Congenital cytomegalovirus infection

Amelia Joseph
Nikunj Mahida
Gemma Clark
William Irving
Shiu Soo

Abstract

Congenital cytomegalovirus is the most common intrauterine infection and the leading non-genetic cause of sensorineural hearing loss. Worldwide, the birth prevalence is estimated at 7 per 1000 with the highest rates seen in developing countries. The highest intrauterine transmission rates and risk of neurodevelopmental sequelae are associated with primary maternal infections. Transmission occurs less frequently after non primary maternal infections due to reactivation or reinfection. 10–15% of infected infants are symptomatic at birth, with neurological symptoms present in two-thirds. Infants who are asymptomatic at birth may go on to develop late neurodevelopmental sequelae, with sensorineural hearing loss being the commonest late consequence. Prenatal, neonatal and retrospective diagnosis can be challenging. Early treatment of symptomatic neonates with the antiviral drug valganciclovir can reduce the long-term neurodevelopmental sequelae. Universal or targeted screening for congenital CMV is not currently advocated. The development of an effective vaccine appears to be some years away. This review highlights the important considerations for clinicians regarding the diagnosis, investigation and management of children with possible or confirmed congenital CMV infection.

Keywords congenital infection; cytomegalovirus; ganciclovir; screening; sensorineural hearing loss; valganciclovir

Amelia Joseph ***BMedSci BMBS FRCPath PGCert MedEd*** *is Consultant Microbiologist in the Department of Clinical Microbiology, Nottingham University Hospitals NHS Trust, Nottingham, UK. Conflicts of interest: none declared.*

Nikunj Mahida ***MBChB MSc FRCPath*** *is Consultant Microbiologist in the Department of Clinical Microbiology, Nottingham University Hospitals NHS Trust, Nottingham, UK. Conflicts of interest: none declared.*

Gemma Clark ***BSc (Hons) PgDip MSc PhD*** *is Clinical Scientist in the Department of Clinical Microbiology, Nottingham University Hospitals NHS Trust, Nottingham, UK. Conflicts of interest: none declared.*

William Irving ***MBBCh FRCPath PhD*** *is Professor of Virology & Consultant Virologist in the Department of Clinical Microbiology, Nottingham University Hospitals NHS Trust, Nottingham, UK. Conflicts of interest: none declared.*

Shiu Soo ***MA PhD MB BChir FRCPath*** *is Consultant Microbiologist in the Department of Clinical Microbiology, Nottingham University Hospitals NHS Trust, Nottingham, UK. Conflicts of interest: none declared.*

Introduction

Human cytomegalovirus (CMV) is one of the most frequent congenital infections in humans. It is the commonest non-inherited cause of childhood sensorineural hearing loss (SNHL) as well as a significant cause of neurodevelopmental delay. It is under-diagnosed because the majority of maternal infections during gestation are asymptomatic. Moreover, many newborns are also asymptomatic at birth but may manifest signs later in life and retrospective diagnosis is difficult.

Natural history

CMV is an enveloped, double-stranded DNA β herpesvirus. Primary entry is usually via a mucosal site, followed by a viraemic phase where the virus infects a wide range of human tissues and subsequent secretion of the virus in bodily fluids such as saliva, urine, breast milk and genital secretions. The primary infection is usually asymptomatic in the immunocompetent host, but may produce an infectious mononucleosis-like syndrome in around 10% of older children or adults.

Infection causes well described features in human cells such as cytomegaly, intranuclear inclusion bodies and multinucleated giant cells. In immunocompetent individuals this is followed by an immune response, clearance of the viraemia and subsequent viral latency. In the latent phase, the virus either stops replicating or undergoes low level replication at an undetectable level inside blood monocytes, tissue macrophages and bone marrow stem cells. Intermittently, the virus reactivates from these sites, leading to viraemia and viral shedding in bodily secretions.

Epidemiology

Seroprevalence of CMV increases with age and is closely related to the socioeconomic levels within a community. In developed countries 50% of women of child-bearing age are seropositive. In developing countries CMV is often acquired earlier in life due to higher breastfeeding rates and crowded living conditions, and up to 90% of childbearing aged women may be seropositive. The incidence of congenital CMV infection parallels maternal CMV prevalence. Acquisition of CMV during pregnancy often occurs through contact with young children who may shed the virus in their urine and saliva, or through sexual transmission from a partner. The reported rates of congenital CMV infection in developed countries are between 0.6% and 0.7% of live births, with rates in developing countries of between 1% and 5%.

Routes of transmission

Vertical transmission of CMV can occur through three routes: intrauterine, intrapartum and post-natal. Intrauterine transmission is the most important route because it leads to congenital infection and its subsequent complications. Intrauterine transmission occurs through transplacental maternal leucocyte translocation, or direct infection of the placenta and amniotic fluid. Congenital CMV may result from either a primary maternal infection, reactivation of the latent maternal virus, or reinfection with a different viral strain during pregnancy. Primary maternal infection occurs in 1–4% of seronegative pregnant women. Transmission rates vary from 30 to 40% in the first trimester to up to approximately 75% in the third trimester. However, transmission to the fetus in the first trimester is associated with the greatest risk of severe fetal infection and subsequent

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developmental sequelae. Congenital infection after non-primary infection in the mother has significantly lower rates (1–3%) of fetal transmission and sequelae.

