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Congenital cytomegalovirus – who, when, what-with and why to treat?

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Summary Congenital cytomegalovirus (CMV) is the commonest cause of congenital infection worldwide and the leading non-genetic cause of sensorineural hearing loss in children. Appropriate investigations and timely decision on treatment is required as studies have shown that treatment with antiviral therapy leads to improved hearing and neurodevelopmental outcomes in the long term when started in the first month of life. This paper outlines the epidemiology, investigations in the diagnosis of congenital CMV infection and current evidence surrounding treatment.

Introduction

Human cytomegalovirus (CMV), a member of the *Herpesviridae* family of viruses, is the commonest cause of congenital infection worldwide. Congenital CMV infection can result in serious congenital malformations, neurodevelopmental delay, and it is the leading non-genetic cause of sensorineural hearing loss in children.

Epidemiology

CMV is found universally but seroprevalence varies widely between different geographic locations. Within a population, CMV's seroprevalence shows an age-dependent rise and correlates with race and socioeconomic status.[1]

Around 40% of women of reproductive age are seronegative in developed countries and 1-3% of these women can develop primary CMV infection during pregnancy. Women who are most at risk include adolescents, women with frequent contact with young children such as day care workers and mothers with young children themselves. Transmission rate to the fetus is 30–40% in primary maternal CMV infection. Importantly, CMV reactivation or reinfection can occur in women who are seropositive prior to pregnancy.[2,3] The rate of CMV transmission is only around 1% after reactivation or reinfection. However, in populations with high seroprevalence, there will be more infants with congenital CMV born to mothers who have had previous CMV infection than to women with primary seroconversion in pregnancy.[4–6] See Figure 1.

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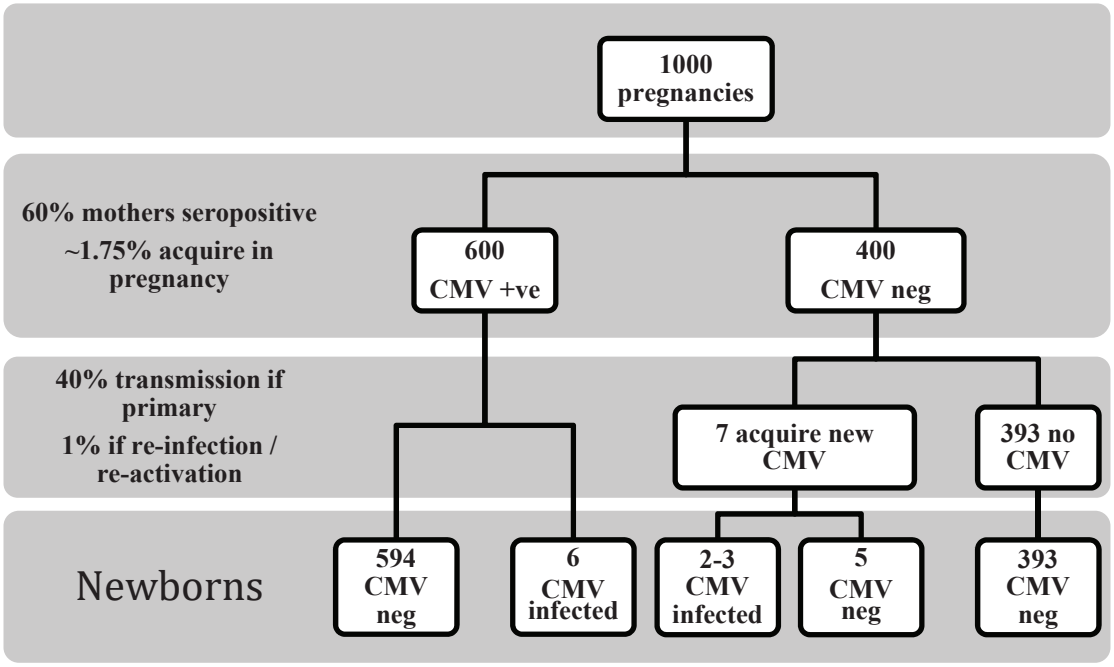

Figure 1 Illustration of the epidemiology of congenital CMV infection.[9] In the context of the United Kingdom, with 700,000 births per year, there will be 4200 newborn infants with congenital CMV contributed by mothers who are already seropositive and 1400 to 2000 newborn infants with congenital CMV secondary to primary maternal infection.

Primary and non-primary maternal CMV infection leads to an overall incidence of congenital CMV of approximately 0.4–0.8% in developed countries.[7] Risk of transmission is higher with later stages of pregnancy but early transmission is associated with more severe consequences for the fetus.[8]

Definitions and clinical features

Approximately 10–15% of infants with congenital CMV present with symptoms at birth. This is termed symptomatic congenital CMV infection where the infant presents with signs and symptoms in utero and/or in the immediate postnatal period. There is no standard definition for symptomatic CMV infection but studies have used the presence of one or more of the following to define symptomatic disease – thrombocytopenia, petechiae, splenomegaly, hepatomegaly, hepatitis, intrauterine growth restriction (IUGR), central nervous system involvement such as microcephaly, intracranial calcifications, chorioretinitis, sensorineural hearing loss, or detection of CMV in cerebrospinal fluid.[10] An example of symptomatic congenital CMV could be an infant, born at 36 weeks gestation, who had echogenic bowel on 20 week scan, and is noted to have hepatosplenomegaly and microcephaly with a birth weight of 1.9 kg. Up to two-thirds of these infants develop long-term neurological sequelae such as hearing loss, visual impairment and motor or cognitive deficit.[8]

The remaining 85–90% of newborn infants with congenital CMV presents with little or no signs and symptoms at birth and this is termed asymptomatic congenital CMV infection. However, around 15% of these infants can go on to develop sequelae, in particular sensorineural hearing loss.[8] Unfortunately, it is not possible to predict which infants will go on to develop late-onset hearing loss and it is these children that account for the majority of morbidity associated with CMV infection.

Since the advent of newborn hearing screening, more children have been diagnosed with congenital CMV, and the difference between 'symptomatic' and 'asymptomatic' cases has become less clear. Infants previously considered 'asymptomatic' may actually be found to have significant abnormalities on brain MRI, so the clinical paradigm is shifting as more infants are being detected and investigated.

Additionally, perinatal or postnatal CMV infection in premature infants can cause severe symptoms. Infection is acquired during or after birth via the birth canal, breast milk, or rarely via blood transfusion.[11,12] Whether this can lead to long-term sequaelae remains uncertain.

Diagnosis

During the antenatal period, diagnosis may be suspected when signs such as echogenic bowel, IUGR, intracranial calcification or ventriculomegaly are detected on ultrasound scans. However, these are non-specific signs with a wide differential diagnosis including chromosomal abnormalities, cystic fibrosis and other congenital infections like toxoplasmosis. Maternal serology is only helpful in the case of a primary infection with detection of IgM or IgG seroconversion and low avidity IgG. Fetal infection can be confirmed with detection of CMV DNA through polymerase chain reaction (PCR) testing via amniocentesis.[13]

In the newborn infant, diagnosis of both symptomatic and asymptomatic CMV infection can be made with detection of CMV DNA via PCR in body fluids or tissue samples (saliva, urine, blood, CSF and placenta) that were obtained before Day 21 of life. Dried blood spots from Guthrie cards can be used to detect CMV DNA by PCR retrospectively with variable sensitivity up to 80%.[14]

Perinatal/postnatal CMV infection diagnosis is more difficult as it requires demonstration of a negative sample