Review Article

A REVIEW OF OCULAR FINDINGS IN PATIENTS WITH LASSA FEVER

[1]Alikah AA, [1]Enock ME, [2]Omoti AE, [3]Alikah S, [4]Omoti CE

[1]Department of Ophthalmology, Irrua Specialist Teaching Hospital, Irrua, [2]Department of Ophthalmology, School of Medicine, University of Benin, [3]Department of Pediatrics, Irrua Specialist Teaching Hospital, Irrua, [4]Department of Haematology, School of Medicine, University of Benin.

Aim: To review the ocular manifestations of Lassa fever.

Methods: Information about Lassa fever and other haemorrhagic fevers and their ocular manifestations from existing literature from journal publications, public health releases and internet search were analyzed.

Results: There is a paucity of literature on ocular findings in Lassa fever but it has been demonstrated that there is a high frequency of ocular findings in other viral haemorrhagic fevers such as West Nile Virus infection uveitis, retinal vasculitis, optic neuritis, subconjunctival haemorrhage, sixth nerve palsy, nystagmus, bilateral visual loss and congenital chorioretinal scarring; Dengue fever with ptosis, uveitis and retinal haemorrhages and macular oedema; Chikungunya with uveitis, retinitis, panophthalmitis, optic neuritis, keratitis, episcleritis, neuroretinitis, central retinal artery occlusion, lagophthalmos, and sixth nerve palsy; Rift Valley fever with macular or paramacular necrotizing retinitis, retinal haemorrhages, vitritis, optic disc oedema, and retinal vasculitis. Lassa fever has been reported to manifest with ocular discharge, ptosis, lid oedema, tearing, diffuse conjunctival injection, subconjunctival haemorrhage, uveitis, bilateral dendritic corneal ulcers in one case, flame shaped retinal haemorrhages and retinal oedema.

Conclusion: Lassa fever like other haemorrhagic fevers manifest with ocular features which include ptosis, conjunctivitis, subconjunctival haemorrhages, corneal ulcers, uveitis and retinitis.

Key words: Lassa fever, ocular manifestations, uveitis, conjunctivitis, haemorrhage.

INTRODUCTION

Lassa fever is an acute, highly contagious, often fatal haemorrhagic fever caused by the Lassa Virus. It is transmitted by the multimammate rat, *Mastomys natalensis* which is widely distributed throughout West Africa hence the endemicity of the disease in West African countries particularly in Guinea, Liberia, Sierra Leone, as well as Nigeria.[1]

All correspondence to: Dr Alikah A Anita, Department of Ophthalmology, Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria. Email: anita.alikah@npmcn.edu.ng

The Lassa virus is an RNA virus which belongs to the family *Arenaviridae*.[2] Its structure is being studied with a view to improving treatment modalities available as well as determining a possible vaccine for prevention.

The number of Lassa virus infections per year in West Africa is estimated at 100 000 to 300 000, with approximately 5000 deaths.[1] This number may be an underestimation since it is hospital based and many victims of Lassa fever may not present to any health facility or may recover

without treatment. In the year 2012, Nigeria experienced a major outbreak of Lassa fever. By the end of March, 623 cases including 70 deaths (Case Fatality Rate of 11.2%) had been reported from 19 out of 36 States. Of these, 108 had been laboratory confirmed. Three doctors and four nurses were reported to be among the fatalities.[3]

About a third of Lassa fever patients have conjunctivitis and a few have conjunctival haemorrhages.[4] Conjunctival injection, retro-orbital pain and eyelid oedema have also been reported to occur in Lassa fever.[5,6,7,8] There is a paucity of literature documenting ocular findings in Lassa fever and no study designed to document ocular findings by doing complete eye examinations was found. However, the abundance and frequency of ocular findings in other viral haemorrhagic fevers makes it likely that Lassa fever may also have significant ocular findings.

In Nigeria, the Federal Ministry of Health published clinical criteria for classifying patients into suspected Lassa fever cases, probable Lassa fever and possible Lassa fever. Conjunctivitis is the only ocular finding included in the clinical criteria.[9] Since ocular findings have not been extensively studied, there may be ocular findings beyond conjunctivitis which may be specific and sensitive enough to enhance clinical diagnoses particularly where laboratory confirmatory tests are not available.

Clinical findings such as bleeding from mucosal surfaces, conjunctival haemorrhages, facial oedema, encephalopathy and seizures have been found useful in predicting outcome in Lassa fever while sore throat and vomiting are highly correlated with a poor outcome.[3,4] It is possible that eye findings other than conjunctival haemorrhages could be useful in prognosticating.

