Predictors of sensorineural hearing loss (SNHL) in infants with symptomatic congenital CMV infection

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Abstract

Background: Congenital CMV (cCMV) is the leading non-genetic cause of sensorineural hearing loss (SNHL) in the U.S. Approximately 40-60% of infants with symptomatic cCMV infection develop long term sequelae such as hearing loss. Currently, there are no identified predictors of hearing loss.

Objective: To determine clinical predictors of SNHL in infants with symptomatic cCMV infection.

Methods: Findings from a longitudinal follow-up study of children with symptomatic cCMV at the University of Alabama (UAB) were analyzed. Infants were considered to have symptomatic cCMV if they were positive for CMV by saliva or urine rapid culture and had findings suggestive of congenital infection at birth. Infants with jaundice, petechiae, purpura, hepatosplenomegaly, elevated aspartate aminotransferase, thrombocytopenia and lack of CNS involvement were considered to have transient symptoms. Infants with microcephaly, seizures, abnormal neurological examination, and abnormal neuroimaging findings with/without any of the transient symptoms were categorized as the group with CNS involvement. Incidence of SNHL was compared between the groups with transient symptoms, CNS involvement and only petechial rash.

Results: 176 infants with symptomatic cCMV infection were followed at UAB. CNS involvement and transient findings were found in 56% and 31% of infants, respectively while 13% of infants only had a petechial rash. Hearing outcome was available in 96% of study children. The overall incidence of hearing loss was found to be highest in the group with CNS involvement followed by those with transient findings and infants with only a petechial rash (59% (54/92) vs. 39% (21/54) vs. 22% (5/23) respectively; p = 0.0004). SNHL at birth was significantly more frequent in infants with CNS involvement compared to infants with transient findings or only petechial rash (42% (39/92) vs. 24% (13/54) vs. 13% (3/23) respectively; p = 0.0019). The incidence of late onset hearing loss was not significantly different between these groups (p = 0.08).

Conclusions: Among infants with symptomatic cCMV infection, those with evidence of CNS involvement in the newborn period are at the greatest risk for SNHL overall and congenital hearing loss. However, findings in the newborn period are not predictive of late onset hearing loss.

Introduction

• Congenital CMV (cCMV) is a common congenital infection and the leading non-genetic cause of sensorineural hearing loss (SNHL) in the U.S.1-3
• 40-60% of infants with symptomatic cCMV and 10-15% with asymptomatic infection develop long term sequelae including SNHL, cerebral palsy, neurodevelopmental delay and retinopathy. In a third of children with CMV-associated SNHL, the deficits appear later during childhood (delayed-onset SNHL).4
• The presentation of symptomatic cCMV at birth is highly variable5 and newborn clinical findings predictive of congenital and late-onset SNHL or other sequelae have not been defined.
• At birth, identification of infected infants at increased risk for sequelae will allow appropriate counselling of parents, targeted monitoring and a more judicious utilization of resources.

Objectives

The objective of this study is to determine the estimates of risk for sequelae based on clinical findings at birth in a large cohort of infants with symptomatic cCMV.

Materials and Methods

• Study population: The study population consisted of 176 infants with cCMV enrolled in a longitudinal follow-up study at UAB between 1980 and 2002.
• Diagnosis and Follow-up: cCMV was confirmed by virus isolation or the presence of CMV antigens in urine or saliva by culture-based testing within the first 3 weeks of life. Audiologic evaluations were performed every 6 months until 24 months of age and then annually. SNHL was defined as air conduction thresholds ≥25 dB on brainstem auditory response audiometry or ≥20 dB on behavioral audiometric evaluations appropriate for child’s developmental level in conjunction with normal bone conduction thresholds and normal middle ear function. Delayed SNHL was defined as having ≥ 1 hearing evaluations with normal threshold documented for each year before SNHL was detected. Developmental and intellectual evaluations were administered using standard psychometric tests appropriate for age, perceptual function, and physical abilities.
• Methods: Infants confirmed to have cCMV and any findings suggestive of congenital infection including jaundice, petechiae, purpura, hepatosplenomegaly, seizures, chorioretinitis and microcephaly were considered to have symptomatic cCMV. Infants with jaundice with conjugated hyperbilirubinemia, petechiae, purpura, hepatosplenomegaly, elevated aspartate aminotransferase, thrombocytopenia and without CNS involvement were considered to have transient findings. Infants with microcephaly, seizures, abnormal neurological examination, and abnormal neuroimaging findings with/without any of the transient symptoms were categorized as a group with neurological involvement. Infants with only a petechial rash on physical examination in the newborn period comprised a third group. Incidences of SNHL (congenital and late-onset) and cognitive deficits were compared between the three groups.

