Epidemiological and clinical description of Lassa fever in Jos, Nigeria

[1,2] Samson E Isa,[1,2] Nathan Y Shehu , [3]Raymond N Juryit , [1,2]Samuel G Simji, [4]Joy A Shuaibu, [5,6]Daniel Z Egah, [5,6]Edmond B Banwat, [7,8]Ogbonna Chikaike

Abstract

Background: The epidemiological, clinical and laboratory description, and treatment outcome of Lassa Fever (LF) in Jos, Nigeria.
Methods: A retrospective study from January 2012 - February 2013. Data analyzed included patients' demographics and clinical features. Main laboratory variable of interest was LF polymerase chain reaction (PCR) test. Categorical variables were compared using Chi square test or Fisher's exact test. Continuous variables were expressed as mean ± standard deviation or as median with range. Means were compared by student's t test or Mann-Whitney U test. $P < 0.05$ was considered significant.
Results: Six (40%) had confirmed LF by PCR while nine (60%) had negative PCR results. Mean age (years) was 31.0 ± 10.2 for confirmed cases compared with 22.0 ± 17.9 for unconfirmed cases (p=0.45). Two (33.3%) males and four (66.7%) females were confirmed cases compared with 5 (71.4%) males and 4 (50%) females that were unconfirmed cases (p=0.38). Median, with range, duration from onset of symptoms to presentation at hospital was 8 (4-11) days in confirmed cases compared with 4 (1-7) days in unconfirmed cases (p=0.01). Select findings among confirmed cases were as follow: rural/sub-urban residence 6 (100%); p= 0.01, fever 6 (100%), hemorrhagic manifestations 5 (83.3%), cough 4 (66.7%), sore throat 2 (33.3%), proteinuria 2 (33.3%), retrosternal pain 1 (16.7%). None of those with confirmed LF received ribavirin within 6 days of illness and the case fatality ratio was 83.3%.
Conclusion: LF is lethal and clinical diagnosis is unreliable. Laboratory testing should be made widely available to guide early diagnosis and treatment.

Keywords: Clinical Features, Epidemiology, Laboratory Description, Lassa, Nigeria

High Med Res J 2013;13:3-7

Introduction

Although Lassa Fever (LF) is a disease of West Africa, it can occur anywhere in the world because of the increased ease of international travels and the potential for use as a biological weapon. The disease is an acute hemorrhagic zoonotic illness caused by *Lassa virus* (LAV) which is an RNA virus of the family *Arenaviridae*. LF is widespread in West Africa and affects 2 million persons per annum with 5,000–10,000 fatalities annually.[2] The first reported case of LF occurred in 1969 in a nurse who was working in a small missionary hospital at Lassa, a town in North East Nigeria.[1] In a recent LF outbreak between January to March 2012 in Nigeria, 623 cases and 70 deaths were reported of which only 108 of the cases were laboratory confirmed.[3]

The modes of LAV transmission are not completely known, but they are almost certainly multiple. Endemic transmission is related to infected rodents by aerosolized urine, excreted virus and direct contact, and most probably to person-to-person spread in homes.[4] For nosocomial outbreaks, parenteral inoculations of body fluids, contact with infected body fluids and aerosols generated by patients have all been incriminated.[5]

Most infections with LAV in Africa are mild or subclinical[6] but case fatality in hospitalized patients average 15-25%.[7] Clinical manifestations are variable, and are present in many febrile patients not infected with LAV making clinical diagnosis extremely difficult. The incubation period of LF is between three and 21 days,[8] and in a case-control study of patients hospitalized with LF in Sierra Leone, the frequencies

[1.] Department of Medicine, Jos University Teaching Hospital, Nigeria [2.] Department of Medicine, University of Jos, Nigeria [3.] Epidemiology Unit, Ministry of Health, Plateau State [4.] Department of Family Medicine, Bingham University Teaching Hospital, Jos, Nigeria [5.] Department of Medical Microbiology, Jos University Teaching Hospital, Nigeria [6.] Department of Medical Microbiology, University of Jos, Nigeria [7.] Department of Public Health, Jos University Teaching Hospital, Nigeria [8.] Department of Public Health, University of Jos, Nigeria

