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Clinical Presentation and Outcome of Ribavirin Treated RT-PCR Confirmed Lassa Fever Patients in ISTH Irrua: A Pilot Study

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Abstract

Background: *Lassa fever is a viral hemorrhagic fever that is endo-epidemic in Edo state, with case fatality of 90-100% if not treated. It has been claimed that early treatment with Ribavirin reduces mortality to less than 20%. This study was carried out to assert/confirm or refute/reject this claim.*

Aim: *To review the clinical features, laboratory findings of Lassa fever and the outcome of confirmed cases treated with Ribavirin.*

Methodology: *The study was a case series study of the first 41 cases that were treated with Ribavirin in the Lassa fever isolation ward from 28th November 2010 to 26th May 2011.*

Results: *Up to 63.4% of cases presented late (onset of illness greater than 6 days at presentation). Fever remains the predominant presenting feature of the disease (97.5%). Of the cases that were admitted, 41 were treated, 31 recovered and 9 died, giving a case-fatality rate of 22%. One discharged against medical advice.*

Conclusion: *Lassa fever victims still present late at the hospital and fever remains the predominant presenting feature. Early Ribavirin treatment improves treatment outcome of Lassa fever in confirmed cases.*

Recommendations: *The Federal, States and Local government area council members must make efforts to* ***c****reate public awareness on early presentation, diagnosis and prompt treatment with Ribavirin.*

Keywords

lassa, fever, ribavirin, presentation, outcome, definition

1. Introduction

Lassa fever is an acute viral hemorrhagic fever (Frame et al., 1970). It is Endo-endemic in most states in Nigeria (Akpede et al., 2009; Ehichioya et al., 2012) with Edo state accounting for a high number of cases (Reliefweb, 2016). It is the cause in 1.6% of all children admissions at the apex health institute in Edo central senatorial district (Akpede et al., 2009). The early symptoms of the disease are similar to those found in other common febrile illnesses in our environment (McCormick et al., 1987; Richmond et al., 2003; Month et al., 1975), which poses serious challenges to the early diagnosis and treatment of Lassa fever cases and resulting in case fatalities of 50-90% (Richmond et al., 2003). Ribavirin is the drug of choice for the treatment of Lassa Fever (LF). It is a nucleoside analogue which is more effective when given within the first 6 days of onset of illness (McCormick et al., 1986). The recommended case definition for Lassa fever in the current National Technical Guidelines for Integrated Disease Surveillance and Response is not sensitive in detecting the disease at the early stage. According to the guidelines, a suspected case of the disease is any person with an acute onset of fever who does not respond to treatment for the usual causes of fever in the area, with at least one of the following signs: bloody diarrhea, bleeding from the gums, bleeding into skin, eyes and urine (FMOH, 2009). This results in many false negatives in the early phase because in most cases, bleeding does not occur in the early stages of the disease (Akpede et al., 2009). This makes an appraisal of the current IDSR and the development of an appropriate case definition with higher degree of certainty necessary in order to reduce the public health impact of the disease. This study attempts to identify and describe clinical features and laboratory findings in early stage of LF in order to arrive at an accurate case definition for Lassa fever. The study will also confirm or reject the claim that Ribavirin improves outcome. There is limited country capacity with respect to laboratory diagnosis of Lassa fever. There are only three reference laboratories for the diagnosis of LF. Thus, an improved case definition is needed for quick action.

2. Method

2.1 Study Area

The study was carried out at the Institute of Lassa Fever Research and Control (ILFRC), Irrua Specialist Teaching Hospital (ISTH), Irrua, in Esan Central area of Edo State, Nigeria. It is the foremost institute for the diagnosis, treatment and control of Lassa fever, which is endemic in the area. It is located at Kilometer 87, on the Benin-Auchi Express way and lies on latitude $06^0$48' north and longitude $06^0$14' east of the equator. It is bounded by Etsako West LGA in the north, Esan West LGA in the west, Esan North-East and Esan-South East LGAs in the east and Igueben LGA in the south. The Institute became operational in 2008 and has the following units: BSL3 diagnostic laboratory, a case management unit that provide curative services in a dedicated isolation ward, outreach (contact tracing and health education) including psycho-social care. The training and research unit provide technical support to staff offering direct health care services by organizing periodic training programmes. It

collaborates with other sectors by making the necessary linkages. The institute is supported by both international and local bodies, including the Bernhard-Nocht Institute for Tropical Medicine Germany, Harvard University, Public Health England, Federal Ministry of Health and other International agencies like the WHO.

2.2 Study Design

Descriptive cross sectional study.

2.3 Study Population

All RT-PCR confirmed cases of LF (41) admitted into the LF isolation ward.

