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Review Article

Postnatally Acquired Cytomegalovirus Infection in Preterm Infants: When we Need to Treat?

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Abstract

With an estimated prevalence of 0.6% in newborn infants, human cytomegalovirus (CMV) is the most common congenital infection worldwide [1]. Such an infection can result in a wide range of brain abnormalities, affecting both grey and white matter [2,3]. A postnatal infection with CMV is defined as an infection (proven by virus detection) within the first year of life but later than 2 weeks after delivery [4].

Transmission of the virus from mother to child may occur during pregnancy (congenital CMV infection), during childbirth (perinatal CMV infection) or after birth (postnatal CMV infection) [5]. Infected breast milk is the major source in the postnatal period. Recent studies utilizing the more sensitive polymerase chain reaction (PCR) technology have demonstrated the presence of CMV DNA in breast milk from more than 90% of seropositive women [4]. CMV infection acquired postnatally in a healthy, full-term infant is typically asymptomatic and without sequelae [6]. In contrast, very low birth weight (VLBW) preterm infants who acquire CMV postnatally may be completely asymptomatic or can have a sepsis-like syndrome with abdominal distention, apnoea, hepatomegaly, bradycardia, poor perfusion, and respiratory distress [4,7].

In this review, we will discuss the evidence of postnatal transmission of CMV to VLBW preterm infants, resulting clinical syndromes, diagnosis and treatment in symptomatic babies.

Keywords: *Postnatally; Cytomegalovirus; Preterm Infants*

Epidemiology of Postnatal CMV Infection

Acquisition/Transmission

Human cytomegalovirus (CMV) is ubiquitous. Acquisition of primary CMV infection is usually asymptomatic, and healthy subjects will usually be unaware that they have been infected. Once acquired, CMV remains latent in the cells primarily of the myeloid lineage [8].

The virus has been found to reactivate intermittently even in healthy people, but is generally kept in check by a functioning immune system. In immunocompromised hosts, including foetuses acquiring infection transplacentally from their mothers in utero, CMV disease may occur, affecting multiple organs and causing significant morbidity and mortality.

Newborns, in particular those of low birth weight or extreme prematurity, should also be considered as immunocompromised hosts. Research in this group has been limited, although serious morbidity following CMV infection has been increasingly reported [9].

Risk factors for postnatal CMV transmission:

Viral and transmission route risk factors

Infection in the neonatal period can occur either in utero, usually via the placenta, in which case it is referred to as congenital infection, or perinatally/ postnatally from the birth canal, maternal breast milk, blood transfusion, or other body fluids from infected people excreting virus [9]. The risk of CMV transmission via breast milk was first identified in the late 1960s by Diosi., *et al*. [10], and, in term infants, infection was found to be nearly always asymptomatic. Using PCR to detect CMV in breast milk separated into cell containing and cell-free whey fractions, it was found that up to 96% of seropositive women had CMV DNA detectable in their breast milk, termed DNAlactia [11]. Human CMV transmission has been found to occur despite maternally derived neutralising antibodies. No difference has been found between transmitters and non-transmitters with respect to age, race, duration of lactation, duration of human CMV excretion in milk, presence of human CMV specific IgA antibody or infectivity titres of virus in milk (using viral culture methods) [12]. However, a relationship has been found between both the proportion of breast milk intake given as fresh breast milk in the first 4 weeks of life and early appearance of virus in milk with acquisition of CMV infection [7,13].

The recognition of the risk of CMV transmission from blood transfusions has led to the universal use of leucodepleted and/or CMV-negative blood, virtually eliminating the risk of acquisition via this route [14].

Infant host risk factors

The developmentally immature preterm immune system may facilitate viral pathogenicity, although the exact mechanisms remain unclear. It has been proposed that subsets of NK cells are up regulated in infants with postnatal CMV infection, reflecting an inadequate T-cell response [15]. Despite heavily relying on innate immunity, antiviral cytokines such as IFN-a are produced in limited amounts in preterm infants [16].

