name _____)

Hospital 63 64 (name _____)

Admission No. 65

First language 66 67

68-80 Blank

Form No. 12

LASSA FEVER RESEARCH PROJECT

OUTBREAK INVESTIGATION

Country (Name)
 01 02
 Province (Name)
 03 04
 District (Name)
 05 06
 Chiefdom (Name)
 07 08
 Village (Name)
 09 10 11

 Deaths in family in past month
 50
 Death associated with fever
 51
 Age of person
 52 53 54 55
 Attended funeral of person dying in
 56 past 3 weeks

Ecologic data

Individual

Reason sampled
 12
 Accession No.
 (13-20)
 Family
 (21-28)
 Age Sex
 29 30 31 32
 Ill with fever in past 21 days
 33
 Ill with fever and hospitalized during
 34 past year
 Date of illness requiring
 35 36 37 hospitalization
 Hospital
 38

 Village accessibility
 57
 Rice production
 58
 If swamp rice, year began
 59
 Rice storage
 60
 House construction
 61
 Roof construction
 62
 Floor construction
 63
 Rooms
 64
 Toilet
 65
 Water
 66
 Distance to closest house
 67
 Distance to bush
 68
 Location of house in village
 69
 Number of rooms in house
 70
 Type of beds
 71
 Cooked food stored overnight in house
 72
 Compound around house
 73
 Other
 74
 Other
 75
 Rodent infestation evidence
 76
 Rice storage in house
 77
 Nearest rice storage area out of house
 78
 Date of collection
 79 80 81 82 83 84
 Serum collected
 85

Sociologic data

 Education level
 39
 Occupation
 40
 Works in rice field
 41
 Persons/room where this person sleeps
 42
 Caught rat in past month
 43
 Ill with fever at time of this visit
 44
 Other persons with fever in family in
 45 past 21 days
 Attended ill person in house
 46
 Injection in past 3 weeks
 47 (reason)
 Slept in same bed with ill person in
 48 past 3 weeks
 Ate from same plate with ill person in
 49 past 3 weeks

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