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Clinical Presentations of Lassa Fever in Non-Endemic Parts of the World: A Systematic Review

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Abstract

Background: Lassa fever cases outside Africa are seen as *imported cases* of Lassa fever. Timely diagnosis of *imported Lassa fever* is important for timely intervention necessary to reduce the morbidity and mortality associated with Lassa fever, and this requires the knowledge of the clinical manifestations of Lassa fever. **Purpose:** This review was done to see how clinical diagnosis of *imported Lassa fever* can be facilitated based on the clinical presentations of *imported cases of Lassa fever* in Lassa fever non-endemic region. **Methods:** The relevant articles for the review were obtained from the databases of PubMed and Google Scholar. **Results:** The clinical presentations of the *imported Lassa fever cases* consisted of multisystem involvement and were similar to those of Lassa fever patients who were treated in the Lassa fever endemic region. **Conclusions:** History of recent travel to, or residence in, Lassa fever endemic region is an important clue for clinical diagnosis of Lassa fever. The 2011 CDC surveillance case definition and the modified Khan case definition for Lassa fever may aid clinical diagnosis of Lassa fever. Any clinically suspected case of Lassa fever should have a laboratory confirmation.

Keywords

Imported Lassa Fever, Clinical Features of Lassa Fever, Clinical Diagnosis of Lassa Fever

1. Introduction

Lassa fever is endemic to West Africa. The incidence of primary cases of Lassa

fever presenting in other different countries of the world all originated from West Africa [1]-[29]. These are seen as *imported cases of Lassa fever* in those regions, and they present diagnostic and management challenges. The asymptomatic nature of most cases of Lassa virus infection (about 80%), the long incubation period of Lassa fever, which can be up to three weeks, and air travel are factors that can favor Lassa fever importation to non-endemic countries.

West African sub-region has many endemic febrile illnesses such as malaria, gastroenteritis and typhoid fever. These are more common than Lassa fever. Secondly, a medical practitioner practicing in a non-Lassa fever endemic region, when attending to an *imported case of Lassa fever*, is unlikely to have a high index of suspicion because of lack of experience and the other more common febrile illnesses will be higher in the possible diagnosis to consider.

Even for the practitioners in the Lassa fever endemic region in West Africa, who are assumed to be very familiar with Lassa fever, clinical diagnosis of Lassa fever can be challenging. For example, cases of Lassa fever have been misdiagnosed in which the patients were subjected to unnecessary laparotomy [30] [31]. Cases of Lassa fever have also been misdiagnosed as respiratory tract infection and malaria in pregnancy [32].

Lassa fever is associated with a high mortality rate among hospital-treated patients [33]. In those that survive the Lassa virus infection, there may be residual disability such as hearing loss which may remain permanent [34]. Timely diagnosis of Lassa fever is important for timely and appropriate interventions necessary to reduce the morbidity and mortality associated with Lassa virus infection. The knowledge of clinical manifestations of Lassa fever is necessary for the timely diagnosis of Lassa fever.

Few reviews have systematically examined the problem of making a clinical diagnosis of *imported Lassa fever* based on the presenting symptoms and signs of the patients. The aim of this paper is to do a systematic review of the clinical presentation of the cases of Lassa fever in order to highlight how a clinical diagnosis of Lassa fever can be made based on the presenting symptoms and signs of the *imported cases* of Lassa fever.

2. Methodology

The protocol was a systematic search for publications on primary cases of *imported Lassa fever*. These were cases of Lassa fever that originated from the endemic region of West Africa but were treated outside the endemic region. Such publications were to have all the relevant data complete. Literature on Lassa fever was searched using PubMed and Google Scholar databases. Articles published between January 1969 and April 2021 that were relevant to the scope of the review were retrieved. The keywords used were "*Imported cases of Lassa fever*" and "*Lassa fever case report*." These articles and their references were checked for publications of cases reported from outside the West African sub-region. Additional information was also sourced from the websites of the

Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO).

Between January 1969 and April 2021, only thirty-eight (38) cases of Lassa fever were reportedly treated in different countries outside Africa [1]-[29]. Out of these, 35 cases were primary cases while three were secondary cases which originated in non-endemic countries from some of the primary cases. Out of the 35 primary cases, only 22 cases had the relevant data and it was only those 22 cases that were included in the review. Data analysis was done by descriptive statistics. Frequencies were described as numbers and percentages. The review does not include secondary cases of *imported Lassa fever*.

