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Can clinical features predict Lassa virus positivity and outcome in children suspected of Lassa virus disease in a tertiary hospital, Southeast Nigeria?

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Abstract: *Background:* Lassa virus disease (LVD) is of public health concern in endemic countries of Africa. Majority of Lassa virus infections are asymptomatic while symptomatic cases can mimic other infections. This study was aimed at determining the clinical features seen in children with positive Lassa virus PCR and symptoms that determine outcome of LVD in an endemic community, Southeast Nigeria.

Materials and methods: It was a prospective observational study that enrolled 183 children that met the criteria for LVD suspects. These were subjected to the Lassa virus polymerase chain reaction test (PCR). Structured questionnaire was used to obtain relevant information from suspects.

Results: Twenty-four out of the 183 were positive to Lassa virus PCR, giving a positivity rate of 13.1%. The odds of having a positive Lassa PCR result was about 4 times in children with history of

abdominal pain (OR= 3.65, p= 0.010) and about 3 times in Lassa fever suspects with vomiting (OR= 2.63, p= 0.040). However these symptoms had low sensitivity and positive predictive values of 42% and 28% for abdominal pain, and 42%, 23% for vomiting respectively. Seven out of 24 children died during the study period, giving a case fatality rate of 29.2%, with bleeding (83.3%) and poor urine volume (83.3%) as major causes of case fatality.

Conclusion: Vomiting and abdominal pain though were common presentations besides fever, had low sensitivity and positive predictive values for LVD, therefore cannot predict a positive Lassa PCR result. Awareness creation for a Lassa virus PCR test after 2 days of treatment of febrile illness is advocated.

Key Words: Clinical features, Lassa virus, Predict, Outcome

Introduction

Lassa fever is an acute and sometimes severe viral hemorrhagic fever caused by 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 mostly seen in the West African sub-region, where it causes over 5,000 deaths and 10-16% admissions yearly, the observed case fatality among hospitalized patients is 15-50%.^{3,4} In Nigeria, 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 Lassa virus disease has an incubation period ranging from 3 to 21 days. Clinical features of the Lassa fever typically occurs 1-3 weeks after the patient comes

into with the virus. Majority of Lassa virus infections (approximately 80%) are mild and undiagnosed. Mild symptoms include low grade fever, general malaise and weakness.⁶ When the disease is symptomatic, it is usually gradual with non specific symptoms such as fever, malaise, headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhea, cough, and abdominal pain, these may progress to facial edema, mucosal bleeding, disorientation, coma, and death in the late stages.⁷⁻⁹ Features of shock, seizures, deafness and disorientation were thought to be signs of terminal illness and complications of the disease, but symptom such as deafness may develop in mild as well as in severe cases.¹⁰ Death occurs within two weeks after symptom onset due to multi-organ failure with case fatality rates ranging from 15-50% among hospitalized patients.^{4,6} There is paucity of data on symptoms that most likely predict positive Lassa PCR result and poor outcome among suspected

cases. This study was therefore aimed at determining symptoms seen in LVD cases and their outcome among children with LVD in a tertiary hospital in Ebonyi state. It is hoped that findings from this study will guide in better surveillance and management of children with Lassa virus 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 21^oC to 30^oC. 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, majority of which are Ibos.¹² Lassa virus disease has been reported throughout the year but more in the dry season.^{13,14} The study was a hospital based observational study carried out in the children emergency room and the virology center of Alex-Ekwueme Federal University Teaching Hospital Abakaliki from January 2019 to January 2020.

