SUPPLEMENT ARTICLE

Congenital Cytomegalovirus Infection: Clinical Outcome

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Congenital cytomegalovirus (CMV) infection is a leading cause of hearing loss and neurologic disabilities in children worldwide. Infants with symptomatic congenital CMV infection at birth are at significantly increased risk for developing adverse long-term outcomes. The vast majority of infants with congenital CMV infection have no clinical findings at birth (asymptomatic infants), and about 10%–15% of these children develop long-term sequelae. Currently, predictors of adverse outcome in asymptomatic congenital CMV infection are not known, and it is important that future studies address this issue.

Keywords. cytomegalovirus; congenital; outcome; sensorineural hearing loss.

Cytomegalovirus (CMV) is the most common cause of congenital viral infection affecting 20 000 to 30 000 infants in the United States annually [1]. Congenital CMV infection is also a leading nongenetic cause of sensorineural hearing loss (SNHL) and neurodevelopmental sequelae [2–4]. Infants with congenital CMV infection are categorized into symptomatic and asymptomatic based on the presence of clinical findings suggestive of congenital infection at birth. This categorization has important prognostic implications because infants with symptomatic infection are at much higher risk for adverse neurodevelopmental sequelae. Newborn disease and long-term outcome are discussed herein.

NEWBORN DISEASE

The majority of children with congenital CMV infection (approximately 85%–90%) do not have clinical findings at birth (asymptomatic infection) [1, 5, 6]. The remaining 10%–15% born with clinical abnormalities are categorized as having clinically apparent or symptomatic infection. In infants with symptomatic congenital CMV infection, the disease manifestations can range from mild nonspecific findings to multiple organ system involvement, with particular predilection for the reticuloendothelial and central nervous system (Table 1) [5]. The most commonly observed physical findings are petechial rash, jaundice and hepatosplenomegaly with neurologic abnormalities such as microcephaly and lethargy. Ophthalmologic examination reveals chorioretinitis and/or optic atrophy in approximately 10% of symptomatic infants [5]. About half of symptomatic infants are small for gestational age, and one-third are born prematurely. Although early studies suggested that about 10% of symptomatic infants die in the newborn period, more recent data suggests that the mortality rate is probably <5% [3, 5, 7].

The exact prevalence of symptomatic congenital CMV infection and disease severity are difficult to ascertain because of the lack of a standard definition for symptomatic infection. For example, some studies have categorized infants who have low birth weight or are small for gestational age without other clinical abnormalities as symptomatic whereas other studies have not [3, 5, 7]. In addition, symptomatic infants identified at newborn screening generally have milder newborn disease than those referred for follow-up studies based on clinical abnormalities at birth [3, 5, 7]. Therefore, published studies that included large numbers of referral infants may have overestimated the proportion of symptomatic infants and the severity of newborn disease among

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Table 1. Clinical and Laboratory Findings in Infants With Symptomatic Congenital Cytomegalovirus Infection[a]

Finding	Infants With Abnormality, %
Clinical findings	
Petechiae	76
Jaundice	67
Hepatosplenomegaly	60
Microcephaly	53
Intrauterine growth retardation	50
Chorioretinitis/optic atrophy	20
Purpura	13
Seizures	7
Laboratory findings	
Elevated AST (>80 U/L)	83
Conjugated hyperbilirubinemia (direct bilirubin >4 mg/dL)	81
Thrombocytopenia (<100 000/mm^3)	77
Elevated CSF protein (>120 mg/dL)	46

Abbreviations: AST, aspartate aminotransferase; CSF, cerebrospinal fluid.

[a] Data from Boppana et al [5].

children with congenital CMV infection. Although earlier studies reported that most (>80%) symptomatic children will develop sequelae, more recent data that included more infants identified at newborn screening reveal that only about half of symptomatic children develop sequelae [3, 7].

Laboratory findings in children with symptomatic infection reflect the involvement of the hepatobiliary and reticuloendothelial systems and include conjugated hyperbilirubinemia, thrombocytopenia, and elevations of hepatic transaminases in more than half of symptomatic newborns. Transaminase and bilirubin levels typically peak within the first 2 weeks of life and can remain elevated for several weeks thereafter, whereas thrombocytopenia reaches its nadir by the second week of life and normalizes within 3–4 weeks of age [5]. Radiographic findings in the brain are abnormal in approximately 50%–70% of children with symptomatic infection at birth. The most common finding is intracranial calcifications, with ventricular dilatation, cysts, and lenticulostriate vasculopathy occurring in varying proportions.

