Lassa Fever and Hearing Loss

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57.1 Definition

The Arenaviridae have a genome consisting of single-stranded RNA. They infect rodents without causing symptoms and may be transmitted to humans as a zoonosis from an infected rodent. This usually occurs through contact with rodent urine or faeces. Since the rodents pass the virus on to their offspring, these animals remain a steady reservoir of infection. The Arenaviridae consist of 22 different viruses, with a further 9 types that were recently identified, but have not yet been definitively assigned to a taxon. The first arena virus, which is considered prototypical for the grouping, was discovered in 1934, the lymphocytic choriomeningitis virus (LCMV). At that time the St Louis encephalitis virus made its first appearance in an epidemic. A sample obtained from a patient who died at that time was found by chance to contain the LCMV, too. This became apparent after the virus had been transmitted through several monkeys, one after another. LCMV was the first pathogen found to underlie aseptic meningitis in human patients [1].

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57.2 Classification

Among the Arenaviridae endemic to South America and Africa, there are various viruses which classically cause viral haemorrhagic fevers. There are also certain viral species which do not infect humans or do not cause disease when transmitted to a human being. The majority of the Arenaviridae are still actively being researched [1].

The Arenaviridae are classified into two divisions. One group can infect members of the Murina subfamily, the other group those of the subfamily Sigmodontina, within the family Muridae. The former are found in the Old World (i.e. Eastern Hemisphere), while the latter are indigenous to the New World (i.e. Western Hemisphere). Those Arenaviridae infecting Western Hemisphere rodents are assigned to 3 clades, labelled A, B and C, which reflect different lineages. LCMV can, in fact, infect both the Murinae and Sigmodontinae, but it is taxonomically placed among the Old World viruses. The following list gives the names of the most prominent Arenaviruses and indicates which rodent species serves as the reservoir of infection [1].

57.2.1 LCMV-Lassa Virus Complex (Eastern Hemisphere)

57.2.1.1 Lymphocytic Choriomeningitis Virus

- The reservoir of infection consists of 3 rodent species: *Mus musculus*, *Mus domesticus* (both are house mice) and *Mesocricetus auratus* (the Syrian hamster).
- This virus is found in Europe, Asia and North and South America.
- It is associated with human habitation and grassland.
- Infections occur in September of October.

Human patients come into contact with the virus within houses [1].

57.2.1.2 Lassa Virus

- The rodent reservoir is members of the genus *Mastomys* (the multimammate mouse).
- The virus inhabits West Africa.
- Viruses are associated with areas of Savanna or where trees have been cut down.
- Infections occur between January and April.
- The virus mainly comes into contact with a human within houses [1].

57.2.1.3 Mopeia Virus

- The infective reservoir is *Mastomys natalensis.*
- The viral habitat is Savanna in Southern Africa.
- It is unclear at what time of year infections usually occur, nor is it known how the virus usually comes into contact with humans [1].

57.2.1.4 Mobala Virus

- The infective reservoir is members of the *Praomys* genus, the soft-furred rats.
- The viral habitat is Savanna in the Central African Republic.
- It is unclear at what time of year infections usually occur, nor is it known how the virus usually comes into contact with humans [1].

57.2.1.5 Ippy Virus

- The infective reservoir is members of the *Arvicanthus* genus, the Nile grass rat.
- The viral habitat is grassland and savanna of the Central African Republic.
- It is unclear at what time of year infections usually occur, nor is it known how the virus usually comes into contact with humans [1].

57.2.1.6 Lujo Virus

- The reservoir of infection is not yet known.
- The habitat is an unknown location within Zambia. It probably occupies a similar ecological niche to Lassa virus.
- It is unclear at what time of year infections usually occur, nor is it known how the virus usually comes into contact with humans, but similarities with Lassa virus are suspected [1].

There are also a number of other Eastern Hemisphere members of the Arenaviridae, namely the South African Merion Walk virus, the Tanzanian Morogoro, the Guinean Kodoko and the Australian Dandenong [1].

57.3 Pathophysiological Features

57.3.1 Characterisation of the Virus

The Arenaviridae are spherical particles, wrapped in an envelope of plasma membrane derived from the host and with a diameter of between 50 and 300 nm. The spherical form coexists with other shapes. The virion is encased by an envelope studded with irregularly spaced glycoproteins, which appear as clubs or spikes, and are named GP1 and GP2 [1].