Epidemiology

Lassa fever is most commonly diagnosed in parts of West Africa where it is endemic. The number of Lassa virus infections per year in West Africa is estimated at 100 000 to 300 000, with approximately 5000 deaths.[10] The disease is endemic in several countries of West Africa, namely Sierra Leone, Guinea, Liberia, and Nigeria. A case of Lassa fever imported to Europe in the year 2000 indicates that the virus (and probably the disease) is endemic in larger areas of West Africa.[11] Since the index patient travelled through Ghana, Cote D'Ivoire and Burkina Faso during the incubation period, it was not possible to exactly determine the origin of the infection.[11] The geographically restricted occurrence of the disease is not well understood as its rodent host (Mastomys species) is prevalent in much larger areas of sub-Saharan Africa. The importation of Lassa virus into other regions, for example by travellers, is rare, with only a few cases documented.[12]

The dissemination of the infection can be assessed by the prevalence of antibodies to the virus in the population which is 8-52% in Sierra Leone,[11] 4-55% in Guinea,[13] and 21% in Nigeria.[14]

Seropositivity has also been found in the Central African Republic, Democratic Republic of the Congo, Mali, and Senegal.[15]

Peak incidence was thought to be in the dry season (January to March), but data collected in Sierra Leone shows peaks in the period of overlap of the dry season with the wet season (May to November).[16]

Investigations in the 1970s and 1980s pointed to the existence of 3 disease-endemic zones within Nigeria: the northeastern region around Lassa, the central region around Jos, and the southern region around Onitsha.[11,18] The current epidemiologic situation is less clear because no surveillance system is in place. From 2005 through 2008, 10 cases of Lassa fever were confirmed by virus detection in Nigeria.[18] The Lassa fever activity were in the states of Edo, Ebonyi, Federal Capital Territory, and Plateau as at 2008.[18]

Several cases of viral haemorrhagic fever (VHF) from the northern part of Edo State, including

Ekpoma, Uromi, Irrua, Igueben, Iruekpen, Igarra, Ibillo, Ozalla, Ubiaja, Agenebode, Auchi, Afuze, Akoko Edo, Ewu, Okpella and environs have been treated at the University of Benin Teaching Hospital, Benin City, from 1970 to 2000 with high fatality.[5] There was no specific mention of Lassa fever in all those years and no specific drug treatment or precautionary measure was available or adopted. However, in 1984, the first cases of Lassa fever in Edo State were reported when a family of four, from Ihumudumu, Community of Ekpoma died.[19] With the establishment of the Irrua Specialist Teaching Hospital, Irrua, in the northern part of Edo State in 1992, several highly trained and motivated specialist doctors became available for teaching, research and treatment of diseases. The identification of large number of Mastomys natalensis, led to attempts to identify the virus in patients with febrile illness in the area.[20] Careful history, clinical examination and assessment of patients with febrile illnesses that had periodic outbreaks led to the clinical diagnosis of Lassa fever. Between January and December, 2010,in Irrua Specialist Teaching Hospital, 76 (8.7%) of the 869 suspected cases of Lassa fever had positive ReverseTranscription-Polymerase Chain Reaction for Lassa fever.[21]

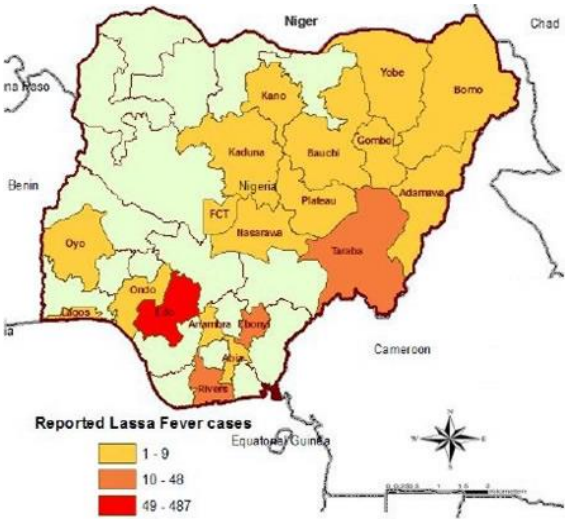

FIGURE 1: Geographical distribution of Lassa Fever in Nigeria-courtesy of WHO[3]

Pathogenesis

Pathogenesis of arenavirus diseases is believed to involve initial replication at the site of infection in nonreservoir hosts, usually following aerosol deposition in the lung.[11] The hilar lymph nodes are an important site of virus growth, as are the lung, and later, other parenchymal organs. Pneumonic foci are usually not present, although interstitial infiltrates and oedema may occur during the course of infection. In infections by any route, the macrophage is usually identified as an early and prominent cell involved. As infection spreads, additional cell types reach equal prominence.[11] Many epithelial structures are readily identified as containing antigen and nucleic acids. Widespread infection of the marginal zone and necrosis of lymphoid follicles of the spleen and lymph nodes is a common lesion with the potential to blunt an effective curative immune response and is associated, at least in the adult mouse infected with the Lymphocytic Choriomeningitis virus, with cytotoxic T lymphocyte destruction of critical antigen-presenting lymphoid cells. In spite of the extensive involvement of different cell types throughout the body, the pathologic changes are relatively subtle with comparatively little frank necrosis.

The pathogenesis of Lassa fever is still poorly understood. Humans often die without bleeding, and pathological and histopathological lesions do not appear severe enough to explain organ failure and death.[11] Macroscopic changes include pulmonary oedema, pleural effusion, ascites, and signs of haemorrhage from the gastrointestinal mucosa. Microscopic lesions include hepatocellular necrosis (1%-50% of hepatocytes) with a phagocytic macrophage reaction but with absent or minimal lymphocyte infiltration, splenic necrosis, renal tubular injury, interstitial nephritis, interstitial pneumonitis, and myocarditis. No lesions have been reported to occur in the central nervous system.[11] Histopathologically, the liver is a major and most consistently affected target organ in humans.[22] This is also evidenced by elevations of aspartate transaminase (AST) and

