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Original Article

Positivity Rate, Predictors, and Outcome of Paediatric Lassa Fever Disease (LFD) in a Lassa Fever Endemic State, South-East Nigeria

***[1]Maria-Lauretta Orji, [2]Nnennaya Anthony Ajayi, [1]Nnamdi Benson Onyire, [2]Uche Sonny Unigwe, [3]Chiedozie Kingsley Ojide**

[1]Department of Paediatrics, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Ebonyi State
[2]Department of Internal Medicine, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Ebonyi State.
[3]Virology Unit, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Ebonyi State.

Abstract

Background: The pattern and case fatality rate of Paediatric Lassa fever disease (LFD) is not well documented even in Lassa fever endemic communities.
Aim and Objective: This prospective observational study was aimed at determining the pattern and outcome of Paediatric LFD.
Methodology: A total of 183 children that met the criteria for LFD suspects were subjected to the Lassa virus PCR test. The suspects that tested positive were recruited into the study and a structured questionnaire was used to collect information on socio-demographics.
Results: Of the 183 LFD suspects that were tested, 24 of them were positive to Lassa virus PCR, giving a positivity rate of 13.1%. The mean duration of illness before hospital presentation was 8.54 ± 3.83 days. All the subjects had a history of fever. Abdominal pain and vomiting were the two highest presenting complaints after fever. Seven out of 24 children died during the study period, giving a case fatality rate (CFR) of 29.2%. Subjects who presented with convulsions and unconsciousness (OR =10.00, 95% CI= 1.2, 81.81, p=0.020), bleeding (OR =40.00, 95% CI= 12.96, 539.67, p=0.020), poor urine output (OR =40.00, 95% CI= 12.96, 539.67, p=0.020) were more likely to die of LFD compared to their colleagues without such symptoms.
Conclusion: The positivity rate and case fatality rate of LFD in children were high. Public enlightenment on the common features of Lassa fever disease and the need to seek health care early for children with febrile illness is advocated.

Keywords: Case fatality; Lassa virus; Positivity rate; Outcome; Ribavirin.

Corresponding Author: *Maria-Lauretta Orji, Department of Paediatrics, Alex-Ekwueme Federal University Teaching Hospital Abakaliki, P.M.B 102, Abakaliki, Ebonyi State, Nigeria
Email: orjimarialauretta@gmail.com.

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Quick Response Code:

Introduction

Lassa fever is an acute and sometimes severe viral hemorrhagic fever caused by the Lassa virus; a single-stranded RNA virus of the Arenaviridae family.[1] Lassa fever is one of the viral hemorrhagic fevers that are rodent-borne. Mastomys natalensis is the species of rat responsible for the transmission of Lassa fever. [2] Lassa fever is endemic in the West African sub-region; an estimated 300,000 Lassa fever cases occur in the sub-region yearly, resulting in over 5,000 deaths. [3] Lassa fever accounts for 10-16% of total hospital admissions yearly in the sub-region. [3] The observed case fatality rate among hospitalized patients with severe disease in the sub-region is 15-50%. [3, 4] In Nigeria, a country domicile in West Africa, 17 states are said to be endemic for Lassa fever with Edo, Ondo, and Ebonyi States having more than 75% of the cases reported and case fatality rates of 14.6%, 24.2%, and 23.4% respectively. [4, 5]

The seroprevalence of Lassa fever in Nigeria is 21%. [6] Akhuemokhan et al [7] studied the prevalence of Lassa fever disease (LFD) in febrile children aged one month and above to 15 years of age in Irrua specialist hospital and reported a total prevalence rate of 5.7%. Webb et al [8] carried out a similar study among children and reported a prevalence rate of 21%. Of the 20 cases reported by Ajayi et al [9] in Ebonyi in a study carried out 9 years ago, only 2 (10%) were between ages 10-19 years.