All children admitted to newborn and Children emergency room that were less than 18 years of age with a history of unremitting fever (38^oC) for more than 2 days despite administration of anti-malarial and/or antibiotics and any other symptom suggestive of Lassa virus disease such as sore throat, bleeding from orifices, vomiting, diarrhea/constipation, body pain, convulsion and loss of consciousness were tagged as Lassa virus disease (LVD) suspects according to the guideline by National Center for Disease Control.¹⁵

Blood samples from LVD suspects were subjected to Lassa virus reverse transcriptase Polymerase chain reaction (RT-PCR) tests. The PCR was used to detect viral antigens in the child. Those suspects with positive Lassa virus PCR result were cases while those with negative results were controls. Cases were transferred to the virology unit and followed up until discharge or death. Structured questionnaires were used to collect information on bio-data, socio-demographics, symptoms and signs at presentation, management given while on admission in virology center and outcome of the case. All Lassa fever suspects whose caregivers gave informed written consent were included in the study while children admitted in the emergency room with complaint of fever but responded to anti malarials and /or antibiotics treatment within 2 days of admission were excluded

Ethical considerations

Approval for the study was sought and obtained from the Health Research and Ethical Committee of the research institution. REC APPROVAL NUMBER 07/02/2019-08/03/2019) Informed written consent was

obtained from caregivers and assent from children 7 years and above.

Data analysis

The data analysis was done using the Statistical Package for Social Sciences version 22.0 (SPSS 22 IBM, Chicago, IL, USA). Quantitative variables were summarized using means and standard deviations. Frequency tables were constructed as appropriate. The significance of associations between variables was tested using Fischer’s exact test for comparison of proportion and to determine the sensitivity, specificity, positive predictive value and negative predictive value of symptoms in study participants that had Lassa positive PCR result. The level of statistical significance was achieved if *P*< 0.05

Results

Of the 183 suspected to have LVD and were tested for Lassa fever virus, 24 had positive Lassa virus PCR, giving a Lassa PCR positivity rate of 13.1%. Mean age of cases was 8.25 ± 5.13 years; male to female ratio of 1:1.7 while 8.91±42 years was mean age for controls with a male to female ratio of 1:1.2. Majority of the study participants were between 6 and 12 years of age for both cases (10/24, 41.6%) and controls (87/159, 54.7%). Fifteen (62.5%) of the 24 that tested positive to the Lassa virus PCR were females while among the controls, 84 (52.8%) were females. Seventeen (70.8%) of the cases were of lower socio-economic class while a total of 99 (62.3%) of the controls were from lower socio-economic class. Table 1

Table 1: Socio-demographics of study participants (children with Lassa fever disease-Cases and children without the disease- Controls)

Socio-demographics	Cases (%) n=24	Controls (%) n=159
<i>Age (In years)</i>		
<6	7 (29.2)	29 (18.2)
6-12	10 (41.6)	87 (54.7)
>12	7 (29.2)	43 (27.1)
<i>Gender</i>		
Male	9 (37.5)	75 (47.2)
Female	15 (62.5)	84 (52.8)
<i>Social class</i>		
Upper	2 (8.4)	12 (7.5)
Middle	5 (20.8)	48 (30.2)
Lower	17 (70.8)	99 (62.3)

Table 2a: Fischer’s test to determine the relationship between clinical presentations and LVD

Symptoms	Cases (%)	Controls (%)	P value	OR (95%CI)	Sensitivity (PPV)	Specificity (NPV)
Abdominal pain	10 (41.7)	26 (16.4)	0.010	3.65	0.42	0.84
No Abdominal pain	14 (58.3)	133(83.6)		(1.41-8.60)	(0.28)	(0.90)
Sore throat	4 (16.7)	19 (11.9)	0.512	1.47	0.17	0.88
No sore throat	20 (83.3)	140 (88.1)		(0.50-4.72)	(0.17)	(0.87)
Convulsion± coma	6 (25.0)	38 (23.9)	0.999	1.06	0.25	0.76
No convulsion	18 (75.0)	121 (76.1)		(0.39-2.88)	(0.14)	(0.87)
Headache	3 (12.5)	13 (8.2)	0.445	1.60	0.13	0.91
No headache	21 (87.5)	146 (91.8)		(0.45-5.73)	(0.19)	(0.87)
Vomiting	10 (41.6)	34 (21.4)	0.040	2.63	0.41	0.79
No vomiting	14 (58.3)	125 (78.6)		(1.04-6.66)	(0.23)	(0.89)
Diarrhoea	3 (12.5)	52 (32.7)	0.055	0.29	0.13	0.67
No diarrhoea	21 (87.5)	107 (67.3)		(0.09-0.95)	(0.05)	(0.84)