Corresponding Author:
Dr. Samson Ejiji Isa
Tel: +234 802 840 2227 Email: ejijisa@yahoo.com

of selected findings were as follows: retrosternal chest pain (74%), sore throat (60%), back pain (62%), cough (62%), abdominal pain (50%), vomiting (49%), diarrhea (26%), conjunctivitis (25%), facial edema (10%), proteinuria (43%) and mucosal bleeding (17%). However, a combination of fever, pharyngitis, retrosternal pain and proteinuria correctly predicted 70% of laboratory-confirmed LF cases and 80%, by exclusion, of the control illnesses.[9] Similarly, fever, sore throat and vomiting together with high viraemia and aspertate aminotransferase (AST) levels have been found to predict a worse outcome.[7,10]

Ribavirin, a nucleoside analogue, is the only drug with significant therapeutic benefit in humans when administered within six days of onset of illness.[11] Although there has been renewed interest in LF vaccine development,[12] it may still take decades for one to be approved for use in humans. At the moment, studies to guide clinicians to suspect LF early and quickly request laboratory confirmation with the aim of instituting treatment when therapeutic benefit of ribavirin is maximum are scarce but imperative. In this study, we describe the epidemiological, clinical and laboratory features, and the treatment outcomes of LF in Jos, Nigeria.

Methods

Study design and data collection

In this retrospective study of patients who were managed for LF at the Jos University Teaching Hospital (JUTH) and Bingham University Teaching Hospital (BUTH) from January 2012 to February 2013, the case notes of patients with clinical diagnosis of LF were retrieved. The data which included patients' demographics and their clinical features were collected and entered into a standard template. The main laboratory variable of interest was LF polymerase chain reaction (PCR) test which were carried out hundreds of kilometers from Jos at Irrua Specialist Hospital reference laboratory, Nigeria. Those with positive PCR results were referred to as confirmed cases while those with negative PCR results as unconfirmed cases. Patients for whom PCR results were not available were excluded from the study. Other laboratory variables considered were AST, leukocyte counts and the presence or absence of proteinuria. AST levels > 40 IU/L was taken as elevated, and the normal range for total white blood cells (WBC) was 2.2 – 11.0 X 10^6/L. The normal range for neutrophil differential count was 40 - 70% while it was 20 - 40% for lymphocytes in adults and 20 - 60% in children. The time from development of symptoms to initiation of treatment with ribavirin and the treatment outcome were also recorded.

The JUTH and BUTH are both tertiary health institutions which serve urban and rural populations in Plateau State and some eight neighboring states in Nigeria. The elevation of the plateau is about 4,000 feet above sea level. Rainfall, averaging between 50 and 60 inches per year, usually begins in April and ends by November.

Ethics

Approval for this study was sort and obtained from the Jos University Teaching Hospital and Bingham University Teaching Hospital Ethics Committee. To maintain anonymity of patients, identifiers of individual patients were disguised across our data set by immediately transcribing their names to initials and serial numbers, and by presenting the results of this study in aggregates.

Statistical Analysis

The data collected were analyzed using Epi Info statistical software 3.5.1 (CDC, Atlanta Georgia). Categorical variables were compared using the Chi square test or Fisher's exact test where appropriate. Continuous variables were expressed as mean ± standard deviation or as median with range. Means were compared by student's t test or Mann-Whitney U test where appropriate. Probability values less than 0.05 ($P < 0.05$) were considered statistically significant.

Result

Twenty case notes of patients with suspected LF were retrieved and PCR results were available for 15 (75%) patients.

Demographic Characteristics

The mean age in years of all those with PCR results was 26.0 ± 15.4, and 31.0 ± 10.2 for confirmed cases compared with 22.0 ± 17.9 for unconfirmed cases (p=0.45). Four (66.7%) of the confirmed cases were aged between 19 to 28 years. There were seven (46.7%) males and eight (53.3%) females out of which two (33.3%) males and four (66.7%) females were confirmed cases compared with 5 (71.4%) males and 4 (50%) females that were unconfirmed cases (p=0.38). All six (100%) confirmed cases were rural/sub-urban dwellers. There were three (50%) unemployed confirmed cases which constituted the highest single occupational group. The demographic characteristics of suspected LF cases are shown in Table 1.