alanine transaminase (ALT) in serum. However, unlike a typical acute viral hepatitis, the AST is much higher than the ALT both in humans and monkeys, suggesting that the enzyme elevations do not solely reflect liver cell damage.[23] Indeed, the virus shows a broad tropism. It can be isolated from virtually all organs (liver, lung, spleen, kidney, adrenal, pancreas, heart) in human and animal models, with the lowest titers being found in the central nervous system.[22] The pantropism may be explained by the high affinity of Lassa virus for the receptor alpha-DG that is expressed in most tissues. Lassa fever does not seem to be associated with a decrease in the coagulation factors or disseminated intravascular coagulation in human and animal models.[23] However, some functional haematologic disturbances have been found by *in vitro* tests, namely suppressed platelet and neutrophil function due to unknown inhibitor(s) in the plasma of patients with severe Lassa fever. The titre of virus in serum correlates with the risk of death, suggesting that the level of virus replication is involved in the pathophysiology. Taken together, the currently available data are not sufficient to reconstruct the chain of pathophysiological events in Lassa fever. However, some mechanisms are likely to play a role:[24]

i. early during infection Lassa virus may target immune cells and interfere with their activation
ii. the high affinity of Lassa virus for the receptor alpha-DG may allow virus replication in several organs
iii. the relatively low susceptibility of the virus to IFN may facilitate virus spread
iv. a continuous and uncontrolled rise in virus load in several organs may eventually trigger a fatal inflammatory syndrome in the terminal stage of the disease.[24]

Clinical features of Lassa Fever

About 80% of human infections are asymptomatic; the remaining cases have severe multi-system disease, where the virus affects several organs in the body, such as the liver, spleen and kidneys. The incubation period is generally between 7 and 10 days, but may be as short as 3 or as long as 17 days.[25]

The clinical symptoms in the early phase of a viral haemorrhagic fever are very similar irrespective of the causative virus and resemble a flu-like illness or a common enteritis. Headache, myalgia, gastrointestinal symptoms, and symptoms of the upper respiratory tract dominate the clinical picture.[26] The onset of the disease is insidious with fever and general malaise over a 2- to 4-day period. In more severe cases; weakness, retro-orbital pain, joint and lumbar pain, myalgia, headache, pharyngitis, cough and conjunctival injection are seen. In the most severe form of the disease; prostration, abdominal pain, facial and neck oedema, haemorrhages (conjunctival haemorrhages, mucosal bleeding, melena, haematochezia, haematuria, vaginal bleeding, haematemesis), encephalitis, capillary leak syndrome and shock may occur. Hepatitis is frequent.[26] Pulmonary manifestations can be significant with adult respiratory distress syndrome.

A possible long-term sequelae of Lassa infection is sensorineural deafness.[10,27] The illness develops fairly rapidly but is not as abrupt in onset as in some other haemorrhagic fevers, notably Congo haemorrhagic fever. The patient complains of chills, fever and malaise, headache, myalgia and arthralgia, neck pain and sore throat. There may also be difficulty in swallowing, and vomiting and diarrhoea may develop followed by pains in the chest and abdomen.[25] The abdomen is tender in 50% of the patients, but bowel sounds are usually normal to marginally reduced.[4]

Bilateral or unilateral eighth-nerve deafness has also been reported.[10,27,28] Onset of deafness among patients with Lassa fever is a feature of both the acute and the convalescent phase of the illness and may be immune mediated.[40] Deafness was first reported as a complication of Lassa fever by White and Henderson in 1972.[29,30] White noted that during a 1970 nosocomial hospital outbreak in Jos, Nigeria, deafness occurred in 4 of 23

hospitalized patients; a fifth patient reported intermittent tinnitus, and 3 patients experienced dizziness.[29] Bleeding and oedema, late symptoms occurring only in a small fraction of patients, are not sensitive (approximately 20%), but highly specific for Lassa fever (approximately 90%).[11] Some patients develop facial oedema during the advanced stage of the disease, which is associated with poor prognosis. Oedema of the face and neck, conjunctival haemorrhages, mucosal bleeding, central cyanosis, encephalopathy, and shock characterize the most severe cases.[31] Among the clinical signs, sore throat, vomiting, and bleeding are highly correlated with a poor outcome. Neurological signs are infrequent, but carry a poor prognosis, ranging from confusion to severe encephalopathy with or without general seizures but without focal signs.[4] More than two-thirds have pharyngitis, half with exudates, diffusely inflamed and swollen posterior pharynx and tonsils, but few if any ulcers or palatal petechiae.[4] Severe pulmonary oedema and adult respiratory distress syndrome is common in fatal cases with gross head and neck oedema, pharyngeal stridor, and hypovolemic shock.[28] Diffuse rales may be heard by auscultating the chest, and pleural and pericardial friction rubs may sometimes be detected.[31] Lassa fever in pregnant women is associated with infection of the foetus and loss of the foetus or new born in 90% of the cases.[4] The risk of death is also higher for mothers in the third trimester. Evacuation of the uterus significantly improves the mother's chance of survival.[4] Abnormal electrocardiograms, including non-specific ST-segment and T-wave abnormalities, ST-segment elevation, generalized low voltage complexes, and changes reflecting electrolyte disturbance may be seen in Lassa fever patients, but none of these correlate with clinical or other measures of disease severity or out come and are not associated with clinical manifestations of myocarditis.[4] The disease can clinically hardly be distinguished from other febrile illnesses seen in West African hospitals.[11]

Ocular features

There is a paucity of documentation of ocular findings in Lassa fever. However, the abundance and frequency of ocular findings in other viral haemorrhagic fevers makes it likely Lassa fever will also have significant ocular findings. About a third of patients have conjunctivitis and a few have conjunctival haemorrhages.[4] Conjunctival injection, retro-orbital pain and eyelid oedema have also been reported to occur in Lassa fever.[5,6,7,8] However, these studies were not targeted at ocular findings and did not report carrying out complete ocular examinations.