The arenavirus genome consists of 2 subgenomic segments, which contain 2.4Mbp and 1.3Mbp. The former is referred to as the L (=large) segment, the latter as the S (=small) segment. The genome contains predominantly anti-sense sequences, but there are positive sense sequences at the 5′ end of both the subgenomic segments. Thus, although arenaviruses are generally classed as anti-sense viruses, they may be more properly considered ambi-sense viruses. The L and S segments contain a long open reading frame, with no overlap, but read in opposite directions. There is a viral RNA-dependent RNA polymerase encoded within the L segment, as well as the Z protein. This molecule plays a key part in viral budding

from the host cell as well as other roles inside the host cell. The nucleocapsid protein (N) and glycoprotein precursor polypeptide (GPC) are both encoded on the small subsegment. The GPC undergoes cleavage at various points and lycosyl residues are added, thereby producing the glycoprotein spike proteins. The viral N protein provokes the most vigorous antibody response. Immunoglobulins targetting the N protein are detected with an indirect fluorescent antibody (IFA) test for diagnostic purposes [1].

The Arenaviruses get their name from the presence of grain-like structures within the virus when visualised using electron microscopy. These structures are between 20 and 25 nm across and resemble sand (arena = sand in Latin). They are in fact ribosomes belonging to the host and captured, while the arenavirus buds off from the host cell. No functional role has yet been assigned to the ribosomes captured in this way.

57.3.2 Lassa Virus (The Cause of Lassa Fever) [1]

Lassa fever is an endemic disease in West Africa. The first cases were reported in Nigeria, but there have since been cases in Sierra Leone, Liberia and Guinea. The Lassa virus was first identified in members of the genus *Mastomys*. These rodents are often found in human dwellings, which they actively seek to enter. The dry season corresponds to when Lassa fever becomes frequent. Lassa fever is unusual among arenoviruses insofar as human-to-human transmission is possible. The viruses endemic to South America also possess some capability of human-to-human transmission [2–4]. Lassa fever takes between 3 and 16 days to incubate. The risk of a fatal outcome overall is 1%. However, for pregnant women in the last trimester, there is a greater than 80% risk of death, and foetal loss virtually invariably occurs. Aborting the foetus makes maternal death somewhat less probable [1].

57.4 Clinical Presenting Features of Lassa Fever

In 80% of patients with Lassa fever, the clinical features are sufficiently mild that the diagnosis may be missed. It has been estimated that Lassa fever affects multiple systems and is of high severity in 20% of cases overall. There is an incubation period lasting between 1 and 3 weeks. The disease has an insidious onset, with symptoms of pyrexia, weakness, feeling generally unwell, arthralgia and lumbar pain [1].

If the severity is high, the patient may be unable to rise from bed, become dehydrated and experience pain in the abdomen. There may be swelling of the face and cervical region [1, 5, 6].

57.5 Physical Examination

The majority of cases present with mild pyrexia, headache and feeling generally unwell. If Lassa fever is of high severity, respiratory distress and features of shock are potential manifestations. There may be swelling of the face, with bleeding from the gingiva, nose and oral cavity. Furthermore, the patient may be severely nauseous and vomit. There may be pain in the chest, back and abdomen. Central nervous system involvement may appear as a tremor, cognitive disorientation, encephalopathy and fits. There should be no localising signs [1].

The cerebrospinal fluid does not show any abnormalities [1]. The aminotransferases in serum are sometimes raised. The only cause of viral hepatitis in which the aspartate aminotransferase level is well above that of alanine aminotransferase is Lassa fever. This pattern of abnormality would normally indicate alcoholic hepatitis. No more than 15–20% of cases feature haemorrhage. Where haemorrhage does occur, it is from the mucous membranes and is not severe [6].

57.6 Complications

The complication which occurs with highest frequency in Lassa fever, irrespective of disease severity, is hearing loss. This complication is present in approximately 30% of cases and is commonly irreversible [1].

Pregnant patients are at elevated risk of a fatal outcome. The death of the foetus occurs in approaching 95% of cases [1].

Overall, mortality from Lassa fever is between 15 and 50% [6].

57.7 Clinical Management

For patients infected with an arenavirus of any sort, if the disease is of mild severity, no particular treatment is indicated [7]. Infections with arenaviruses leading to haemorrhagic fevers do, however, need to be treated specifically and with attention to alleviating symptoms [1].