Clinical Features of Lassa Fever

Lassa fever is a viral haemorrhagic fever. Lassa virus, which is the aetiological agent for Lassa fever, is transmitted by multimammate rat (*Mastomys natalensis*) which serves as the animal reservoir [35] [36]. Its transmission is either by direct contact with the rat such as eating the rat or by the contamination of human food by the rat's urine or faeces [35] [36]. Human-to-human transmission can also occur through contact with the body fluid of a Lassa fever patient. Both sexes and any age can be affected by Lassa fever [37] [38]. Lassa fever specific reverse transcriptase polymerase chain reaction is one of the reliable tests for laboratory confirmation of Lassa virus infection [39]. In the management of Lassa fever, supportive care is very important [35] [36] and treatment with ribavirin has been shown to be beneficial [40] [41].

The epidemiology of Lassa fever has been discussed by several authors [33] [42]. Lassa fever is a major public health problem with yearly outbreaks, with associated morbidity and mortality.

3. Results (Findings)

The findings are summarized in **Table 1**.

3.1. Findings of Clinical Features of Lassa Fever Cases in Non-Endemic Regions and Discussions of Findings

1) The Demographic Characteristics of the *Imported Cases* of Lassa Fever in non-endemic regions

Out of the 35 primary cases of *imported Lassa fever* identified, only the twenty-two cases which had all the relevant data were analyzed. All of the 22 cases originated from West Africa. The destination non-endemic countries were the United States, United Kingdom, Germany, Netherlands, Israel, Japan, Canada and Sweden. The 22 cases are listed in **Table 1** with their years of presentation, destination countries, sources of information [1]-[27] and the frequencies of involvement of the various organs or organ systems of the body.

Among the 22 cases, 59.1% were males while 40.9% were females, giving a male: female ratio of 1.44:1. The ages of three of them were unknown. These were case

Table 1. The clinical manifestations of the 22 cases of *imported Lassa fever*.

S/No	Imported to	Age/Sex	H/ach	Resp	CV	Gast	UGS	ENT	Eye	MSS	Rib	Survived
1 [1] [2]	USA 1969	52 F	Yes			Yes	Yes	Yes	Yes	Yes	No	Yes
2 [3]	UK 1971	F				Yes			Yes		No	Yes
3 [3]	UK 1971	M	Yes	Yes						Yes	No	Yes
4 [4]	UK 1972	35 F	Yes		Yes	Yes	Yes			Yes	No	Yes
5 [1] [5]	Germany 1974	M				Yes		Yes	Yes	Yes	No	Yes
6 [6]	USA 1975	43 F	Yes		Yes	Yes		Yes		Yes	?	Yes
7 [6]	USA 1975	26 F	Yes	Yes		Yes		Yes	Yes	Yes	No	Yes
8 [1] [7]	Netherlands 1980	34 M				Yes		Yes	Yes		No	Yes
9 [8] [9]	UK 1981	18 F	Yes			Yes	Yes	Yes			No	Yes
10 [10]	UK 1982	21 F	Yes			Yes					No	Yes
11 [1] [11]	Israel 1987	47 M	Yes		Yes	Yes		Yes		Yes	No	Yes
12 [12]	Japan 1987	48 M				Yes	Yes	Yes	Yes		No	Yes
13 [13]	Canada 1989	38 M	Yes	Yes		Yes	Yes	Yes	Yes		No	Yes
14 [14]	USA 1989	43 M	Yes					Yes		Yes	No	No
15 [1] [15]	Germany 2000	22 F				Yes	Yes	Yes			Yes	No
16 [16] [17]	Germany 2000	56 M				Yes				Yes	?	No
17 [1] [18] [19] [20]	Netherland 2000	48 M				Yes	Yes			Yes	Yes	No
18 [21]	USA 2009	47 M		Yes		Yes		Yes		Yes	No	Yes
19 [22] [23]	USA 2014	46 M			Yes	Yes	Yes	Yes			No	Yes
20 [24]	USA 2015	55 M			Yes		Yes	Yes		Yes	No	No
21 [25]	USA 2016	33 M	Yes		Yes	Yes	Yes	Yes			Yes	Yes
22 [26] [27]	Sweden 2016	72 F			Yes	Yes	Yes	Yes		Yes	No	Yes
N			11	4	7	19	11	15	6	12		17
%			50.0	18.2	31.8	86.4	50.0	68.2	27.3	54.5		77.3

Key: H/ach, headache; CV, cardiovascular system features; Gast, gastrointestinal system features; UGS, urogenital system; ENT, ear, nose and throat and head and neck features, Eye, eye features; MSS, musculoskeletal system features; Freq, frequency; Rib, Ribavirin: Yes, it was given; No, it was not given?, not known if it was given or not.

numbers 2, 3 and 5. Of the remaining 19 cases, their ages ranged from 18 years to 72 years, with a mean age of 41.3 ± 13.70 years.