Other viral haemorrhagic fevers such as West Nile Virus infection have ocular findings such as a typical multifocal chorioretinitis, anterior uveitis, retinal vasculitis, optic neuritis, subconjunctival haemorrhage, sixth nerve palsy, nystagmus, bilateral visual loss and congenital chorioretinal scarring.[32,33] Dengue fever, has been reported to being associated with ptosis, uveitis and retinal haemorrhages and macular oedema.[34,35] Ocular findings in Rift Valley fever have been reported to occur in 1–20% of infections, after a mean interval ranging from 4 to 15 days after the onset of the disease.[36] Macular or paramacular necrotizing retinitis is the most common finding with early hypofluorescence and late staining and retinal vascular leakage on fluorescein angiography. Other posterior segment lesions include retinal haemorrhages, vitritis, optic disc oedema, and retinal vasculitis.[37] Treatment is entirely supportive.[36,37] Symptoms resolve spontaneously within 2–3 weeks, but permanent visual loss is common, resulting from macular and paramacular scarring, vascular occlusion, or optic atrophy.[36,37] In Chikungunya, ocular involvement can be unilateral or bilateral, and may be present at the time of systemic illness or after the resolution of systemic disease. Ocular symptoms include redness, blurred vision, floaters, pain, watering, photophobia, irritation, and diplopia.[38] Acute anterior uveitis and retinitis are the most common ocular manifestations of Chikungunya. Anterior uveitis may be nongranulomatous or

granulomatous, and can be associated with increased intraocular pressure.[38,39] Posterior synechiae are not common. Chikungunya anterior uveitis may closely mimic herpetic anterior uveitis. Chikungunya retinitis is usually accompanied by mild vitritis, and is present in the form of areas of retinal whitening in the posterior pole with surrounding retinal and macular edema.[40,41] An associated retinal vasculitis, accurately detected by fluorescein angiography, is also common. Other ophthalmic manifestations of Chikungunya include panuveitis, panophthalmitis, optic neuritis, keratitis, episcleritis, neuroretinitis, central retinal artery occlusion, lagophthalmos, and sixth nerve palsy.[38,41]

A study in the Irrua Specialist teaching Hospital, Irrua, Nigeria,[42] which is a referral centre for Lassa fever showed that nearly a quarter of the cases (24.1%) had significant adnexal abnormalities such as eyelid discharge, ptosis, lid oedema and tearing. More than 50% of the cases had diffuse conjunctival injection. Subconjunctival haemorrhage (3.4%) and circumcorneal injection (3.4%) were also seen among the cases of Lassa fever. Keratic precipitates were seen on the corneas of 2 cases (6.9%) and bilateral dendritic corneal ulcers in one case (3.4%). Significant retinal findings in the cases of Lassa fever included flame shaped haemorrhages and retinal oedema mainly. More than 65% of the Lassa fever cases had flame shaped haemorrhages in the macula. There was a statistically significant difference between the mean IOP (SD) of the 58 eyes of the cases which was 8.4mmHg (2.16) and the 100 eyes of the controls which was 13.3 (2.64).

Diagnosis

In Nigeria, the Federal Ministry of Health published criteria for diagnosis of LF in the year 2000.[9] Major criteria are abnormal bleeding (from the mouth, gums, nose, vagina and haemoptysis), swollen neck and/or face, red eyes or conjunctivitis, spontaneous abortion, deafness during illness and low blood pressure (systolic BP less than 100mmHg) or shock. Minor criteria are sore throat, headache, leukopenia (less than $400mm^{-3}$), nausea and vomiting, abdominal pain, diarrhoea, cough, pleural effusion or ascites, swollen lymph nodes, weakness and proteinuria.

The diagnosis of a suspected case is based on seeing a patient with fever (37.8^{o}C or more), not responding to antimalarial and antibiotic drugs while probable Lassa fever is based on persistent fever with any of the major criteria. Possible Lassa fever is considered when there is persistent fever with two or more minor criteria and known contact with Lassa fever cases.[9] Since ocular findings have not been extensively studied, there may be ocular findings beyond conjunctivitis which may be specific and sensitive enough to enhance clinical diagnoses particularly where laboratory confirmatory tests are not available.