Different presentations of Lassa fever disease have been projected by different authors. [7,8,9, 10] Akhuemokhan et al [7] reported vomiting and bleeding as common symptoms, Ajayi et al[9] noted fever (100%), sore throat (70%), abdominal pain (85%), and vomiting (50%), headache (35%), body pain and weakness (25%) in their study. Akpede et al [10] in their five-case series noted that fever was a constant feature while vomiting, gastritis, and tonsillitis were common. Similarly, Webb et al [8] reported that 60% of the children with LFD presented with fever, vomiting, and cough. Features of shock, seizures, deafness, and disorientation are seen in terminal illnesses and may also be complications of the disease. [10] In Lassa fever endemic regions with high case fatality rates, are there clinical presentations that are commoner in Lassa fever disease in children which may heighten the index of suspicion among clinicians, to prevent late presentation and improve prognosis?

This study was therefore aimed at determining the prevalence, clinical presentations, and outcome of paediatric Lassa fever in Ebonyi State. It is hoped that findings from this study will guide in better surveillance and management of children with Lassa fever disease.

Materials and methods

Ebonyi State is located in the rain forest zone; the climate is tropical. The annual rainfall varies from 2,000mm in the Southern areas to 1,150mm in the Northern areas. [11] The temperature throughout the year ranges between 210C to 300C. It has two seasons, dry and wet. The dry season lasts from November to March while the rainy season lasts from April to October. [11] It has a total population of 2,173,501 people, the majority of which are Ibos. [12] Lassa fever disease has been reported throughout the year but more in the dry season. [13, 14]

Study design.

The study is a hospital-based observational study carried out in the children's emergency room and the virology centre of the Alex-Ekwueme Federal University Teaching Hospital Abakaliki (AE-FUTHA), Ebonyi State, from March 2019 to February 2020.

Sample selection.

All children aged 0-17 years admitted to newborn and Children emergency room with a history of unremitting fever (≥380C) for more than 2 days despite administration of anti-malarial and/or antibiotics and any other symptom suggestive of Lassa fever disease such as sore throat, bleeding from orifices, vomiting, diarrhoea/constipation, body pain, convulsion and loss of consciousness were tagged as Lassa fever disease (LFD) suspects according to the guideline by National Center for Disease Control. [15]

Blood samples from LFD suspects were subjected to Lassa virus reverse transcriptase Polymerase chain reaction (RT-PCR) tests. The PCR was used to detect viral antigens in children. Those infected with the Lassa virus as identified with a positive PCR test were transferred to the virology unit and followed up until discharge or death. A structured questionnaire was used to collect information on biodata, socio-demographics, symptoms, and signs at presentation, management gave while on admission in virology centre, and outcome of the case.

All Lassa fever suspects with positive Lassa virus PCR results were included in the study while those with negative results were excluded.

Ethical considerations

Approval for the study was sought and obtained from the Health Research and Ethical Committee of Alex-Ekwueme Federal University Teaching Hospital Abakaliki (AE-FUTHA). Informed written consent was obtained from caregivers and assent from children 7 years and above. REC APPROVAL NUMBER 07/02/2019-08/03/2019

Data analysis

The data obtained were entered into a spreadsheet using Microsoft excel 2007 and the analysis was done using the Statistical Package for Social Sciences version 19.0. Quantitative variables were summarized using means and standard deviations. Frequency tables were constructed as appropriate. The significance of associations between variables was tested using the Chi-square Fisher's exact test (FT) for comparison of proportion. The level of statistical significance was achieved if $p < 0.05$.

Results

Of the 183 LFD suspects enrolled during the study period, 24 tested positive to Lassa PCR, giving a positivity rate of 13.1%. The mean duration of illness before presentation to hospital was 8.54 ± 3.83 days, range of 2 to 14 days. Table 1 shows that 41.6% (10/24) of the Lassa fever-infected children were within the 6-12 years age bracket. Females accounted for the majority with a male to female ratio of 1:1.7 and children from the lower social class were mostly affected.