Clinical Features

The clinical features of the suspected LF cases are shown in Table 1. The median, with range, duration from onset of symptoms to presentation at hospital was 8 (4-11) days in confirmed cases compared with 4 (1-7) days in unconfirmed cases (p=0.01).The proportion of various features among confirmed cases were as follows: fever (axillary temperature=38°C) six (100%), hemorrhagic manifestations five (83.3%), cough four (66.7%), sore throat two (33.3%),

abdominal pain two (33.3%), vomiting two (33.3%), diarrhea two (33.3%), proteinuria two (33.3%), retrosternal pain one (16.7%), conjunctival suffusion one (16.7%), meningoencephalitis one (16.7%). There was also one (16.7%) case of bilateral deafness that occurred during convalescence among the confirmed cases.

Table 1. Characteristics and treatment outcome of patients with suspected Lassa Fever in Jos

Variable	Total	LF confirmed	LF unconfirmed	P-Value
Age mean (±SD)	26.0 (±15.4)	31.0 (±10.2)	22.0 (±17.9)	0.45
Sex, N (%) Female	8 (53.3)	4 (50)	4 (50)	0.38
Residence N (%) Rural/Sub-urban	8 (53.3)	6 (75)	2 (25)	0.01
Occupation N(%)				
Skilled	2 (13.3)	0 (0)	2 (100)	
Unskilled	2 (13.3)	2 (100)	0 (0)	0.79
Student	4 (26.7)	1 (25)	3 (75)	
Unemployed	7 (46.7)	3 (42.9)	4 (57.1)	
Fever > 38°C N (%)	14 (93.3)	6 (42.9)	8 (57.1)	0.60
Bleeding manifestation N (%)	10 (66.7)	5 (50)	5 (50)	0.30
Sore throat N =4 (%)	4 (100)	2 (50)	2 (50)	0.41
Cough N=6 (%)	6 (100)	2 (33.3)	4 (66.7)	0.93
Retrosternal Pain N=2 (%)	2 (100)	1 (50)	1 (50)	0.67
Other clinical features N (%)*	18 (100)	9 (50)	9 (50)	0.71
Proteinuria N=3 (%)	3 (100)	2 (66.7)	1 (33.3)	0.05
AST mean (±SD) IU/L N=10	154.5 ± 49.5	188.5 ± 59.1	91.2 ± 31.1	0.50
WBC mean (±SD) $X10^9$/L N=11	7.3 ± 2.1	5.7 ± 1.5	9.3 ± 4.0	0.29
Neutrophils mean differential (%)N=11	64.7 ± 10.5	63.5 ± 6.4	66.0 ± 18.3	0.87
Lymphocyte differential median (%) N=11	31.2 ± 17.0	29.0 ±16.4	33.2 ± 18.6	0.77
Duration of symptoms before admission in days (Median[range])	4(1-11)	8(4-11)	4(1-7)	0.01
Ribavirin administered N=12(%)	12 (100)	3 (33.3)	9 (66.3)	0.32
Outcomes; Number of days on admission Median (range)	5 (1-25)	5 (1-11)	7 (1-25)	0.58
Alive N= 6 (%)	6 (100)	1 (16.7)	5 (83.3)	0.55

*= Vomiting, Abdominal pain, Diarrhoea, Conjuctival suffusion, Meningoencephalitis

Laboratory Parameters

The laboratory parameters are similarly shown in Table 1. The mean WBC count in those with confirmed LF was 5.7 ± 1.5 X 10^9/L compared with 9.3 ± 4.0 X 10^9/L in unconfirmed cases (p=0.29). Similarly, the mean neutrophil differential counts were 63.5 ± 6.4 and 66.0 ± 18.3 for confirmed and unconfirmed cases respectively (p= 0.87) while the median lymphocyte differential counts were 29.0 ±16.4 and 33.2 ± 18.6 for confirmed and unconfirmed cases respective (p=0.77). The mean AST was 188.5 ± 59.1 IU/L in those with confirmed LF as compared to 91.2 ± 31.1IU/L in unconfirmed cases (p=0.50).

Treatment Outcome

The treatment outcome is summarized in Table 1. Among the confirmed cases, only three (50%) received ribavirin but none of them received ribavirin within the first six days since onset of symptoms. All of the nine (100%) unconfirmed cases received ribavirin and six (85.7%) were within six days since onset of symptoms. The overall case fatality ratio in this study was eight (57.1%); five (88.3%) was among confirmed cases and three (37.5%) in unconfirmed cases. The median (range) duration on admission in days was 5 (1-11) in confirmed cases compared with 7 (1- 25). There was no statistically significant difference (p= 0.58).