Laboratory

Virological testing plays an important role in the diagnosis of Lassa fever because of the difficulty in diagnosing the disease on the basis of clinical parameters. The classical method to detect Lassa virus is inoculation of Vero cells with serum, CSF, throat washing, pleural fluid, or urine of the patient. The virus often induces a cytopathic effect in culture that can disappear upon further passage.[24] Specific detection of the isolate is done by detection of virus antigen in cells by immunofluorescence using virus-specific antibodies. Despite the availability of novel molecular techniques for Lassa virus detection, conventional virus culture has still major advantages. Growth in cell culture and immune detection are hardly affected by the variability of the virus, a problem that is relevant for Lassa virus PCR.[24] Furthermore, virus isolation facilitates a detailed genotypic and phenotypic characterization of the isolate. Major disadvantages are the long period of time (days to weeks) required to isolate a virus as well as the need for BioSafetyLevel-4 facilities. Virus antigen can be detected by enzyme-linked immunosorbent assays (ELISA) using Lassa virus-

specific antibodies.[43,44] These tests are easy to handle, rapid, and can be performed with inactivated specimens, which is advantageous in the field if sophisticated equipment is not available. The minimal concentration of infectious virus required for detection by ELISA ranges from 10^2 to 10^5 plaque forming units per ml (PFU/ml) depending on the material tested. However, for unknown reasons the antigen ELISA becomes increasingly insensitive concomitant with the appearance of specific antibodies. Accordingly, antigen ELISA is clinically less sensitive than virus isolation (36%), although the high concentration of virus early in the course of Lassa fever often allows antigen detection in serum.[24,43,44] IgM and IgG antibodies are detectable in about half of the patients during the first days of illness, with about 15% being only IgM-positive. Therefore, serological testing is not suitable for early diagnosis of Lassa fever. Furthermore, patients with fatal Lassa fever show lower antibody titres or may not develop antibodies at all. The fraction of seropositive patients increases further during the course of disease and is close to 100% by day 18, when viraemia is already decreasing. Therefore, serological assays are the methods of choice for diagnosis of Lassa fever in the convalescence phase. Specimens can be inactivated by heat to facilitate testing under standard laboratory conditions.[24] Indirect immunofluorescence using virus-infected cells is the most common test for detecting IgM and IgG antibodies to Lassa virus. IgG seroconversion with a greater than 4-fold increase in the IgG titer or detection of IgM together with an IgG titre greater than or equal to 256 is considered evidence of acute infection. Although the interpretation of immunofluorescence requires some experience, the assay has advantages over other methods.[44] First, there is a long experience with this technique, which is important when only a limited number of sera are available to evaluate new assays. Second, all Lassa virus proteins expressed in the infected cell serve as antigen, and third, Lassa virus antibodies generate a characteristic fluorescence pattern (cytoplasmic dots) which adds specificity to the assay compared to an ELISA readout. The distinction of specific signals from non-specific fluorescence can be further improved by counterstaining Lassa virus antigen using monoclonal antibodies (double-labelling procedure). However, the immunofluorescence test probably is not completely specific for Lassa virus because of the extensive cross reactivity among African arenaviruses. This aspect should be taken into consideration if the laboratory diagnosis is solely based on serology.[24] ELISA or immuno blot tests using recombinant protein (NP, GPC, and Z protein) as antigen have also been developed and used for seroprevalence studies or for diagnosis of acute infection.[44] The great advantage of these assays is that their preparation does not require BioSafetyLevel-4 laboratories. On the other hand, the high background in African sera of antibodies against components of bacterial or insect cell expression systems complicates the use of recombinant proteins for serological diagnostics in endemic regions. IgG and IgM ELISA were also developed using gamma irradiated virus from infected cells as an antigen. The clinical sensitivity of these assays is comparable to indirect immunofluorescence.[24,44] The IgM ELISA detected acute Lassa virus infection in 72% of confirmed cases, and when combined with ELISA for antigen detection, sensitivity reached 88%. Despite these achievements, immunofluorescence using Lassa virus infected cells can still be regarded as the gold standard for the serological diagnosis of Lassa fever.[24] RT-PCR is currently the method of choice for rapid and early diagnosis of Lassa fever. Since Lassa virus is an RNA virus, its RNA must be reverse transcribed into cDNA prior to PCR. In the early PCR assays published for Lassa virus, cDNA synthesis was performed in a separate step (2-step RT-PCR).[24,43] Furthermore, in order to reach high sensitivity and specificity, nested PCR steps were included in the assay or the PCR products were subjected to Southern blotting. The disadvantages of these assays are the long processing time and the increased risk of cross-contamination due to the additional manipulations. Recently, 1-step RT-PCR systems became available that are based on an optimized mixture of a retroviral RT and a Taq polymerase that is heat-activated only following the reverse