LONG-TERM OUTCOME IN CONGENITAL CMV INFECTION

Symptomatic Congenital CMV Infection

A large proportion of infants born with symptoms at birth will suffer mild to severe psychomotor and perceptual handicaps. Prospective studies have shown that approximately half of the children born with symptomatic infection will develop SNHL, mental retardation with IQs <70, and microcephaly [1, 3, 8, 9]. Findings early in life that are predictive of adverse neurologic outcome in children with symptomatic congenital CMV infection include microcephaly, chorioretinitis, and the presence of other neurologic abnormalities at birth or in early infancy and cranial CT abnormalities detected within the first month of life [4, 10]. In a study of 190 children with symptomatic congenital CMV infection, petechiae and intrauterine growth retardation were the only factors that were independently predictive of hearing loss [10].

Asymptomatic Congenital CMV Infection

In general, children with asymptomatic congenital CMV infection have a better long-term prognosis than children with symptomatic infection. However, approximately 10% of asymptomatic children will develop SNHL. This is much higher than the 0.1%–0.4% incidence of hearing loss within the general population. Many prospective studies of children with asymptomatic congenital CMV infection showed that approximately half of children with asymptomatic infection who develop hearing loss will have bilateral deficits, which can vary from mild high-frequency loss to profound impairment. Moreover, hearing loss in these children is often progressive and/or delayed onset requiring ongoing audiologic evaluation [4, 11]. The natural history and predictors of CMV-associated SNHL is discussed in more detail in the section by Fowler [1]. Other neurologic complications may also occur in children with asymptomatic congenital CMV infection but at a much lower frequency than in symptomatic infection. Approximately 5% of children born with asymptomatic infection develop microcephaly and motor defects, and chorioretinitis is observed in about 2%. It is unknown, however, whether these children are at risk for learning disabilities and behavioral problems [1, 3]. The pathogenesis and mechanisms of hearing loss and other neurologic sequelae in children with congenital CMV infection, especially in those with asymptomatic infection, have not been understood. Furthermore, predictors of adverse outcome in asymptomatic children have not been defined. This inability to identify infants at risk for the development of hearing loss and other sequelae necessitates monitoring and follow-up in all children with congenital CMV infection.

FACTORS ASSOCIATED WITH ADVERSE OUTCOMES IN CONGENITAL CMV INFECTION

Type of Maternal Infection

It has been thought that symptomatic infection with severe newborn disease and long-term sequelae are much more frequent in children born to mothers with primary CMV infection during pregnancy. However, more recent data from Townsend and colleagues [6] in Sweden and the United Kingdom and

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studies in Alabama [12] and Brazil [13] have shown that symptomatic infection occurs with similar frequency in children born to women with primary CMV infection and those born to women who were CMV seroimmune before pregnancy (nonprimary infection). In addition, the severity of newborn disease and the rates of CMV-associated SNHL also do not differ between primary and nonprimary infection groups [12–15].

Viral Load and Outcome

Early natural history studies of congenital CMV infection demonstrated that symptomatic infants excreted increased amounts of CMV in their urine compared with asymptomatic infants. Because peripheral blood viral load monitoring is useful in the management of invasive CMV infections in immunocompromised individuals, it was suggested that viral load measurement could identify congenitally infected infants at increased risk for sequelae. Studies have confirmed that symptomatic infants have increased levels of viral DNA in urine and blood compared with asymptomatic infants [16, 17]. However, a more recent study examining blood viral load in 135 congenital CMV infection infants demonstrated no difference in viral load in the first months of life and beyond among children with and without SNHL [17]. Therefore, in individual children with congenital CMV infection, an elevated viral load may not identify a child at risk for CMV-related hearing loss.

Gestational Age

The gestational age at the time of intrauterine CMV infection has been associated with more significant sequelae [18, 19]. Studies suggested that maternal seroconversions occurring in the late first and early second trimester were more often associated with more severe congenital CMV infection with central nervous system disease than maternal seroconversions occurring in the late second and third trimesters. However, the inability to define the timing of virus transmission to the fetus limits definitive interpretation of these studies.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Continual advances are being made in our understanding of the pathogenesis and the natural history of congenital CMV infection. There is growing interest in the feasibility of screening all newborns for congenital CMV infection in conjunction with universal newborn hearing screening. Recent work has demonstrated that reliable and simple molecular diagnostic methods of testing newborn saliva specimens for CMV with high-throughput capacity are currently available [20]. It is hoped that the newer molecular methods may provide the capability to identify congenitally infected infants at increased risk for hearing loss and other sequelae early in life. However, the conflicting data in the literature suggests that the role of viral load measurements in predicting CMV-associated SNHL is unclear at this time. Therefore, identification of predictors of adverse outcome, in particular in children with asymptomatic congenital CMV infection is an important gap in our knowledge. Ongoing large newborn CMV screening studies will improve our understanding of the natural history of congenital CMV infection and may identify the predictors of outcome.

Notes

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