Some of them received antimalarial or antibiotics or both. Only three of them (13.6%) were confirmed to have received ribavirin. One patient, in addition to

ribavirin was given favipiravir which is an investigational drug [25]. In two of the cases, it was not known whether ribavirin was given or not. Among the 22 *cases of imported Lassa fever*, five died and 17 survived, giving a case fatality rate of 22.7%.

2) Ear, Nose and Throat and Head and Neck (Otorinolaryngological Features)

Among the *imported cases of Lassa fever*, sore throat was the most common otorhinolaryngological symptom (36.4% or 8/22) and inflamed pharynx or pharyngeal ulcer was the most common otorhinolaryngological finding on examination (36.4% or 8/22). Among the eight Lassa fever patients with pharyngitis, three or 37.5% of them had associated cervical lymph adenopathy.

In a prospective study on Lassa fever patients by Ehichioya *et al*. in Lassa fever endemic region, sore throat was found to be the most common otorhinolaryngological symptom [37]. Other otorhinolaryngological symptoms seen in Lassa fever include dysphagia, vertigo, tinnitus, hearing loss and bleeding.

Four of the 22 *imported Lassa fever cases* (18.2%) had hearing loss. Hearing loss is a common finding among Lassa fever patients in the endemic region, especially when assessed by pure tone audiometry rather than by self-reported hearing loss [43]. Because Lassa fever related hearing loss is not among the early symptoms of Lassa fever, it may not be a very helpful diagnostic symptom if an early diagnosis of Lassa fever is desired.

Oral and nasal oozing of blood was observed in one of the *imported cases of Lassa fever* [24]. Bleeding was also observed among Lassa fever patients treated in the Lassa fever endemic region. The first case of Lassa fever reported from Ghana was a severe disease in which there was bleeding from the ears, nose and mouth before the patient died. This happened just three days after he hunted and ate the flesh of game animals, which included a rat [44].

3) Eye manifestations

Five of the 22 *imported cases of Lassa fever* had eye features of conjunctivitis, subconjunctival hemorrhage or iridiocyclitis.

The animal model provided an opportunity for a detailed examination of the eye in Lassa virus infection. There was extensive ocular involvement in fatal Lassa virus infection in guinea pigs. The eyes of guinea pigs that succumbed to Lassa virus infection had extensive ocular manifestations involving the anterior uvea, ciliary body, iris, conjunctiva and cornea [45]. On the other hand, the eyes of the guinea pigs that survived Lassa virus infection had little or no ocular inflammation [45]. Postmortem examination of the eye in humans will help us to understand if a similar thing occurs in man.

4) Neurological Features

The neurological clinical features in the *cases of imported Lassa fever* include headache, which was the most common, occurring in 50% (11/22) of cases. Confusion, myelitis, and generalized seizures were also reported. There was a case of viral encephalitis who had a far more Lassa viral load in the cerebrospinal

fluid than in the blood [16] [17].

Headache was the most frequent neurological symptom found in Lassa fever cohorts in Lassa fever endemic region followed by impaired consciousness. Light headedness, meningitis, encephalitis and paraparesis have all been reported in Lassa fever in the endemic region. In cases of Lassa fever presenting with meningitis, the cerebrospinal fluid was clear with predominance of lymphocytes and low glucose levels.

5) Respiratory Features

The respiratory features among the imported cases of Lassa fever were cough, pleuritic chest pain and shortness of breath. Pleural effusion was also reported. One of the patients died from a suspected pulmonary embolism [17].

Cough was found to be the most common respiratory symptom of Lassa fever in Lassa fever endemic region followed by chest pain and difficulty in breathing [37]. Acute respiratory distress syndrome can occur in severe disease.

Chest radiograph may be normal in Lassa virus infection, but there may be radiological changes if there is pleural effusion. Radiological changes may also be seen in acute respiratory distress syndrome.