Table 2b: Fischer’s test to determine the relationship between clinical presentations and LFD

Symptoms	Had LFD (%)	No LFD (%)	P value	OR (95%CI)	Sensitivit (PPV)	Specifi-cit (NPV)
Cough± dyspnoea	6 (25.0)	25 (13.7)	0.253	1.78	0.25	0.84
No cough± dyspnoea	18 (75.0)	134 (84.3)		(0.65-4.64)	(0.19)	(0.88)
Jaundice	2 (8.3)	28 (17.6)	0.377	0.425	0.08	0.82
No jaundice	22 (91.7)	131 (82.4)		(0.09-1.62)	(0.07)	(0.86)
Bleeding	6 (25.0)	32 (20.1)	0.593	1.32	0.25	0.79
No bleeding	18 (75.0)	127 (79.9)		(0.49-3.68)	(0.16)	(0.88)
Poor urine volume	6 (25.0)	21 (13.2)	0.132	2.19	0.25	0.86
No urinary problem	18 (75.0)	138 (86.8)		(0.77-5.87)	(0.22)	(0.88)
Deafness	1 (4.2)	0 (0.0)			0.04	1.000
No deafness	23(95.8)	159(100.0)	0.131	Infinity	(1.000)	(0.87)
History of contact	12 (50.0)	3 (1.9)	<0.001	52.00	0.50	0.98
No history of contact	12 (50.0)	156 (98.1)		(12.62-181.2)	(0.80)	(0.93)

A relationship between clinical symptoms and PCR diagnosis of Lassa fever disease was sought using Fischer’s exact test. The odds of having a positive Lassa PCR result was about 4 times in children with history of abdominal pain (OR= 3.65, p= 0.010) and about 3 times in Lassa fever suspects with vomiting (OR= 2.63, p= 0.040) and 52 times in suspects with a history of contact with a probable or confirmed case (OR= 52.0, p= <0.001) as seen in Tables 2a and 2b. History of contact with a probable or confirmed case had the highest sensitivity of 50% and positive predictive value of 80%. Presence of abdominal pain and vomiting in a Lassa virus disease suspect had low sensitivity of 42% and 41% respectively. Positive predictive values of 28% in cases with abdominal pain and 23% in cases with vomiting were also very low (Tables 2a and 2b)

A descriptive statistics of the outcome versus the clinical presentations showed that the only subject that developed deafness died, 4 (66.7%) out of the 6 children that had convulsion with or without coma died, 5(83.3%) of the 6 that presented with bleeding and poor urine volume died while majority of suspects with vomiting (70.0%), diarrhoea (66.7%), abdominal pain (80.0%) survived. All the subjects with sore throat, headache and a history of contact survived. Table 3

Table 3: The outcome of children with LFD versus their clinical presentation

Symptoms	Outcome	
	Died (n=7)	Well and discharged (n=17)
Deafness	1 (100.0)	0 (0.0)
Convulsion± coma (n= 6)	4 (66.7)	2 (33.3)
Vomiting (n=10)	3 (30.0)	7 (70.0)
Bloody diarrhoea (n= 3)	1 (33.3)	2 (66.7)
Cough± dyspnoea (n= 6)	3 (50.0)	3 (50.0)
Bleeding (n= 6)	5 (83.3)	1(16.7)
Poor urine volume (n= 6)	5 (83.3)	1 (16.7)
Abdominal pain (n=10)	2 (20.0)	8 (80.0)
Jaundice (n=2)	1 (50.0)	1 (50.0)
Sore throat (n= 4)	0 (0.0)	4 (100.0)
Headache (n=3)	0 (0.0)	3 (100.0)
History of contact (n= 12)	0 (0.0)	12 (100.0)