Discussion

Our study revealed that most four (66.7%) of individuals with confirmed LF were young adults. Although LF occurs in all age groups,[9] hunting and handling rats for food is one of the important risks for acquiring infection in our environment. [13] Troupe et al[14] in a study of 13 confirmed cases in an outbreak in Jos in 1970 reported that young adults where mostly affected but there were no reasons suggested for this observation. Also, our finding of significantly more cases of confirmed LF among rural/sub-urban dwellers (p= 0.01) is supported by the predominant distribution of multimammate rats *Mastomys natalenses,* the reservoirs of LAV, in rural areas and in dwellings in surrounding country side.[6]

The clinical features of LF are protean and are often difficult to distinguish from other common febrile illnesses on clinical grounds alone. The time from becoming ill to presentation at hospital was significantly longer in confirmed cases when compared with unconfirmed cases. This observation might have been due to the gradual onset of illness after an incubation period of three to 21 days in LAV infection with more severe illness after seven days. [15] In addition, since all those with confirmed LF resided in rural/sub-urban areas, access to a health facility could have also contributed to delayed presentation.

LF may be clinically distinguished from other febrile illnesses by the presence of sore throat with white exudative pharyngitis and cough with underlying bronchitis or pneumonia.[16] Whereas hemorrhagic manifestations are reportedly seen in less than one third of patients with LF,[6,14,17] 83.3% of those with confirmed LF had mucosal bleeding in our study. The difference could be attributed to variation in sample size, virulence of the LAV or delayed presentation to hospital. The clinical manifestations of severe illness like hemorrhage generally occur in the second week of

illness, which also referred to as stage 3 illness.[9,15] While hemorrhagic manifestation may not be a very helpful clinical feature to aid early diagnosis and case management, it's presence may trigger infection control activities aimed at preventing nosocomial transmissions which are often explosive and lethal. Although deafness alone was reported in 29% of a prospectively studied patients,[18] neurologic disease is not usually a dominant clinical manifestation in Lassa fever.[19] In our study, there was occurrence of one (16.3%) meningoencephalitis and one (16.3%) bilateral deafness , and deafness during convalescence may in fact be a diagnostic clue of LF.[20]

The WBC and differential counts were all within normal limits in this study, and are consistent with the findings of Fisher-Hoch et al[21] who had shown that the leucocytes count can be low, normal, or modestly elevated. The ALT levels were above 4 times ULN and the results were available for only two patients who also had confirmed LF. Although AST levels are known to parallel viraemia and levels above 150 IU/L is a useful predictor of mortality,[9] there was no statistically significant association between AST levels and fatality in this study.

The case fatality ratio among those with confirmed LF was 83.3% in this study and it is a sharp contrast to the generally reported figures of between 15-25% in hospitalized patients.[7,22] Nonetheless, our case fatality ratio is comparable to the 78% reported in selected cases in which AST levels were greater than 150 IU/L and the infective dose of LAV per milliliter was at least 10^3. [9] Therefore, our high mortality rate could be due to combination of severe illness in our cases and to the delay in ribavirin administration as none of those with confirmed LF received ribavirin within 6 days of onset of illness.

Our study has important limitations due to its retrospective design whereby some case notes were missing and there were missing data in some of the case notes that were traced. In addition, the small number of suspects and those with confirmed LF further limits this study. Notwithstanding, our study has highlighted relevant information that must be obtained in the evaluation of a suspected LF case and the need for prompt diagnosis and institution of therapy.

Conclusion

LF presents with protean clinical features and is a lethal infection in our environment where presentation to hospital is late. Larger studies with appropriate controls are required to determine the discriminatory values of the myriad features of LF. There is also a need to intensify and sustain strategic public enlightenment campaigns to prevent infection acquisition in the first place, and for ill individuals to promptly report to the health facility. In addition to all of these, laboratory testing for LF diagnosis should be made widely available.

Acknowledgment

We wish to sincerely thank Dr. Tolu Afoloramin of the department of Public Health, Jos University Teaching Hospital for assisting greatly with data analysis.