2.4 Study Period

November 2010 to May 2011.

2.5 Data Collection Method

Patients' medical records from the time of admission to discharge were examined to obtain information on socio-demographics, clinical features, hematological findings and treatment.

2.6 Measurement of Variables

Variables were measured as nominal and numerical variables.

2.7 Data Analysis

Data were entered and analysed using the Epi Info version 3.5.

2.8 Ethical Approval

Obtained from the Ethics and Research Committee; ISTH. Confidentiality was maintained as names were not recorded during data collection.

3. Results

Table 1. Sociodemographic Characteristics of Patients

Characteristics	Frequency (n=41)	Percent
Age (years)		
≤10	1	2.4
11-20	3	7.2
21-30	15	36.6
31-40	6	14.6
41-50	6	14.6
51-60	6	14.6
≥61	4	10.0
Sex		
Male	15	36.6
Female	26	63.3

Education		
None	1	2.4
Primary	1	2.4
Secondary	22	53.7
Tertiary	17	41.5
Religion		
Muslim	4	9.8
Christian	30	73.1
Others	7	17.1
Travel History (Last One Month)		
Yes	6	14.6
No	35	85.4
Duration of illness at presentation (in days)		
3-6	15	36.6
7-10	14	34.1
>10	12	29.3
Duration of admission		
6-10 days	22	53.7
11-15 days	10	24.3
>15days	9	22.0

Table 2. Clinical Features of Patients with Lassa Fever

Symptoms/signs*	Frequency (n=41)	Percent
Early		
Abdominal pain	18	43.9
Diarrhea	12	29.3
Fainting	4	9.7
Fever	40	97.5
Headache	19	46.3
Muscle pain	6	14.6
Retrosternal pain	13	31.7
Sore throat	15	36.6
Late		
Altered sensorium	9	22.0
Bleeding	12	29.2
Cough	31	75.6

Dyspnoea	5	12.2
Jaundice	2	4.8
Irrational talk	3	7.3
Seizures	5	16.1
Vomiting	24	58.5
Weakness	28	68.3
Systolic BP (mm Hg) day 1		
≤90	6	14.6
91-119	9	22.0
120-139	13	31.7
≥140	4	9.7
BP not taken	9	22.0
Systolic BP (mm Hg) day 2		
≤90	5	12.1
91-119	8	19.5
120-139	12	29.4
≥140	4	9.7
BP not taken	12	29.3
Systolic BP (mm Hg) day 3		
≤90	5	12.1
91-119	9	22.0
120-139	12	29.4
≥140	4	9.7
BP not taken	11	26.8
Diastolic BP (mm Hg) day 1		
≤60	4	9.7
61-79	21	51.3
80-89	4	9.7
≥90	3	7.4
BP not taken	9	21.9
Diastolic BP (mm Hg) day 2		
≤60	4	9.7
61-79	14	34.2
80-89	3	7.4
≥90	8	19.5
BP not taken	12	29.2

Diastolic BP (mm Hg) day 3		
≤60	2	4.9
61-79	14	34.1
80-89	10	24.4
≥90	4	9.7
BP not taken	11	26.9

* Multiple responses.

Table 3. Laboratory Results of Patients with Lassa Fever (n=21)

Investigation	**Mean±2SD**	**Normal value**
FBC/ESR		
PCV	36.31±25.0%	F=36-47%, M=40-54%
WBC	$8.6\times10^9\pm1.6.0\times10^9$/L	$4.0\text{-}11.0\times10^9$/L
Lymphocytes	$3.9\times10^9\pm2.8\times10^9$/L	$1.5\text{-}4.0\times10^9$/L
Neutrophils	$6.0\times10^9\pm2.0\times10^9$/L	$2.0\text{-}7.5\times10^9$/L
Monocytes	$0.8\times10^9\pm0.2\times10^9$/L	$0.2\text{-}0.8\times10^9$/L
ESR	56±26mm/hr	2-8mm/hr
Platelets	$251\pm208\times10^9$/L	$150\text{-}450\times10^9$/L
E&U&CR		
Sodium	135.4±12.2mmol/L	135-145mmol/L
Potassium	4.3±2.2mmol/L	4.5-5.3mmol/L
Urea	5.7±12.6mmol/L	2.5-6.6mmol/L
Creatinine	71.4±142.4μmol/L	60-120μmol/L
RBS		
RBS (day 1)	142±109mg/dl	
RBS (day 2)	175±123mg/dl	
RBS (day 3)	212±166mg/dl	
LFT		
ALT	80.83±86.9U/L	10-50U/L
AST	168±176.2U/L	10-45U/L
ALP	78.3±58.5U/L	40-125U/L
Total protein	7.3±3.2g/dl	6-8g/dl
Albumin	2.9±0.9g/dl	3.5-5.0g/dl
Globulin	6.6±2.5g/dl	2-3.5g/dl
Total bilirubin	3.49±5.5mg/dl	0.2-1.2mg/dl
Conjugated bilirubin	2.52±4.1mg/dl	0.1-0.4mg/dl