Intrapartum transmission occurs through exposure to the virus in the maternal genital tract. Around 10% of seropositive mothers shed CMV in the genital tract at the time of delivery, with about 50% of exposed neonates acquiring infection through this route. Post-natal transmission occurs primarily through viral shedding in breastmilk and in oral secretions, and along with intra-partum transmission, usually causes asymptomatic infection in term neonates. In premature neonates very early acquisition of CMV may lead to more significant symptoms.

Pathogenesis

Studies of fetuses and neonates with congenital CMV show that the virus infects numerous cell types, with associated inflammatory infiltrate and organ damage. Brain cells of many different types show inclusions with focal necrosis. Epithelial cells of the semi-circular canals, vestibulae, cochlear and other ear structures are affected. Cytomegalic cells and focal necrosis can be seen in the retina, liver, lung and kidney. In addition to direct fetal effects, villitis and vascular necrosis can impair placental function. Neonates with congenital CMV infection are less able to control the infection due to immaturity of the immune system. This contributes to the commonly progressive nature of SNHL. Infants infected early in life may continue to shed virus in their urine and other secretions, acting as reservoirs of the virus.

Clinical manifestations

Symptomatic congenital CMV infection

Table 1 summarises the common clinical and laboratory findings recorded in a review of 106 infants with symptomatic congenital CMV. 10–15% of congenitally infected neonates are symptomatic at birth, and jaundice, petechiae and hepatosplenomegaly are the most common clinical signs. Prematurity, small for gestational age growth parameters, thrombocytopenia and anaemia are frequently present. Other features include chorioretinitis, hepatitis, pneumonitis, colitis, and bone or dental abnormalities. Some degree of neurological abnormality is present in around two-thirds of symptomatic neonates.

Neonates with symptomatic congenital CMV at birth should be considered high risk for long-term sequelae even if initial clinical findings are mild. Studies have shown that between 40 and 90% of symptomatic newborns develop long-term neurodevelopmental sequelae. SNHL occurs in approximately 35%, visual impairment in 22–58%, and cognitive deficits in up to two-thirds. Computer tomography, ultrasound and magnetic resonance techniques can provide evidence of CNS involvement with abnormal CNS imaging being predictive of neurological sequelae. Mortality rates in symptomatic, congenitally affected infants have been reported as ranging from 4% to as high as 20–30%.

Radiological features

Prenatal ultrasound scanning may detect structural or growth abnormalities caused by CMV infection. However, the sensitivity and specificity can be poor as these abnormalities are common to many other congenital conditions. Ultrasound findings are present in less than 25% of congenitally infected fetuses, therefore negative scans can only suggest reduced risk, but cannot exclude congenital CMV infection. Intrauterine growth restriction, abnormal amniotic fluid volume (usually oligo-rather than polyhydramnios), hyperechogenic bowel, pleural effusions and liver calcifications may be visible. Microcephaly, cerebral ventriculomegaly and intracranial calcifications are the commonest neurological abnormalities detected on prenatal ultrasound scanning. Cerebral ultrasound abnormalities are strongly associated with a poor prognosis in relation to neurological and cognitive development. Placental pathology, for example placental enlargement or infarcts, may also be visible on ultrasound.

Clinical findings and laboratory abnormalities in symptomatic congenital CMV infection

Clinical finding	Frequency (%)
Petechiae	76
Neurologic, one or more of the following:	68
Microcephaly	53
Lethargy/hypotonia	27
Poor suck	19
Seizures	7
Jaundice	67
Hepatosplenomegaly	60
Small for gestational age (weight $<10^{th}$ centile)	50
Prematurity <38 weeks	34
Laboratory finding	
Elevated ALT >80 units/L	83
Thrombocytopenia $<100 \times 10^3/mm^3$	77
Thrombocytopenia $<50 \times 10^3/mm^3$	53
Conjugated hyperbilirubinaemia:	
Direct bilirubin >2mg/dL	81
Direct bilirubin >4mg/dL	69
Haemolysis	51
Elevated CSF protein >120mg/dL	46

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Table 1

Differential diagnosis

There are a number of congenital infections causing differential diagnostic problems including toxoplasmosis, rubella, parvovirus B19 and syphilis. Toxoplasmosis may cause cerebral calcifications, chorioretinitis and usually a macular, rather than petechial, rash. Rubella may present with petechiae, bone defects and SNHL. Parvovirus B19 can cause hepatomegaly and anaemia. Early congenital syphilis may cause hepatosplenomegaly, bony changes and lymphadenopathy. Neonatal infections may also mimic the symptoms of congenital CMV. Disseminated herpes simplex infection, enteroviral infection and bacterial sepsis may have similar clinical or biochemical abnormalities. Non-infectious conditions including a large number of metabolic disorders may also produce similar features.

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