6) Cardiovascular Features

Cardiovascular findings among the *cases of imported Lassa fever* include cardiac arrhythmia, hypotension, heart murmur and cardiogenic shock. In one of the cases, there was massive bloody pericardial effusion with cardiac tamponade as part of polyserositis in which there was also pleural effusion and ascites [12]. In Lassa fever patients studied by Maigari *et al*. [38] in the endemic region, 26% of the patients had hypotension.

7) Gastrointestinal Features in Lassa fever

Nausea, vomiting, diarrhoea, abdominal or epigastric pain and hepatomegaly occurred in some of the *imported Lassa fever patients*. Elevated serum alanine transferase or aspartate amino transferase was also reported.

Gastrointestinal symptoms and signs are common in Lassa fever [37]. However, diarrhea, vomiting, and abdominal pains are also seen in typhoid fever [46]. Gastrointestinal bleeding can occur in Lassa fever. Bowel dilatation may be evident on abdominal radiograph and free intraperitoneal fluid may be evident on abdominal ultrasound examination.

8) Urogenital System

Eleven of the 22 cases (11/22 or 50%) had renal features consisting of proteinuria, microscopic hematuria or acute kidney injury.

In the Lassa fever endemic region, Okokhere *et al*. found an overall incidence of acute kidney injury of 28% among Lassa fever patients [47]. Acute kidney injury was associated with a high incidence of proteinuria and a high case fatality rate.

One of the *imported Lassa fever patients* had epididymitis and Lassa virus was cultured from his seminal fluid [25]. Lassa virus is known to be present in the seminal fluid of male Lassa fever patients even in those in whom epididymitis

was not reported. It is not actually known for how long Lassa virus can be excreted in the seminal fluid. Thus, the transmission of Lassa virus from a male Lassa fever patient during sexual intercourse is a definite risk even during the immediate recovery period.

9) Haematological Findings

Among the *imported cases of Lassa fever* under review, anemia was reported. Both leucopenia and leukocytosis were also reported, with more cases of leucopenia than leukocytosis. Both thrombocytopenia and thrombocytosis were also reported, with more cases of thrombocytopenia than thrombocytosis. Bleeding disorders manifesting as subconjunctival hemorrhage, microscopic hematuria and coagulation abnormalities were also reported among the *imported cases of Lassa fever*.

However, anemia can occur in severe malaria [48] just as in typhoid fever. Also, leucopenia or leukocytosis can occur in typhoid fever. Even when platelet count is normal, platelet may be abnormal in function in Lassa fever. Just like in Lassa fever, bleeding occurs in Ebola Virus Disease and in Marburg hemorrhagic fever.

10) Others

Dermatological findings in Lassa fever include body rash and hair loss. Musculoskeletal symptoms and signs in Lassa fever include myalgia, arthralgia and neck and back pain. These dermatological and musculoskeletal features were present in some of the *imported Lassa fever* patients.

In our review, 100% of the *imported Lassa fever* patients had fever compared to 59% reported by Kofman *et al*. [1] in their own review. While Kofman *et al*. fever prevalence of 59% was based on 29 out of 33 *cases of imported Lassa fever* that occurred between 1969 and 2016 [1], our own review was on 22 *cases of imported Lassa fever* with detailed symptoms and physical signs who presented between 1969 and April 2021.

11) Mortalities in Lassa fever

Five out of the 22 patients with *imported Lassa fever* died, giving a case fatality rate of 22.7%. This case fatality rate is close to 24% reported by Okokhere *et al*. [47] and 29% reported by Ehichioya *et al*. [37] in Lassa fever endemic region. In their own review of *cases of imported Lassa fever* between 1969 and 2016, Kofman *et al*. [1] reported a case fatality rate of 39% among 31 patients for whom the outcomes were known.

3.2. Predicting Case Definitions of Lassa Fever Using the Modified Khan Case Definition of Lassa Fever and the 2011 CDC Surveillance Case Definition of Viral Haemorrhagic Fevers, Including Lassa Fever

In the non-endemic countries where those 22 cases were seen, what raised the clinical suspicion for Lassa fever were history of recent travel to (or residence in) Lassa fever endemic region, non-responsiveness of the patients to antimalarials or/and antibiotics and negative tests for other known causes of febrile illness.