Table 4. Patients Treated with Ribavirin and Outcome

Outcome	Frequency (n=41)	Percent
Survived	31	75.6
Died	9	22.0
DAMA	1	2.4

Table 5. Duration of Illness at Presentation and Case Fatality Rate (CFR)

Duration of illness at presentation (in days)	Frequency	Deaths
3-6	14	0
7-10	14	3
>10	12	6

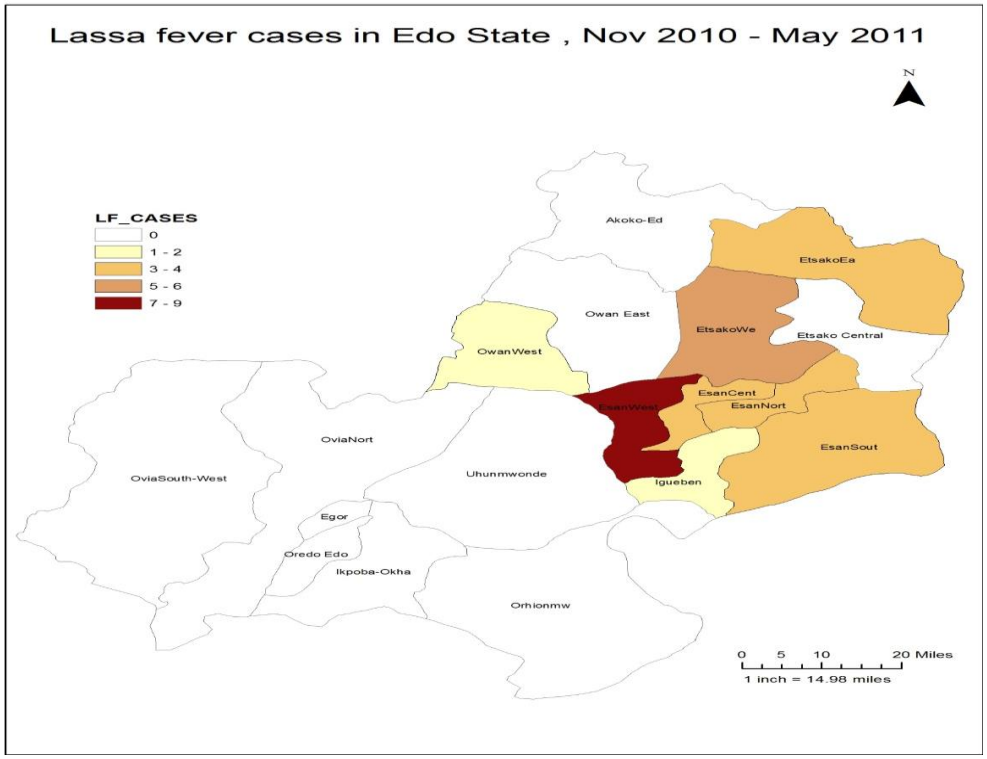

Figure 1. Lassa Fever Cases in Edo State, November 2010-May 2011

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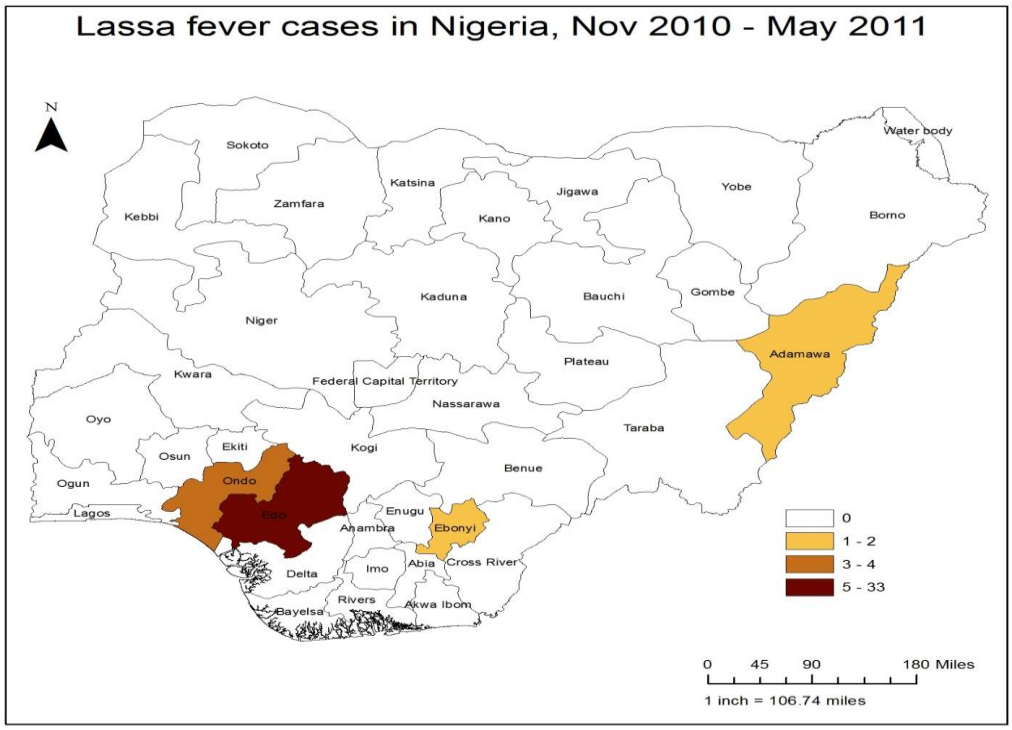

Figure 2. Lassa Fever Cases in Nigeria, November 2010-May 2011

4. Discussion

Clinical features and laboratory findings were similar to those described in available literature (Richmond et al., 2003; Month et al., 1975). About half of the patients were young adults aged between 21 to 40 years. This is important since this age group is also the provider group in the Nigerian society (Odimegwu et al., 2008). Thus, adverse socioeconomic consequences can be anticipated from Lassa fever outbreaks and the death of breadwinners.

Most of the patients were women. An overwhelming proportion of patients had at least secondary education. This is of importance because the Lassa fever virus vector—the multimammate rat—thrives in unhygienic peri-domestic conditions. In our society, women are the homemakers. There may be a public health benefit from educating women's groups and associations about the mode of transmission of Lassa fever and how to prevent infection.

Common early symptoms were fever, headache, abdominal pain and sore throat. The most common late symptom was cough. Vomiting and weakness were also frequent. These symptoms are non-specific, and are also seen in other common diseases such as malaria and typhoid fever. Laboratory diagnosis remains the gold standard, and in since the geographical area affected during Lassa fever outbreaks is so expansive, more laboratories may need to be built, equipped and appropriately staffed to facilitate early diagnosis and treatment.

It is evident from this study that one of the factors which drive high case fatality is late presentation. The reasons for this may include long distance to hospitals and transportation constraints, being

admitted in private hospitals without appropriate diagnosis and referral, and fear of presenting to a teaching hospital.