Statistical Analysis: The incidence of SNHL in the newborn period and late onset SNHL between the three groups and the neurodevelopmental outcome for the groups were compared and statistical significance was determined using χ² or Fisher exact test.

Results

• The average length of follow-up of children involved in the study was 4.6 ± 3.77 years
• Of the 176 infants with symptomatic cCMV, 99 (56%) had evidence of neurologic involvement, 54 (31%) presented with only transient findings and 23 (13%) presented with only petechiae.
• Significantly more children with neurologic findings at birth developed SNHL (54/92, 59%) compared to infants with transient findings (21/54, 39%) or only petechiae (5/23, 22%) (p = 0.0004).
• Significantly more infants with evidence of neurologic involvement had congenital SNHL (39/92, 42%) compared with those infants with transient findings (13/54, 24%) or petechiae only (3/23, 13%) (p = 0.0019).
• The frequency of late onset SNHL did not differ significantly between the three groups.
• Significantly more children with neurologic findings at birth had IQ ≤ 70 (29/49, 59%) compared with infants with transient findings (8/40, 20%, p <0.0001). None of the children with petechiae alone had IQ ≤ 70.

Table 1: Sensorineural hearing loss outcome based on presenting symptoms

<table>
<thead>
<tr>
<th>Presenting Symptoms</th>
<th>SNHL in the Newborn Period</th>
<th>Late Onset SNHL</th>
<th>Cumulative SNHL**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic (N=92)</td>
<td>39 (42.4%)</td>
<td>15 (16.3%)</td>
<td>54 (58.7%)</td>
</tr>
<tr>
<td>Transient (N=54)</td>
<td>13 (24.1%)</td>
<td>8 (14.8%)</td>
<td>21 (38.9%)</td>
</tr>
<tr>
<td>Petechiae (N=23)</td>
<td>3 (13.0%)</td>
<td>2 (8.7%)</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Asymptomatic⁶</td>
<td>10 (15.9%)</td>
<td></td>
<td>10 (15.9%)</td>
</tr>
</tbody>
</table>

Table 2: Cognitve outcome based on presenting symptoms

<table>
<thead>
<tr>
<th>Presenting Symptoms</th>
<th>IQ ≤ 70</th>
<th>IQ ≥ 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic (N=49)</td>
<td>29 (59.2%)</td>
<td>20 (41%)</td>
</tr>
<tr>
<td>Transient (N=40)</td>
<td>8 (20%)</td>
<td>32 (80%)</td>
</tr>
<tr>
<td>Petechiae (N=10)</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
</tr>
</tbody>
</table>

p<0.0011 by Mantel-Haenszel chi-sq

p*<0.0044 by Mantel-Haenszel chi-sq

Conclusions

• In this large cohort of children with symptomatic cCMV who were prospectively followed, the risk of hearing loss and neurodevelopmental outcome varied depending on the constellation of physical examination findings at birth.
• The overall risk for SNHL increases with increasing severity of infection in the newborn period [asymptomatic (10-15%) < petechiae only (22%) < transient (40%) < neurologic (59%)].
• CNS involvement with or without the presence of other findings is predictive of poor neurodevelopmental outcome in cCMV.
• Physical findings at birth are not predictive of late onset hearing loss in infants with symptomatic cCMV infection.
• These findings demonstrate that the symptomatic cCMV population is heterogeneous with respect to their risk for adverse outcome. The risk for SNHL in symptomatic children with petechiae alone is similar to asymptomatic infants.

References