Palliation of symptoms is all that is required in cases of LCMV [1]. By contrast, where Lassa fever is symptomatic or in the haemorrhagic fevers of South America, patients require aggressive clinical interventions if the risk of severe morbidity or a fatal outcome is to be diminished [1].

Careful management of the arterial tension, as well as ensuring adequate hydration and satisfactory electrolyte balance has the potential to prevent fatal outcomes.

Ribavirin, an antiviral agent, is utilised for the treatment of Lassa fever, in addition to the haemorrhagic fevers of South American type.

Benefit has been demonstrated for convalescent human plasma in treating infections with Junin virus. However, this use of plasma does not offer similar benefit in Lassa fever. The most probable explanation for this situation is that the neutralising immunoglobulins in Lassa fever cases are present at a lower concentration and do not begin to be synthesised in large numbers until after the main illness has passed [1].

57.8 Auditory Impairment

Deafness of sensorineural type affecting one or both ears and of acute onset is seen in around 1 in 3 cases of non-fatal Lassa fever. In many cases, this hearing loss is irreversible [8]. According to calculations by the WHO (World Health Organisation), globally there are 368 million people living with hearing loss, mostly in developing countries [9]. Sudden-onset sensorineural deafness occurs through trauma to the hair cells of the cochlea or the nervous tissue of the inner ear. By definition, it must involve a loss of at least 30 dB affecting 3 or more frequencies and develop in 72 hours or less [10]. Therapy involves fitting hearing aids, or, in certain patients, a cochlear implant [10]. Unfortunately, in the countries where Lassa fever is endemic, hearing loss of this type cannot usually be treated [9, 11]. There are numerous reasons for deafness to develop in adults, including medications with ototoxicity, occupation-related hazards, neoplasia, otitis and viral infections. The latter category includes measles, mumps, rubella or HIV. Lassa fever is another cause of deafness, but its true prevalence is unknown in the countries where it mostly occurs [12].

At present, Lassa fever is a threat to a population of around 37.7 million [13]. As foreign travel increases and epidemics become more likely, as well as the possibility that Lassa virus may be weaponised, research into the pathogenesis of sudden sensorineural deafness secondary to Lassa fever is more needed than ever. An important piece of missing information is the prevalence of this complication. A deeper knowledge of the pathogenesis would guide the development of vaccinations and medications for use in Lassa fever and help direct therapy for Lassa fever-associated hearing loss [14].

57.9 Pathogenetic Mechanisms Involved in Sensorineural Deafness Secondary to Lassa Virus

Cummins et al. undertook a study examining any association between Lassa fever and auditory impairment [8]. The study used a case-control design, with 3 different groups involved: cases where the patient was admitted to hospital with pyrexia, healthcare workers, individuals whose serology was positive for Lassa fever and people living within a particular region of Sierra Leone (the Eastern Province) with acute onset hearing loss. In the hospitalised patients, the rate of acute onset uni- or bilateral hearing loss in those with positive Lassa serology was 29% in the period 5 to 12 days following resolution of pyrexia. Seroconversion was invariably present

prior to the first manifestations of deafness. In 17.6% of those with sudden sensorineural deafness secondary to Lassa fever, the condition was irreversible. Sensorineural deafness did not occur in any of the patients with pyrexia whose Lassa serology was negative. In the group consisting of healthcare staff and first-year doctors who had a positive result on serology for Lassa fever, if the individual had positive serology for anti-Lassa virus immunoglobulins, there was a 17.6% risk of sensorineural deafness. This rate was elevated compared to a rate of just 3% (2 of 74 ears tested) in those individuals who had negative serology for Lassa virus. Meanwhile, some 81.2% of the individuals living in the Eastern Sierra Leone Province who had evidence of sensorineural deafness had positive serology for Lassa virus, whereas only 18.8% of those without sensorineural hearing loss had positive serology. Of the cases with positive serology and sensorineural deafness, the severity of impairment was at 71.9% (either unilaterally or bilaterally) [8, 14].

The possibility that sensorineural deafness following recovery from Lassa fever is due to ribavirin has also been researched, since this agent is known to be ototoxic [15]. Neither the prognosis nor the way the deafness developed was found to fit with the pattern of ribavirin use, however, which implies that ribavirin is not responsible. The fact that use of ribavirin does lower the level of viraemia but does not prevent sensorineural deafness from occurring shows also that the circulating virus level does not explain the auditory deficit. Indeed, there is no correlation between the risk of sensorineural deafness and the circulating viral titre, liver function tests, or clinical severity. Taken together with the timing of the onset of deafness, these facts have been taken as evidence that sensorineural hearing loss in Lassa fever is not a direct result of the pathogen, but rather of the immune system's response [8, 14].