All the infected children had a history of fever, while half of them gave a history of contact with probable or confirmed Lassa fever patients. Abdominal pain and vomiting were the most common presentations after fever with the frequency of 41.6% (10/24). A quarter of the children presented with convulsions, cough, and dyspnoea, bleeding, and poor urine output as shown in Table 2

A total of 7 out of the 24 children died during the study period, giving a case fatality rate of 29.2%. There were no significant relationships between age (p= 0.387) and gender (p= 0.562) with the outcome of Lassa fever disease in children.

All the children that had abdominal pain, sore throat, and headache were discharged. A total of 66.7% (4/6) of the children who had convulsions died compared to 83.3% (15/18) that did not have convulsions and were discharged home. Two-thirds of the children that had diarrhoea and 70.0% that presented with vomiting were discharged home. There were significant relationships between symptoms such as abdominal pain (p=0.019) and convulsions with or without coma (p= 0.038) and outcome of the Lassa fever disease as shown in Table 3A

Three out of 7 deaths received their results post-mortem as such did not receive intravenous ribavirin medication. Half of the children that had a cough in the course of illness and two-thirds of those with facial puffiness were discharged home. The majority (5/6, 83.3%) of children that bled and had poor urine output in the course of the Lassa fever illness died while 91.7% (11/12) of children with a positive history of contact with a Lassa fever confirmed or the probable case was discharged home. All the children (100.0%) who did not receive intravenous ribavirin medication died of the illness while 4 (19.0%) of the 21 children who received the drug died of the illness. The outcomes of Lassa fever disease among cases were significantly related to the presence of bleeding (p= 0.003), poor urine output (p=0.003), positive history of contact with a probable or confirmed case of the disease (p= 0.034), and commencement of ribavirin (p= 0.017). [Table 3B]

Children who presented with convulsion and coma were 10 times more likely to die from Lassa fever disease compared to other symptoms. Bleeding and poor urine output as symptoms had very high odds for death among Lassa fever-infected subjects. Of the 21 children who received ribavirin, 3 (60.0%) died within the first week of commencement of ribavirin while one death occurred after a week on ribavirin having developed complications of deafness. Subjects that completed ribavirin for more than 7 days were more likely to be discharged. [Table 4].

Table 1: Socio-demographics of children with Lassa fever infection

Socio-demographics	Frequency	%
Age (In years)		
<6	7	29.2
6-12	10	41.6
>12	7	29.2
Gender		
Male	9	37.5
Female	15	62.5
Social class		
Upper	2	8.4
Middle	5	20.8
Lower	17	70.8

Table 2: Pattern of Lassa fever disease presentation

Symptoms/Signs	Frequency of Symptoms (%)	
	Yes	No
Fever	24 (100.0)	0 (0.0)
Sore throat	4 (16.7)	20 (83.3)
Abdominal pain	10 (41.6)	14 (58.4)
Convulsion/coma	6 (25.0)	18 (75.0)
Headache	3 (12.5)	21 (87.5)
Vomiting	10 (41.6)	14 (58.4)
Diarrhoea	3 (12.5)	21 (87.5)
Cough and dyspnoea	6 (25.0)	18 (75.0)
Facial puffiness	3 (12.5)	21(87.5)
Yellowness of the eye	2 (8.3)	22 (91.7)
Deafness	1 (4.2)	23 (95.8)
Bleeding	6 (25.0)	18 (75.0)
Poor urine output	6 (25.0)	18 (75.0)
History of contact	12 (50.0)	12 (50.0)