transcription step. Using this system, high analytical sensitivity of the Lassa virus PCR was achieved without the need of nested steps or Southern hybridization.[24,43] Detection is also faster and the risk of contamination is reduced. Unfortunately, Lassa virus is too variable for the design of reliable detection probes currently used in quantitative real-time PCR (TaqMan or fluorescence resonance energy transfer [FRET] probes). It is possible that future developments in this field will allow probe detection. Meanwhile, Lassa virus PCR products can be detected in real-time using intercalating dyes, like SybrGreen. This technique allows rapid measurement of virus RNA concentration in serum or other body fluids. The RNA concentration could be important as a prognostic parameter, in therapy monitoring, and in the risk assessment of virus transmission to contact persons.[24] All diagnostic Lassa virus PCRs published so far target the S RNA segment encoding GPC and NP. Clinical evaluation data show equal or higher sensitivity of PCR than virus isolation. Virus is detectable by PCR in 80% to 100% of patients between day 3 and day 9 of illness; thereafter the fraction of PCR-positive patients decreases. Quantitative real-time PCR was used to monitor virus RNA concentrations during the course of disease in two imported cases of Lassa fever.[24,43] The RNA concentrations in serum of these patients were 5 $x10^2$ - 2 $x10^6$ fold above the detection limit of the assay Thus, both clinical and analytical sensitivity data indicate that PCR is well suited to diagnose acute Lassa fever. Unfortunately, in the past some of the S RNA-specific PCR assays had to be established on the basis of few sequences, and it was soon noted that some Lassa virus strains escape detection by PCR. Indeed, extensive sequence information on the S RNA segment of Lassa virus has recently become available, showing that some PCR primers published for diagnostic use will not reliably detect all Lassa virus strains.[43] Compared to some Lassa virus sequences, these primers contain 5 or more mismatches, a state of affairs which is known to drastically reduce PCR efficiency.[24] Very recently, sequence information on the L RNA segment of arenaviruses became available. The L gene, encoding the viral RNA polymerase, may be particularly suited as a PCR target because RNA polymerases share conserved amino acid motifs even between different virus families. Indeed, the L gene was found to contain highly conserved regions that have been used to develop a Lassa virus-specific PCR assay. Due to the high degree of conservation at these sites, this assay is also able to detect other Old World arenavirus species such as Lymphocytic choriomeningitis virus, Mopeia virus, and Ippy virus, and may therefore be more robust with regard to virus variability than assays that solely detect Lassa virus. A PCR assay has been developed that predictably amplifies any member of the Arenaviridae by targeting the highly conserved termini of the S RNA segment.[24,43] This assay amplifies the whole 3.4-kb S RNA. Although it is clearly less sensitive than other diagnostic PCR assays, it was able to detect Lassa virus RNA in clinical samples and facilitated sequencing of the S RNA in a short period of time. Due to their broad reactivity, the L gene specific assay and the long-range PCR assay are also useful to detect as yet unknown members of the arenavirus family. A set of consensus primers has been published for S RNA sequencing of unknown arenaviruses. PCR inhibition due to substances circulating in blood appears to be a particular problem with samples from patients with Viral Haemorrhagic Fevers.[43,44] Complete inhibition was observed with diagnostic serum samples from critically ill patients with Lassa fever, yellow fever, and Ebola hemorrhagic fever. It is conceivable that tissue damage in Viral Haemorrhagic Fever patients leads to the release of inhibiting substances. To prevent false negative results, appropriate inhibition controls must be implemented in VHF PCR diagnostics.[24]

Treatment

Ribavirin is effective in the treatment of Lassa fever and it can be used at any point in the illness, as well as for post exposure prophylaxis.[45] Ribavirin has been effective when used orally and/or intravenously for the treatment of Lassa fever and is considered the drug of choice for the

disease. Ribavirin therapy has been associated with decreased mortality in patients with naturally occurring Lassa fever and is most effective when initiated early in the course of the infection (within 6-7 days of onset of symptoms).[46] Fisher-Hoch [47] outlined the principles of management- early antiviral therapy, intensive care, strict isolation, rigorously controlled barrier nursing and avoidance of needlestick injuries. McCormick reported ribavirin more effective than convalescent plasma and recommended this drug at all stages of the illness, as well as for post-exposure prophylaxis.[45] Highly concentrated convalescent plasma might be effective but is not easily stocked in sufficient quantities to treat large numbers. Intravenous ribavirin for first four days followed by oral ribavirin may be the best policy. It is expensive but stable and easy to administer. Haemolytic anaemia may occur but is reversible. Universal precautions against nosocomial infections, with surveillance of known contacts for 21 days is recommended. Virus neutralizing antibodies might add to the effect of ribavirin, thus some workers recommend that these antibodies should be banked and made available for treatment anywhere.[48]

Oral ribavirin is contraindicated in patients with known hypersensitivity to ribavirin or any component of the formulations. The drug should be discontinued immediately and appropriate therapy initiated if an acute hypersensitivity reaction (urticaria, angioedema, bronchoconstriction, anaphylaxis) occurs. Transient rash does not necessitate interruption of treatment.[46] Oral ribavirin is contraindicated in women who are or may become pregnant and also is contraindicated in male partners of such women, patients with hemoglobinopathies (thalassaemia, sickle-cell anaemia) and creatinine clearances less than 50mL/minute.[46] The only important adverse effect of ribavirin in humans is manageable, reversible anemia. In Lassa fever patients, brief episodes of rigor toward the end of the treatment course were reported.[26]

A clinical trial showed a therapeutic effect of the drug in humans with Lassa fever. In patients who had risk factors for a fatal outcome of the disease at admission, like high liver enzyme levels, and were treated within the first 6 days after the onset of fever, the case fatality rate decreased from 55 to 5%. Similarly, in patients showing high viraemia as a risk factor, the therapy reduced the case fatality from 76 to 9%. Even in patients treated at day 7 or later, the case fatality could be reduced in these risk groups from 55 to 26% and from 76 to 47%, respectively.[26] The therapeutic effect of Zidampidine (30-azidothymidine-50-[p-bromophenyl methoxyalaninyl phosphate]) in CBA mice challenged with intracerebral injections of the Josiah strain of Lassa virus is being explored.[49] Treatment may require all the modern intensive-care facilities, including renal dialysis and mechanical ventilation. It is essential to pay attention to fluid and electrolyte balance, maintenance of blood pressure and circulatory volume, and control of seizures.[31]

Prognosis

Clinical findings such as bleeding from mucosal surfaces, facial oedema, encephalopathy and seizures have been found useful in predicting outcome in Lassa fever. Sore throat and vomiting are also highly correlated with a poor outcome.[11] However, the only eye finding reported to be associated with poor prognosis is conjunctival haemorrhages. McCormick and Fisher-Hoch reported it to have a poor prognosis.[4] Their study design did not set out to relate eye findings to prognosis and their methodology did not suggest that a complete ocular examination was carried out. Thus there might be other eye findings that might be useful in assessing prognosis which they did not find or report. It is conceivable that Lassa fever might have eye findings that are useful for assessing the prognosis of the disease.