A Nigerian study of case-control design examined longer term outcomes in cases of Lassa fever where sensorineural hearing loss developed within the acute stage of the illness [16, 17]. Sensorineural deafness of early onset and affecting both ears was found in 13.5% of patients where Lassa virus was confirmed by reverse transcriptase DNA amplification, but in none of the controls who had pyrexia but no confirmation of Lassa virus infection. Some 60% of patients with sensorineural deafness following Lassa fever had positive serology for immunoglobulin M. The death rate, notably, was also more elevated in cases of Lassa fever where sensorineural deafness developed than in cases without hearing loss (60% vs. 21.9%, respectively). The study authors pointed to the fact that immunoglobulins were not detectable in all cases of Lassa fever-associated deafness and that deafness was a risk factor for a fatal outcome, using this to argue that sensorineural deafness was probably not solely due to the immune response but was also directly caused by the pathogen itself [17]. There are, however, significant differences between the definitions used by Cummins et al. and this study, in particular the use of a time-based criterion for diagnosing early onset of sensorineural deafness (i.e. in under 21 days), rather than the use of seroconversion or entering convalescence, which were relied upon by Cummins et al [8, 17] There is a need for future research to standardise the definitions of Lassa fever-related sensorineural deafness when investigating the pathogenetic mechanism by which hearing loss occurs and to allow a more rational approach to treatment. Treatments which have been attempted for sensorineural

hearing loss in Lassa fever include corticosteroids, hyperbaric oxygen delivery, vasodilation of the labyrinth vessels and vitamin supplementation, alongside fitting of hearing aids. No benefit has been demonstrated for any of these treatments so far [17]. It is possible that the lack of benefit from these interventions is due to the fact that Lassa virus produces widespread nervous injury and only cochlear implantation has the potential to improve deafness [14, 17].

One proposed way in which sensorineural deafness may be caused by the immune response is by immunoglobulins accidentally targetting self-antigens in the cochlear, resulting in the loss of hair cells [18, 19]. This explanation cannot, however, account for where sensorineural deafness manifests but no seroconversion occurs [17]. Cochlear hair cells have been noted to sustain minimal damage, which may be directly attributable to the virus. Mice which are deficient in Stat1 generate CD3+ lymphocytes and suffer sensorineural hearing loss, whereas mice deficient in the R gene produce Interferon alpha/betagamma and do not develop deafness. This evidence may corroborate the pathogenetic mechanism proposed by Cummins et al., which attributes injury to the immune response [8, 20]. However, further studies will be required to full understand the details of such a pathogenetic mechanism [14].

The Lassa virus mainly attacks monocytes, macrophages and dendritic cells, thereby disrupting their co-ordinated action. Cells of the myeloid series infected with Lassa virus cease triggering a response by the adaptive arm of the immune system [21]. Furthermore, Lassa virus attacks the human hepatic and renal tissues, as well as the spleen, adrenal glands and bone marrow [22]. Lassa virus is detectable in cerebrospinal fluid of both humans and other species, which indicates that the pathogen can invade the central nervous system [23, 24]. It is common for patients who survive Lassa fever to mount a swift and vigorous T-lymphocytic response, absent in those who go on to die from the disease [21]. As is the case with LCMV, survival is enhanced by a rapid T-lymphocytic response, albeit at the risk of secondary injury due to immune overreaction [25]. It has been demonstrated, using an animal chimaera, that T-lymphocytes play a key role in the pathogenetic mechanism of Lassa fever. In this model, even when the circulating viral level was elevated, reducing the numbers of CD8+ T-lymphocytes was an effective way of preventing a fatal outcome [14, 26].

Sudden onset of sensorineural deafness may also occur with medications of known ototoxicity; the likely way this occurs is also through an immune mechanism. ROS (reactive oxygen species) are generated by activated B-lymphocytes in which the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) has been translocated to the nucleus following stimulation by proinflammatory cytokines, notably interleukins 1β and 6. Eventually, the mitogen-activated protein kinase (MAPK)–c-Jun N-terminal kinase (JNK) pathway becomes active and this then causes cochlear hair cells to undergo apoptosis. Moreover, the atonal transcription factors Atoh1 and Hath 1, which govern growth of the cochlear hairs, are inhibited, preventing them regrowing [14, 19, 27, 28].

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