Table 3A: Relationship between Clinical presentations and Outcome

	Outcome		Fisher's exact test (FT)	*P*-value
Symptoms/Signs	Discharged (%)	Died (%)		
Sore throat				
Yes	4 (100.0)	0 (0.0)	FT	0.224
No	13 (65.0)	7 (35.0)		
Abdominal pain				
Yes	10 (100.0)	0 (0.0)		
No	7 (50.0)	7 (50.0)	FT	0.019*
Convulsion/coma				
Yes	2 (33.3)	4 (66.7)		
No	15 (83.3)	3 (16.7)	FT	0.038*
Headache				
Yes	3 (100.0)	0 (0.0)		
No	14 (66.7)	7 (33.3)	FT	0.336
Vomiting				
Yes	7 (70.0)	3 (30.0)		
No	10 (71.4)	4 (28.6)	FT	0.643
Diarrhoea				
Yes	2 (66.7)	1 (33.3)		
No	15 (71.4)	6 (28.6)	FT	0.664

*Statistically significant

Table 3B: Relationship between Clinical presentations and Outcome Cont'd

	Outcome		Fisher's exact test (FT)	*P*-value
Symptoms/Signs	Discharged (%)	Died (%)		
Cough and dyspnoea				
Yes	3 (50.0)	3 (50.0)		
No	14 (77.8)	4 (22.2)	FT	0.307
Facial Puffiness				
Yes	2 (66.7)	1 (33.3)		
No	15 (71.4)	6 (28.6)	FT	0.664
Bleeding				
Yes	1 (16.7)	5 (83.3)	FT	0.003*
No	16 (88.9)	2 (11.1)		
Poor urine output				
Yes	1 (16.7)	5 (83.3)		
No	16 (88.9)	2 (11.1)	FT	0.003*
History of contact				
Yes	11 (91.7)	1 (8.3)		
No	6 (50.0)	6 (50.0)	FT	0.034*
Commenced Ribavirin				
Yes	17 (81.0)	4 (19.0)		
No	0 (0.0)	3 (100.0)	FT	0.017*

*Statistically significant

Table 4: Relationship between covariates and Outcome

Covariates	Outcome		Odd ratio	95%CI	*P*-value
	Died	Discharged			
Convulsion/coma					
Yes	4 (66.7)	2 (33.3)	10.00	1.2-81.81	0.020*
No	3 (16.7)	15 (83.3)			
Bleeding					
Yes	5 (83.3)	1 (16.7)	40.00	2.96-539.67	0.000*
No	2 (11.1)	16 (88.9)			
Poor urine output					
Yes	5 (83.3)	1 (16.7)	40.00	2.96-539.67	0.000*
No	2 (11.1)	16 (88.9)			
Duration on Ribavirin					
	3 (60.0)	2 (40.0)	22.50	1.51-335.35	0.014*
⩾ 8days	1 (6.3)	15 (93.7)			

*Statistically significant

Discussion

Lassa fever disease positivity rate of 13.1% observed in children that met the case definition of Lassa fever suspect is high when compared to data from earlier research in the same locality where only two paediatric cases were isolated. This may be explained by the study design being prospective and focused on children unlike the previous study in the same locale [9]. Also increased availability of testing kits for Lassa fever disease and provision of Lassa fever case definition by NCDC may be possible explanations to finding. More females than males were affected with LFD in this study. It is possible that because females are more domesticated than males, there are more likely to have contact with the faeces and urine of rodents or food and foodstuffs contaminated by urine and faeces of rodents when engaging in house chores. The majority of the children infected by the Lassa virus were within the age 6-12 age bracket. This is similar to findings by Webb et al [8] who noted an increased propensity to rat hunting among the age brackets.

Presenting symptoms were varied in this study similar to the experience of previous authors and like most studies; a history of fever was obtained in all subjects [8-10]. This study noted abdominal pain and vomiting as common features after fever. Studies by Ajayi et al [9] and Akpede et al[10] also reported sore throat, abdominal pain, and vomiting as common presenting features following fever while Webb et al[8] reported that 60% of the children with LFD presented with fever, vomiting, and cough. In all these studies vomiting was a predominant finding followed by abdominal pain. This suggests that vomiting and abdominal pain in febrile children with unremitting fever spikes despite antimalaria and or antibiotic use should heighten the suspicion of the paediatrician working in the Lassa fever endemic region. The abdominal pain found in the index study was either localized or generalized in character, mimicking typhoid enteritis in most cases, appendicitis (two had surgery for appendicitis and was discovered to be LFD postoperatively), and hepatitis. Dongo et al [16] in their case series noted that Lassa fever disease can present with features suggestive of acute abdomen underscoring the value of the high index of suspicion when evaluating children at every entry point in the health facilities. The masquerading of LFD with non-specific symptoms may explain the average duration of illness of 8.54 ± 3.83 days before presentation at the facility.