REFERENCES

1. CDC Special Pathogens branch. Lassa fever. (Internet). 2013 Available from http://www.cdc.gov/ncidod/dvrd/spb,mnpages/dispages/lassaf.htm (Accessed on 14/1/2014.)

2. Frame JD, Baldwin JM, Gocke DJ, Troup JM. Lassa fever: a new virus disease of man from West Africa. Am J Trop Med Hyg 1970; 19: 680-691.

3. World Health Organisation, Regional Office for Africa. Nigeria: Lassa fever outbreak (Situation as of March, 2012). Epidemic and Pandemic Alert and Response (EPR) 2012 Available from: http://www.afro.who.int/en/clusters-a-programmes/dpc/epidemic-a-pandemic-alert-and-response/out (Accessed on 12/1/2014.)

4. McCormick JB, Fisher- Hoch SP. Lassa fever. In: Oldstone MBA. (Ed.) Arenaviruses I. Berlin, Heidelberg: Springer- Verlag, 2002: 75- 109.

5. Omilabu SA, Badaru SO, Okokhere P, Asogun D, Drosten C, Emmerich P, et al. Lassa fever, NIgeria, 2003 and 2004. Emerg Infect Dis 2005; 11: 1642- 1644.

6. Macher AM, Wolfe MS. Historical Lassa fever reports and 30-year clinical update. Emerg Infect Dis 2006; 12: 835- 837.

7. Edmond RTD, Bannister B, Lloyd G, Southee TJ, Bowen ETW. A case of Lassa fever: clinical and virologic findings. Br Med J (Clin Res Ed) 1982; 285: 1001- 1002.

8. Richmond JK, Baglole DJ. Lassa fever: epidemiology, clinical features and social consequences. Br Med J 2003; 327: 1271-1275.

9. Federal Ministry of Health. What you need to know about Lassa fever. Public Health Leaflets. Abuja: Federal Ministry of Health, 2000: 2-4.

10. Bossi P, Tegnell A, Baka A, VanLoocke F, Hendricks J, Werner A, et al. Guidelines for the clinical management of Haemorrhagic fever Viruses and bioterrorism related haemorrhagic fever viruses. Euro Surveill 2004; 9: E11- E12.

11. Gunther S, Emmerich P, Laue T, Kuhle O, Asper M, Jung A, et al. Imported Lassa fever in Germany: molecular characterization of a new Lassa Virus strain. Emerg Infect Dis 2000; 6: 466- 476.

12. McCormick JB, Webb PA, Krebs JW, Johnson KM, Smith ES. A prospective study of the epidemiology and ecology of Lassa fever. J Infect Dis 1987; 155: 437- 444.

13. Lukashevich LS, Clegg JC, Sidibe K. Lassa Virus activity in Guinea: distribution of human antiviral antibody defined using enzyme-linked immunosorbent assay with recombinant antigen. J Med Virol 1993; 40: 210- 217.

14. Tomori O, Fabiyi A, Sorungbe A, Smith A, McCormick JB. Viral Haemorrhagic Fever antibodies in Nigerian populations. Am J Trop Med Hyg 1988; 38: 407- 410.

15. WHO. Lassa fever. WHO Lassa fever fact sheet No 179; Geneva: 2000. Accessed on 2/9/2012.

16. Healing T, Gopal R. Report on an assessment visit to Sierra Leone, April 12-30th, 2001. London; MERLIN: 2001.

17. Fichet- Calvet E, Rogers DJ. Risk Maps of Lassa fever in West Africa. PLOS Negl Trop Dis 2009; 3: 388.

18. Ehichioya DU, Ôlschlager S, Hass M, Becker-Ziaja B, Onyebuchi- Chukwu CO, Coker J, et al. Lassa fever, Nigeria, 2005- 2008. Emerg infect Dis 2010; 16: 1040- 1041.

19. Women's Health and Action Research Centre. Nigerians at risk of Lassa fever. Available at: http://www.wharc-online.org. (Accessed on 10/2/2014.)

20. Okoror LE, Esumeh FI, Agbonlahor DE, Umolu PI. Lassa Virus: sero-epidemiological survey of rodents caught in Ekpoma and environs. Trop Doct 2005; 35: 16- 17.

21. Eze KC, Salami TAT, Eze IC, Pogoson AE, Omordia N, Ugochukwu MO. High Lassa fever activity in Northern part of Edo State, Nigeria: re-analysis of confirmatory test results. Afr J Health Sci 2010; 17: 52- 56.

22. Walker DH, McCormick JB, Johnson KM, Webb PA, Komba-Kono G, Elliot LH, Gardner JJ. Pathologic and virologic study of fatal Lassa fever in man. Am J Pathol 1982; 107: 349-356.

23. Flatz L, Rieger T, Merkler D, Bergthaler A, Regen T, Schedensack M, et al. T- cell dependence of Lassa fever pathogenesis. PLOS Pathogens 2010; 6: 1-13.