Case number 9 and case number 20 initially denied visiting the rural area where Lassa fever was endemic which delayed their diagnosis of Lassa fever [8] [24]. In Table 2, the modified Khan case definition of Lassa fever and the 2011 CDC surveillance case definition of viral haemorrhagic fevers, including Lassa fever, were applied to the 22 cases of Lassa fever in order to assess their usefulness in identifying possible cases of Lassa fever. The criteria for the modified Khan case definition are a fever of >38˚C plus two major signs or one major sign and two minor signs. The details of the modified Khan case definition of Lassa fever are available elsewhere [49].

Table 2. Using cases of imported Lassa fever to compare the 2011 CDC case definition with the modified Khan case definition for Lassa fever.

S/No	Modified Khan case definition			2011 CDC case definition	
	Number of major signs	Number of minor signs	Met the criteria	Number of clinical criteria excluding fever	Met the criteria
1	0	4	No	3	Yes
2	0	2	No	1	Yes
3	0	3	No	2	Yes
4	1	3	Yes	2	Yes
5	1	4	Yes	4	Yes
6	0	3	No	3	Yes
7	3	3	Yes	3	Yes
8	2	0	Yes	1	Yes
9	1	2	Yes	4	Yes
10	0	1	No	1	Yes
11	1	2	Yes	3	Yes
12	1	3	Yes	4	Yes
13	1	3	Yes	2	Yes
14	0	3	No	3	Yes
15	0	1	No	2	Yes
16	0	1	No	1	Yes
17	1	2	Yes	3	Yes
18	0	2	No	2	Yes
19	0	3	No	3	Yes
20	0	2	No	2	Yes
21	1	3	Yes	4	Yes
22	0	3	No	3	Yes
Total			10/22		22/22
% (Percentage)			45%		100%

The clinical criteria for the 2011 CDC surveillance case definition were a fever of >40˚C plus one of the listed clinical findings [50]. The epidemiologic linkage includes residence in or travels to Lassa fever endemic area. A case is defined as a suspected case if it meets the clinical criteria and the epidemiologic linkage. The details of the 2011 CDC surveillance case definition of viral hemorrhagic fevers, including Lassa fever, are available elsewhere [50].

The modified Khan case definition had an accurate prediction of only 45% (or 10/22) of the *cases of imported Lassa fever*, while the 2011 CDC surveillance case definition had an accurate prediction of 100% (22/22). The modified Khan case definition of Lassa fever appears to be a more stringent case definition which may increase its specificity. However, the disadvantage of Khan case definition is that during Lassa fever outbreaks, it is more likely to miss a significant number of cases because the clinical features listed under "major signs" are mostly clinical features that appear late in the course of the illness such as bleeding, hypotension and hearing loss. For the same reason, the modified Khan case definition may not be very helpful in the timely diagnosis of Lassa fever if the patient presents early with mainly early symptoms and signs.

The 2011 CDC surveillance case definition is simpler, requiring only one clinical feature in addition to fever for a positive result. Another good feature of the CDC case definition is that it takes into consideration proteinuria and thrombocytopenia which are important components of Lassa fever clinical presentation. During Lassa fever outbreaks, the CDC surveillance case definition may be very useful for the timely identification of possible cases of Lassa fever. However, its setback is that it is more likely to give a significant number of false positive results, especially outside the period of outbreaks, because some of the clinical features listed among the criteria can also be found among common febrile illnesses such as malaria and typhoid fever.

4. Conclusions

The pattern of clinical presentation of the *imported Lassa fever cases* was similar to those reported in Lassa fever patients who were treated in the endemic region. The clinical features of the cases of Lassa fever were non-specific, as they could also be found in other febrile illnesses endemic in West Africa. Hemorrhaging, which is a remarkable feature of Lassa fever, can also occur in other viral hemorrhagic fevers.

History of recent travel to, or residence in, Lassa fever endemic region and non-responsiveness of the patients to antimalarials or/and antibiotics are important clues for clinical diagnosis of Lassa fever. The modified Khan case definition for Lassa fever and the 2011 CDC surveillance case definition for viral hemorrhagic fever, including Lassa fever, are additional tools that may aid clinical diagnosis of Lassa fever, but the medical practitioner using the case definitions should be aware of their limitations. Every clinically suspected case of Lassa fever should have a laboratory confirmation.

Conflicts of Interest

The authors declare that there are no conflicts of interests.

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