



Lymphocytic Choriomeningitis Virus (LCMV) Infection in Children and Hearing Loss

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55.1 Introduction

Lymphocytic choriomeningitis virus (LCMV) is a single-stranded RNA virus with an envelope which is within the Arenaviridae viral family. In developed nations, it may infrequently be responsible for infection of the central nervous system [1].

LCMV is found in the saliva, urine, seminal fluid, milk and faeces of rodents. The species which harbour LCMV and can shed virus in this way include rats, mice and hamsters. There is an elevated risk of infection by LCMV in children growing up in poverty, where they may eat food contaminated by infected animal urine, may get contaminated matter into cuts or injuries, or may breathe in viral particles [2].

The first description of LCMV being transmitted vertically via the placenta in an American child was in 1992, although the first report of vertically transmitted LCMV is from England and dates from four decades earlier [2]. Transplacental infection mostly occurs while the virus is detectable within the mother's bloodstream [2]. The peak incidence of infections is over the winter period, as rodents tend to invade patients' homes at that time in search of food and shelter [1].

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55.2 Definition

LCMV (Lymphocytic choriomeningitis virus) is a single-stranded RNA virus. It is within the *Arenaviridae* grouping. This viral family also includes the Lassa, Argentine, Bolivian and Venezuelan haemorrhagic fever viruses. The reservoir for infection is rodents. In mice, infection with LCMV does not result in any symptoms, although hamsters may sometimes exhibit signs of the infection. The virus can be transmitted to a human host when virally contaminated faecal particles are inhaled, ingested, or brought into close proximity. LCMV causes major teratogenic effects on a foetus and is usually a self-limiting infection producing pyrexia and consisting of two phases. Recently, LCMV has also been recognised as a pathogen which may cause congenital infection [3]. The risk of contracting LCMV is raised in people who live in proximity to infected animals or whose occupation exposes them to contact with rodents. Thus, employees who handle pet rodents or laboratory animals have potential infective exposure. There have also been cases noted in which infection has occurred when an organ was transplanted [4–7].

55.3 Pathophysiology

Once the virus invades the body, whether via the respiratory or gastrointestinal systems or by crossing the skin or a mucous membrane, it enters the bloodstream. If an infected organ is transplanted, this also results in viraemia. The pathogen can then take hold outside the central nervous system and produces a pyrexial episode with no clear focus. Some days later, a second episode of viraemia occurs and LCMV can then commonly invade the central nervous system. When this occurs, the characteristic features of meningitis or meningoencephalitis are observable [4].

The clinical features are considered to be produced by the host response to LCMV. The natural killer cells and cytotoxic T-lymphocytes synthesise and secrete interferon and further inflammatory signalling molecules in response to the virus [8]. Other than vertical transmission, or in the unusual case of organ transplantation, LCMV is not transmitted from one human host to another. Congenitally acquired LCMV is generally of considerably greater severity than when the infection is acquired at a later stage. The features may closely resemble those of toxoplasmosis or cytomegalovirus infection, when transmitted congenitally. As in cases acquired after birth, congenital forms of the disease are greatly shaped by the host response to infection. The T- and B-lymphocytic response is the means by which the host tissues are damaged. It is probable that LCMV transmitted transplacentally has a tropism for nervous tissues, becoming focused in the area of the growing central nervous system and eye [4, 9].

55.3.1 Acquired Infection

In acquired infections, the clinical presentation is non-specific. Pyrexia reaching 39–40 °C is commonly noted. There may also be a degree of bradycardia. The lymph nodes are diffusely enlarged and an exanthem of maculopapular type may also occur. Pharyngitis may be noted, but pharyngeal exudates are not seen. Nuchal rigidity is a frequent symptom where the virus has invaded the central nervous system [4].

There are also a number of other, less frequently encountered, clinical presenting features, such as joint inflammation affecting the metacarpophalangeal and proximal interphalangeal joints, enlargement of the liver and spleen, papilloedema, hearing loss, or paralysis. There may also be features indicating orchitis affecting a single testis, myocardial inflammation of viral type, pneumonitis, psychosis, transverse myelitis, Guillain-Barré syndrome, hydrocephalus (which may be temporary or persistent) and encephalitis [4].

55.3.2 Congenital Infection

Congenitally infected infants are usually of the expected size for their gestational age and are not born prematurely. There are abnormalities of the eye in around 88–93% of cases. These abnormalities include chorioretinopathy, chorioretinitis, cicatrization, atrophic areas, nystagmus, esotropia, unusually small eyes, cataracts and inflammation of the vitreous humour [10].

Macrocephaly is present in around 34–43% of cases [10]. It was reported that 90% of neonates who underwent imaging had features of either hydrocephalus or intracranial periventricular calcifications. Microcephaly occurred in between 13 and 38% of cases, the condition generally resulting from either dysplasia or atrophy in the developing cortex [10].

Deafness is present in around 7% of infected neonates and generally affects both ears. It is of sensorineural type and it is either severe or total [11].

The fact that LCMV infections principally affect organ systems beyond the central nervous system (except for infrequent involvement of the skin, manifested as a rash, enlargement of the liver and spleen or myocarditis) acts as a valuable diagnostic clue [3, 4].

55.4 Laboratory Investigations

55.4.1 Serological Testing

Serological testing using an immunofluorescent method to detect specific IgM and IgG antibodies is marketed and is the best technique available [4].