24. Gunther S, Lenz O. Lassa Virus. Crit Rev Clin Lab Sci 2004; 41: 339-390.

25. Gear JHS, Isaacson M. Lassa fever. In: Gear JHS. Handbook of Viral and Rickettsial haemorrhagic fevers. Boca Raton, Florida: CRC Press, Inc, 1988: 137-144.

26. Drosten C, Kummerer BM, Schmitz H, Gunther S. Molecular diagnostics of viral haemorrhagic fevers. Antiviral Res 2003; 57: 61- 87.

27. Okokhere PO, Ibekwe TS, Akpede GO. Sensorineural hearing loss in Lassa fever: two case reports. J Med Case Rep 2009; 3: 1-3.

28. McCormick JB, King IJ, Webb PA, Johnsom KM, O'Sullivan R, Smith ES, et al. A case-control study of the clinical diagnosis and course of Lassa fever. J Infect Dis 1987; 155: 445- 455.

29. White HA. Lassa fever: a study of 23 hospital cases. Trans R Soc Trop Med Hyg 1972; 66: 390- 401.

30. Henderson BE, Gary GW, Kissling RE, Frame JD, Carey DE. Lassa fever: virological and serological studies. Trans R Soc Trop Med Hyg 1972; 66: 409-416.

31. Centre for Disease Control and Prevention. Management of patients with suspected Viral Haemorrhagic Fever. Morb Mortal Weekly Report 1988; 37: 1-16.

32. Shaikh S, Trese MT. West Nile Virus chorioretinitis. Br J Ophthalmol 2004; 88: 1599- 1600.

33. Bains HS, Jampol LM, Caughron MC, Parnell JR. Vitritis and chorioretinitis in a patient with West Nile virus infection. Arch Ophthalmol 2003; 121: 205- 207.

34. Gupta A, Srinivasan R, Setia S, Soundravally R, Pandian DG. Uveitis following Dengue fever. Eye 2009; 23: 1471- 1472.

35. Wen KH, Sheu MM, Chung CB, Wang HZ, Chen C. The ocular fundus findings in Dengue fever. Gaoxiong Yi Xue Ke Xue Za Zhu 1989; 5: 24-30.

36 Khairallah M, Khaloun R, Yahia S. New infectious aetiologies for posterior uveitis. Ophthalmic Res 2013; 49: 66-72.

37. Al- Hazmi A, Al- Rajhi AA, Abboud EB. Ocular complications of Rift Valley fever outbreak in Saudi Arabia. Ophthalmology 2005; 112: 313-318.

38. Mahendradas P, Avadhani K, Shetty R. Chikungunya and the eye: a review. J Ophthalmic Inflamm Infect 2013; 3: 35.

39. Babu K, Murthy GJ. Chikungunya virus iridocyclitis in Fuch's heterochromic iridocyclitis. Indian J Ophthalmol 2012; 60: 73-74.

40. Mahendradas P, Ranganna S, Shetty R. Ocular Manifestations associated with Chikungunya. Ophthalmology 2008; 115: 287- 291.

41. Ranjan P, Guillani BP, Khairallah M, Mishra D. Acute necrotizing panophthalmitis in seropositive case of Chikungunya: a case

report and a review of literature. J Clin Ophthalmol Res 2013; 1: 23-25.

42. Alikah AA. Ocular findings in patients with Lassa fever in Irrua Specialist Teaching Hospital, Irrua, Edo state, Nigeria. A dissertation submitted to the National Postgraduate Medical College of Nigeria in part fulfilment of the requirements for the Award of the Fellowship of the College in Ophthalmology. May 2014

43. Olschlager S, Lelke M, Emmerich P, Panning M, Drosten C, Hass M, et al. Improved detection of Lassa virus by reverse transcription- PCR targeting the 5' region of S RNA. J Clin Microbiol 2010; 48: 2009- 1013.

44. Bausch DG, Rollin PE, Demby AH, Coulibaly M, Kanu J, Conteh AH, et al. Diagnosis and clinical virology of Lassa fever as evaluated by Enzyme-linked Immunosorbent Assay, Indirect Immunofluorescent – Antibody test and virus isolation. J Clin Microbiol 2000; 38: 2670- 2677.

45. McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever; Effective therapy with Ribavirin. New England J Med 1986; 314: 20- 26.

46. American Society of Health System Pharmacists. Ribavirin. In: McEvoy GK. AHFS Drug information handbook. Bethseda, MD, USA: The American Society of Health System Pharmacists Inc, 2006; 826- 840.

47. Fisher-Hoch SP, Price ME, Craven RB, Forthall DN, Sasso DR, Scott SM, McCormick JB. Safe Intensive-care management of a severe case of Lassa fever with simple barrier nursing techniques. Lancet 1985; 2: 1227- 1229.

48. Suresh V. The enigmatic haemorrhagic fevers. J R Soc Med 1997; 90: 622- 624.

49. Uckun FM, Venkatachalam TK, Erbeck D, Chen CL, Petkevich AS, Vasilev A. Zidampidine, an aryl phosphate derivative of AZT: in vivo pharmacokinetics, metabolism, toxicity and antiviral efficacy against Haemorrhagic Fever caused by Lassa Virus. Bioorg Med Chem 2005; 13: 86-88