Prevention of transmission of postnatal CMV

Severe symptomatic postnatal CMV infection may be prevented by treating or withholding infected breast milk. In the general population of preterm infants, the American Academy of Pediatrics suggests that the value of using fresh breast milk from seropositive mothers outweighs the risk of postnatal CMV infection [17]. However, in Germany, Austria and Switzerland untreated fresh breast milk is preferably not given to preterm infants < 32 week GA or < 1500 g BW because of the risk of postnatal CMV infection [18].

Freeze–thawing has been shown to decrease CMV viral titers and infectivity by 90–100% (depending mainly on the duration of freezing) [7]. Pasteurisation at 62.50C for 30 min (Holder pasteurisation) has been reported to efficiently eliminate CMV, but is also known to alter the immunological properties of breast milk [19]. A further method of pasteurising milk at high temperatures for a short time (5 s at 72 °C) is reported to decrease infectivity while preserving marker proteins, thus possibly minimising the adverse effects of heating, but this is not widely available [20].

The risk of CMV-negative babies acquiring CMV from banked breast milk from CMV-positive donors should be considered, but is not generally a problem in the UK, where milk is frozen, Holder pasteurised and then frozen again according to UKAMB 2003 guidance [21].

Diagnosis of Postnatal CMV Infection

Detection of CMV

A CMV PCR of a urine, blood or saliva sample is currently the most commonly used method to determine a postnatal CMV infection. At present, there is no gold standard for the diagnosis of postnatal CMV infection. However, a negative sample taken within 3 weeks postpartum and thereafter a positive sample is indicative of a postnatal CMV infection. This diagnostic standard is used in most studies reported so far [22]. CMV DNA can also be detected after extraction from dried blood spots (Guthrie cards) stored from all babies in the UK. A positive result can therefore be helpful in ascertaining whether a baby was congenitally infected or not [23].

Clinical signs and symptoms

CMV is able to affect various organ systems with varying degrees of severity, leading to a morbidity that ranges from mild and self-limiting to overt and life-threatening. Mortality in postnatal CMV infection in preterm infants is rarely reported in the literature. CMV sepsis-like syndrome (CMV-SLS) in preterm infants is commonly defined as the triad of apneas, bradycardia and gray pallor of the skin which are the most common clinical presentations of symptomatic postnatal CMV infection [24].

Other commonly described signs and symptoms of postnatal CMV infection with unknown prevalence, including acute hepatitis, hepatosplenomegaly and CMV pneumonia [25]. CMV enterocolitis, jaundice, cholestasis, petechiae and lymphadenopathy, are infrequently associated with postnatal CMV infection [22,26].

Laboratory abnormalities

Thrombocytopenia is the most frequently reported laboratory abnormality in postnatal CMV infection. Neutropenia, elevated liver enzymes and (mild) elevation of C-reactive protein are other reported parameters [27]. Frequently, blood abnormalities are the only manifestations of symptomatic postnatal CMV infection and only found coincidentally during standard clinical care of the preterm infant.

Neuroimaging

In term infants with congenital CMV infection, lenticulostriate vasculopathy recognized with cranial ultrasonography was present in 54.3% of the investigated infants [28]. Streblow., *et al*. [29], suggested that CMV infection of the susceptible brain may lead to necrotizing inflammation and subsequent mineralization of the wall of the lenticulostriate arteries. In a recent study by Nijman., *et al*. [30], diffusion tensor imaging was used in preterm infants with postnatal CMV infection and compared with non-infected preterm infants. At term-equivalent age, differences in the white matter microstructure were found in the occipital region.

Predictors of Severity Of Postnatal CMV Infection

Factors that are predictive of more severe symptomatic postnatal CMV infection are increasingly recognized and include GA and time of viral detection. Urine and saliva CMV load and differences in CMV genotype seem less suitable as a severity predictor [24].

Gestational age and birth weight

The main established predictors of severe symptomatic postnatal CMV infection are extreme prematurity and VLBW (<1500 g) [4,22,31].