The US Centres for Disease Control and Preventions (CDC) utilise an ELISA (enzyme-linked immunosorbent assay) for detection of immunoglobulins M and G in cerebrospinal fluid. There is a complement fixation assay available, however it suffers from low sensitivity and is not recommended for diagnosis of LCMV infection, whether congenital or acquired [4].

At an early stage in LCMV infection, the virus can be detected in blood samples. As the disease progresses, the virus becomes detectable in cerebrospinal fluid or, in unusual cases, from a urine sample or from a swab of the nasopharynx, if cell culture is used or there is direct injection into the brains of very young laboratory mice [4].

55.4.2 Analysis of Cerebrospinal Fluid (CSF)

CSF may contain abnormally high amounts of protein. In 25% of cases, the glucose concentration is below normal, but in the remaining 75% the glucose level is normal. There is generally an increased white cell count, with elevated lymphocytes. The level ranges from below 30 to above 8000. There is one case reported in the literature in which eosinophilic meningitis occurred [4].

55.4.3 PCR Amplification of Viral DNA

At present, the use of PCR to detect LCMV is confined to research settings, although a method is under development for routine clinical use [12].

55.5 Auditory Impairment

It has already been established by research that fatality is a rare outcome in cases where aseptic meningitis or encephalitis occur as a result of LCMV infection. In humans, LCMV does not appear to produce persistent infections. Following acute infection, there is complete elimination of the pathogen. Nonetheless, in common with other pathogens that invade the central nervous system, especially if encephalitis results, transient or irreversible neurological injury may occur. There are reported cases of sensorineural hearing loss and chronic arthritis following LCMV infections [13].

If a pregnant woman becomes infected with LCMV, there is a risk of vertical transmission. Foetal infection within the initial trimester of pregnancy may have a fatal outcome for the foetus, whereas infections in the middle and final trimester may result in congenital anomalies. These anomalies may be grave and irreversible, such as damage to the visual system, learning disability and hydrocephalus. In some such cases, the mother may give a history of a flu-like episode whilst she was pregnant, but this is often absent from the history [13]. The risk of mortality in the

mother is no higher than 1%, thus the vast majority of patients survive the episode [13].

Lymphocytic choriomeningitis virus (LCMV) is a single-stranded RNA virus with an envelope which is within the *Arenaviridae* viral family. It is increasingly recognised as a cause of congenital abnormalities [14]. The primary hosts for LCMV are rodents, including the house mouse, and these animals act as the infective reservoir [15]. Transmission of the virus to a human host is generally via the mouse's urine, faeces or saliva. Since rodents tend to invade human dwellings at the coldest time of year, winter is the peak period for human infections to occur [3]. Although human-to-human transmission in normal circumstances is very rare, in the setting of organ transplantation, this route of transmission becomes possible [15, 16].

In adult patients who have no immunosuppression, infection with LCMV generally either produces no symptoms or those of an upper respiratory tract infection, namely pyrexia, headache, nausea and vomiting. Aseptic meningitis or meningoencephalitis are infrequent complications. In pregnant women, the highest risk is for spontaneous abortion to occur. Infections during pregnancy, particularly in the initial and middle trimester, have the potential to cause birth defects, especially microcephaly, hydrocephalus, ventriculomegaly, pachygyria, cerebellar hypoplasia, chorioretinitis, periventricular calcification and deafness [3, 15, 17]. Whereas cytomegalovirus (CMV) or rubella infections in the foetus are strongly associated with deafness, visual impairment and microcephaly are considerably more typical of foetal LCMV than deafness. Furthermore, unlike CMV and rubella, LCMV does not result in enlargement of the liver and spleen, which helps to distinguish between the likely causes in congenital deafness [14, 16].

For confirmation of the diagnosis of congenital LCMV, ELISA for detection of immunoglobulins G and M is a suitable laboratory investigation. Auditory impairment in cases of congenital LCMV is somewhat unusual, and the ears may not be equally affected. The hearing loss is of sensorineural type and is severe or profound [14, 17].

55.6 Clinical Management

Ribavirin is an agent sometimes used to treat LCMV infections affecting adult patients. It inhibits RNA synthesis and the addition of the 5' cap to the RNA string by the virus. Unfortunately, there are no trials in patients which demonstrate definite benefit from use of the agent and there are known adverse effects of ribavirin, especially haemolytic anaemia. Since this medication has been shown to be teratogenic in multiple animal species, it is not suitable for administration in pregnancy [15]. Another agent which may be potentially beneficial in LCMV infections is favipiravir. Since this agent inhibits RNA-dependent RNA polymerase, it may treat a large number of different viruses of RNA types. However, currently, action against LCMV has only been demonstrable in vitro [3, 16].

In suitable candidates, auditory impairment should be compensated using hearing aids or other assistive technologies, according to the child's needs. There may be limited success in remedying the effects of severe or profound auditory impairment of sensorineural type in paediatric patients with congenital LCMV, in whom injury to the eighth cranial nerve explains the loss. This group of patients invariably also have a severe type of visual loss, therefore treatment of hearing loss should at least be tried, as any benefit (even if small) may improve quality of life [16].

There are no specific therapeutic modalities currently available for LCMV infection. The evidence on ribavirin so far indicates that this agent does exert an antiviral action on LCMV in vitro, but this has not yet been satisfactorily established in vivo. Although the evidence base is incomplete, the recommendation in organ transplant recipients found to have acquired LCMV is administration of ribavirin and a reduction in the degree of immunosuppressant treatment [6, 18].

In the future, treatment options may include favipiravir (which is already known to prevent viral reproduction) and agents which inhibit the synthesis of pyrimidines. These latter are still at the developmental stage [3, 19].

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