Discussion

Increased awareness creation of possible clinical features of Lassa virus disease among health care providers in the study locale may have resulted in the high number of suspected cases that eventually led to the high positivity rate of 13.1%. This assertion may not be wrong if this observation was compared to previous data obtained from the same locale.⁸ More females than males were affected with LVD 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. Majority of the children infected by the Lassa virus were within the aged 6-12 age bracket. This is similar to findings by Webb *et al*⁷

Clinical features observed in this study were varied. This was similar to the experiences of previous authors who noted a history of fever in all their subjects.^{7,8,9} Febrile suspects who had abdominal pain and vomiting had the highest number of positive Lassa PCR result in index study. This finding was similar to studies by Ajayi *et al*⁸ and Akpede *et al*⁹ that reported sore throat, abdominal pain and vomiting as common presenting features following fever. Study carried out by Webb *et al*⁷ however that reported 60% of the children with LVD presented with fever, vomiting and cough. Febrile children with abdominal pain and vomiting had higher odds of having a positive Lassa virus PCR result in index study although the sensitivity and positive predictive value of abdominal pain (42% and 28%) and vomiting (41% and 23%) were low. This suggests that the presence of these symptoms in a febrile child cannot predict a positive test result. Abdominal pain in febrile children could either be localized or generalized in character, mimicking typhoid enteritis, appendicitis, hepatitis and peritonitis. Dongo *et al*¹⁶ in their case series reported Lassa virus disease presenting with features suggestive of acute abdomen underscoring the value of high index of suspicion when evaluating children at every entry point in the health facilities. Vomiting in children connotes diseases with multi-systemic involvement such as the gastrointestinal tract, respiratory system, cardiovascular and central nervous system. This is in agreement with Lassa virus disease that can affect any system in the body.

Obtaining a history of previous contact with a confirmed or probable case of LVD patient may be an important aspect of history in managing febrile children from Lassa fever endemic communities. This is study noted a sensitivity of 50% and positive predictive value of 80% of such history in predicting a positive Lassa virus PCR test. Such history when obtained early at presentation to a health facility can expedite the process of LVD case management, hence reducing morbidity and mortality for the patient and disease containment thereby reducing nosocomial spread to health workers.

The presence of complications of Lassa fever disease at presentation poses a high risk of death to the patient and minimal likelihood of survival. Deafness may occur

during mild or severe illness but in index study, it occurred terminally and patient died within 24hours of symptom. Evidences of renal injury, bleeding, convulsions and coma were symptoms with high fatality rates. This may be 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 and death.¹⁷ This was in tandem with observation by Richmond and Baglolle¹⁸ who noted that bleeding, poor urine output, convulsions and coma were ominous signs associated with poor prognosis and Akpede *et al*⁹ who observed that the presence of haemorrhage, acute renal failure, convulsion and coma were indicators of poor outcome.

The case fatality rate (CFR) observed in this study was 29.2%. This is high and unacceptable in an era of availability of highly effective intravenous ribavirin used in treatment of LVD. This high CFR may be attributed to delay in presenting to the health facility and presence of complications at presentation. Many of the cases would have been taken to different peripheral centres and received treatment for malaria and infections to no avail before presenting to the tertiary hospital. This is comparable to 15-50% CFR reported in endemic countries.^{4,5} Similarly Akhuemokhan *et al*⁶ reported CFR of 23% among study participants and attributed it to high fatal nature of the disease especially in terminal stage.

Conclusion

In conclusion, the positivity rate and case fatality rate of LVD in children observed in this study is high. Symptoms of abdominal pain and vomiting accompanying fever were predominant but do not predict Lassa virus PCR result. Intensified health education by way of focused group discussions among stakeholders and community health care workers on the need for Lassa virus testing after treating febrile illness for more than 2 days is advocated.

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