Time of viral detection

Maschmann., *et al.* [25], demonstrated that the age of the infant at the time of first virus detection in urine correlated with the risk of symptomatic infection and depended on birth weight. The authors suggested that preterm infants with a greater birth weight and delayed transmission event are more able to cope with a primary postnatal CMV infection and therefore will experience an asymptomatic course.

Viral load

In the absence of an association of viral load with symptomatic postnatal CMV infection, it seems unlikely that viral load in urine, saliva or breast milk can be used as a predictor of severity [24].

Pre-existing morbidity

In preterm infants with severe comorbidity, postnatal CMV infection may aggravate the clinical course of a preexisting condition, but it is unlikely to cause symptoms in otherwise healthy preterm infants. It is largely confounded by GA as extreme prematurity (i.e., <26 weeks) is generally associated with (severe) comorbidity [24].

Long-Term Sequalae of Postnatal CMV Infection

Sensorineural hearing loss

Sensorineural hearing loss (SNHL) has not been reported among infants with a postnatal CMV infection. Permanent and late onset hearing loss do not seem to be associated with the clinical course of a postnatal CMV infection in preterm infants [32,33].

Neurodevelopmental outcome

Because of limited studies with small patient numbers, there is no clear consensus on the long-term neurodevelopmental outcome of preterm infants with a postnatal CMV infection. However, the majority of studies suggest that long-term outcome of postnatal CMV infection in preterm infants is within the normal range, although infected infants may have impaired cognitive and motor scores when compared to non-infected infants [27,37].

Treatment of Postnatal CMV Infection

Evidence

Severe, life-threatening symptomatic postnatal CMV infection in extremely preterm infants (GA < 26 weeks) may be treated using antiviral medications (i.e., ganciclovir and/or valganciclovir) in the absence of other treatment options. Evidence for treatment in postnatal CMV is sparse and based purely on case reports.

A number of authors have found benefit in using Ganciclovir for treatment of neonatal hepatitis and cholestasis and gastrointestinal manifestations [35]. In babies with congenital CMV, treatment with Ganciclovir showed less incidence of sensory neural hearing loss and better neurodevelopmental outcome in the treated group of infants [34-36]. However, these studies were limited to term infants with congenital CMV infection with CNS involvement and cannot be extrapolated to preterm infants with symptomatic postnatal CMV infection.

Medications and Whom to treat

In preterm infants with severe life-threatening symptomatic postnatal CMV infection, the use of ganciclovir and valganciclovir has been reported taking in consideration of the clinical course of infection and comorbidities. Antiviral treatment was given in the form of intravenous ganciclovir or oral valganciclovir for 4 – 6 weeks on average. Subsequently, it was observed that treatment allows clinical and especially hematological parameters to normalize again. After cessation of therapy, asymptomatic viral shedding may be observed [7,31,38,39]. If antiviral treatment is commenced, toxicity of the antiviral medication (e.g., neutropenia, bone marrow suppression and cholestasis) should be closely monitored.

Intravenous administration of hyperimmune globulin (IVIG) containing anti- CMV antibodies to postnatally infected (and symptomatic) preterm infants has been reported [26,40].

Conclusion

Postnatally acquired CMV infection via infected breast milk is not uncommon and is an underestimated problem. The majority of postnatal CMV infections remain asymptomatic specially in healthy term infants or are associated with mild symptoms or laboratory abnormalities such as thrombocytopenia or elevated liver enzymes.

Extremely preterm infants (GA < 26 weeks) are at high risk of symptomatic postnatal CMV infection and the risk becomes more evident with lower gestational age.

As breast milk is irreplaceable for extreme preterm infants, more efforts are needed to minimize or even eliminate the risk of postnatal CMV infection via breast milk without losing the nutritional and immunological properties of the milk. More studies are needed to identify those who are at risk of severe symptomatic postnatal CMV infection and to work toward a clear and internationally applicable definition of symptomatic postnatal CMV infection with a consensus on the treatment and follow up protocols.

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