Many patients dread presenting to teaching hospitals, as they frequently have the perception that cases that get to teaching hospitals are irremediable. Therefore, many patients visit private hospitals or primary health centers that usually have no diagnostic facilities for Lassa fever. Indeed, it may be that the incidence and case fatality rates for Lassa fever are grossly underestimated. There may be a need to recommend Lassa fever screening as part of private hospitals' routine investigations for febrile patients in endemic areas during epidemics.

This study showed greater benefit from the administration of Ribavirin in the early stages of the disease, confirming a previous report that most patients who receive Ribavirin treatment early in the course of illness survive (McCorrnick et al., 1986). No deaths occurred in those who presented within 6 days of the onset of illness and most deaths occurred in patients who presented more than 10 days after the onset of illness.

One patient got discharged against medical advice. There may be need for more health education outreaches and perhaps legal measures to enforce treatment for epidemic-prone diseases.

5. Conclusion/Recommendations

Thus, early Ribavirin treatment improves treatment outcome of Lassa fever. However early diagnosis still poses a problem, even in teaching hospitals.

In ISTH, the case definition for LF is as follows:

- Patient with 38°C fever for at least 2 days,
- Excluded typhoid fever and malaria negative or just 1+ in thick smear,
- Some or one of the following symptoms: chest pain, sore throat, headache, muscle pain, vomiting, and diarrhea.
- Or: patients with fever who show bleeding or facial edema.
- Or: patients with fever who do not respond to anti-malarials or antibiotics after 2 days of treatment.
- Or: patients with fever who had contact with a confirmed Lassa fever case within the last three weeks.

Clearly, this case definition is limited and many patients may be erroneously diagnosed with Lassa fever. Lassa fever cases that do not present with common findings may also be missed. This is of critical importance in far-flung rural areas where time to appropriate clinical/laboratory referral is of the essence. Further studies are needed in order to arrive at a better case definition for LF.

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