Death from febrile illnesses that were highly suggestive of LFD in the communities is tagged probably case while confirmed cases are those diagnosed with positive PCR results. In LFD endemic communities, there is a need for clinicians to pursue and obtain a history of the previous contact of a confirmed or probable case of LFD patients for every patient presenting with fever to a health facility. This is because out of the 12 children that had a history of contact with a confirmed or probable LFD patient, 91.7% of them were discharged home; only one died (8.3%) compared to half of those without such history that died on admission. Such history when obtained early at presentation to a health facility can expedite the process of LFD case management, hence reducing morbidity and mortality for the patient and disease containment on the part of the healthcare provider, thereby reducing nosocomial spread to health workers.

The majority of the deaths were in children that had bleeding from orifices and puncture sites, convulsions, and eventually coma and poor urine output. This was attributed to the cytokine surge that terminally led to vasodilatation of vessels and consequently coagulation defects and the destruction of infected cells leading to end-organ damage [17]. This was in tandem with the observation by Richmond and Baglole[18] who noted that bleeding, poor urine output, convulsions, and coma were ominous signs associated with poor prognosis and Akpede et al[10] who observed that the presence of haemorrhage, acute renal failure, convulsion, and coma were indicators of poor outcome.

Of the 7 deaths recorded during the study period, three (3) died within 24 -48hours while waiting for the result of RT-PCR, the diagnosis was made postmortem, hence did not receive ribavirin. There is a provision for commencement of ribavirin based on the clinician's discretion of possible cases of Lassa fever disease. However, these three cases had a vague history of bleeding (although not actively bleeding at presentation) from operation sites; one after local uvulectomy and two post-appendectomies following persistent sore throat and abdominal pain respectively in peripheral hospitals. It was possible that at presentation to the facility, the clinicians' first impressions were improperly/poorly managed cases; hence the hurry to commence ribavirin even with Lassa fever suspicion was not there.

Although the average duration of illness before hospital presentation was long, it was observed that children who received ribavirin for more than 7 days had higher chances of recovery. Ribavirin remains the drug of choice in the treatment of LFD. It reduces death by 90% especially when given within the first six days of onset of symptoms [19]. This was corroborated by previous authors that noted that patients on ribavirin were less likely to die compared to those who had no ribavirin [8,10].

The case fatality rate (CFR) observed in this study was 29.2%. This may largely be attributed to the delayed presentation as the mean duration of illness before presentation to the health facility was 8.54 ± 3.83 days and non-commencement of ribavirin medication. This is comparable to 15-50% CFR reported in endemic countries [4, 5]. The prognosis for Lassa fever is generally good considering that 80% of infected persons have a sub-clinical infection requiring no admission; however, the majority of mortalities occur among admitted patients with a late presentation [8].
More females compared to males died from complications of Lassa fever disease. This may be attributed to more females having the disease compared to males. Mortality was also observed more in children less than 6 years of age, this may not be unconnected to poor immune competence in extremes of age, although no significant relationships were found between age/sex and outcome of the disease. This is similar to the finding by Yinka-Ogunleye et al [20].

In conclusion, the positivity rate and case fatality rate of LFD in children observed in this study are high. Symptoms of fever, abdominal pain, and vomiting with or without a history of contact in children should heighten the index of suspicion for LFD by clinicians working in the Lassa fever endemic areas.

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