References

1. Frame JD, Baldwin JM Jr, Gocke DJ, Troup JM. Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings. Am J Trop Med Hyg. 1970; 19: 670.
2. McCormick JB. Lassa fever. In: Saluzzo JF, Dodet B, eds. Emergence and control of rodent-borne viral diseases. Paris, France. Elsevier: 1999; 177–195.
3. World Health Organization regional office for Africa. Nigeria: Lassa fever outbreak (situation as at 22 March 2012). Available at: http://www.afro.who.int/pt/grupos-organicos-e-programas/ddc/alerta-e-resposta-epidemias-e-pandemias/outbreak-news/3593-nigeria-lassa-fever-outbreak-situation-as-of-22-march-2012.html. Accessed 25th March 2013.
4. Keenlyside RA, McCormick JB, Webb PA, et al. Case-control study of Mastomys natalensis and humans in Lassa virus-infected households in Sierra Leone. Am J Trop Med Hyg. 1983; 32: 829-837.
5. Monath TP. Lassa fever: Review of epidemiology and epizootology. Bull World Health Organ. 1975; 52: 593.
6. McCormick JB, Webb PA, Krebs JW, et al. A prospective study of the epidemiology and ecology of Lassa fever. J Infect Dis. 1987; 155: 437.
7. McCormick JB, King IJ, Web PA, et al. A case-control study of the clinical diagnosis and course of Lassa fever. J Infect Dis. 1987; 155: 445.
8. Gunther S, Lenz O. Lassa virus. Crit Rev Clin Lab Sci. 2004; 41: 339–390.
9. Peters CJ. Lymphocytic Choriomeningitis Virus, and the South American Hemorrhagic Fevers. In: Mandell LG, Bennett EJ, Dolin R eds. Principles and Practice of Infectious Diseases. 7th edition. Philadelphia, USA: Elsevier. 3059-3065.
10. Johnson KM, McCormick JB, Webb PA, Smith ES, Elliott LH, King IJ. Clinical virology of Lassa fever in hospitalized patients. J Infect Dis 1987; 155: 456-464.
10. McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, et al. Lassa fever. Effective therapy with ribavirin. N Engl J Med. 1986; 314: 20–26.
11. Demby AH, Chamberlain J, Brown DW, Clegg CS. Early diagnosis of Lassa fever by reverse transcription-PCR. J Clin Microbiol. 1994; 32: 2898–2903.
12. Igor SL. Advanced Vaccine Candidates for Lassa Fever. Viruses 2012, 4: 2514-2557; doi:10.3390/v4112514
13. Ter Meulen J, Lukashevich I, Sidibe K, et al. Hunting of peridomestic rodents and consumption of their meat as possible risk factors for rodent-to-human transmission of Lassa virus in the Republic of Guinea. Am J Trop Med Hyg. 1996; 55; 661-666.
14. Troupe JM, White HA, Fom AL, Carey DE. An outbreak of Lassa fever on the Jos Plateau, Nigeria, in January-February 1970. A preliminary report. Am J Trop Med Hyg. 1970; 19: 695-696.

15. McCarthy M. USA moves quickly to push biodefence research. Lancet. 2002; 360: 732.
16. Ogbu O, Ajuluchukwu E, Uneke CJ. Lassa fever in West African sub-region: an overview. J Vector Borne Dis. 2007; 44: 1–11.
17. Peters CJ. Infections caused by Arthropod and Rodent-borne Viruses. In: Harrison's principles of Internal Medicine (17th ed). Editors; Fauci, Braunwald, Kasper et al. McGraw-Hill. New York, 2008; 1235-1236.
18. Cummins D, McCormick JB, Bennett D, et al. Acute sensorineural deafness in Lassa fever. JAMA. 1990; 264: 2093-2096
19. Solbrig MV. Lassa virus and central nervous system disease. In: Salvato MS, ed. The Arenaviridae. New York: Plenum press, 1993: 325-330.
20. Frame JD. Surveillance of Lassa fever in missionaries stationed in West African. Bull world health organ. 1975; 52: 593-598.
21. Fisher-Hoch S, McCormick JB, Sasso D, Craven RB. Haematologic dysfunction in Lassa fever J Med Viral. 1988; 26: 127-135
22. Buchmeier MJ, Bowen MD, Peters CJ. In: Fields BN, Peter M, Howley MD, et al (eds); Fields-Virology; Philadelphia PA. Lippincott Williams & Wilkins Publishers 4th ed: 2001; 1635-1668