Is lenticulostriated vasculopathy a sign of central nervous system insult in infants with congenital CMV infection?

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ABSTRACT

Background In previous studies, lenticulostriated vasculopathy (LSV) was detected in 0.4–5.8% of neonates who had undergone brain ultrasound studies during the neonatal period. Most infants were referred from neonatal intensive care units. Various clinical conditions were associated with LSV including intrauterine infections.

Objective To investigate whether LSV as a single abnormal finding in neonates with congenital cytomegalovirus (CMV) infection is a sign of central nervous system (CNS) involvement.

Methods Ultrasonographic and clinical data of all infants with congenital CMV infection, followed in our hospital, were collected. All infants with symptomatic congenital CMV infection and CNS involvement were treated with ganciclovir for 6 weeks, followed by valganciclovir until the age of 1 year. Infants with asymptomatic as well as symptomatic infections were followed up with brainstem evoked response and behavioural studies every 4 months until 4 years of age.

Results 92 infants diagnosed with congenital CMV infection were included in the study. In 50 (54.3%) infants, LSV was detected on initial brain ultrasound. Among these patients, 21 (42%) infants had other ultrasonographic findings consistent with congenital CMV infection; 11 (22%) had other symptoms of CNS involvement and in 18 (36%) cases the only abnormal finding was LSV. In 9 of the 18 infants with LSV as the only finding on initial examination, antiviral therapy was not started. Hearing deterioration developed in all nine infants between ages 4 and 34 months. Subsequent to these cases, the authors modified their therapy protocol and began treating congenital CMV infants with only LSV. 9 infants were treated and all maintained normal hearing after 8–27 months of follow-up (p<0.01).

Conclusions LSV is a common finding in infants with symptomatic congenital CMV infection and is a sign of CNS involvement. Moreover, LSV is a possible marker of high risk for sensorineural hearing loss in infants with congenital CMV infection.

Lenticulostriated vasculopathy (LSV), the ‘candlestick-like’ strips observed on a neonatal brain ultrasound, is an echodensity of the lenticulostriated branches of the middle cerebral artery located in the region of the thalamus and the basal ganglia (figure 1).

In previous large series, LSV was detected in 0.4–5.8% of neonates who had undergone ultrasound studies during the neonatal period.14–17 LSV is associated with various clinical conditions including prematurity, intraventricular haemorrhage, congenital heart disease, chromosomal aberrations, metabolic disorders and congenital infections.3–4 Two previous studies have established that congenital infections are a rare cause of LSV12; however, LSV as a solitary finding or in addition to other ultrasonographic findings was reported in infants with congenital cytomegalovirus (CMV) infection.13–15

The aim of the study was to investigate whether LSV as a single abnormal finding in neonates with congenital CMV infection was a sign of central nervous system (CNS) involvement. This is particularly important following the recent development of antiviral treatment for symptomatic CMV infection to reduce hearing damage.

METHODS

The study was conducted at the Schneider Children Medical Center of Israel, the largest paediatric hospital in Israel. The ultrasonographic and clinical data of all infants with congenital CMV infection, followed in our paediatric clinic for intrauterine infections between 2005 and 2010, were collected.

Clinical data

Congenital CMV infection was diagnosed only in infants with a positive urine culture (shell vial)
taken during the first 2 weeks of life. Additional studies of these neonates immediately after birth included a complete blood count, liver and kidney function tests and funduscopy performed by a paediatric ophthalmologist.

**Ultrasound and hearing assessment**

Ultrasound over the anterior and posterior fontanel and asterion was performed by a paediatric radiologist using the Philips HDI 5000 and Philips IU 22 ultrasound imaging platforms with 8.0–5.0 MHz transducers. No additional neuroimaging was conducted.

All infants with asymptomatic as well as symptomatic infections were followed up with brainstem evoked response (BSER) and behavioural studies every 4 months until 4 years of age. The audiologists and technicians were unaware of ultrasound and treatment status. The evoked potentials were assessed using the Bio-Logic system (Bio-Logic System Corporation) within 2 weeks after birth in 77% of the infants and in the remainder by the age of 4 weeks. All infants with abnormal BSER values underwent tympanometry. In cases of conductive problems, only bone-conduction results were used.

**Treatment plan**

During the study period, all infants with symptomatic congenital CMV infection and CNS involvement were treated with ganciclovir for 6 weeks, followed by oral valganciclovir until the age of 1 year. The criteria for symptomatic infection included only infants with CNS involvement: (1) microcephaly (head circumference <2 percentile), (2) hearing impairment detected by the BSER test, (3) chorioretinitis or (4) abnormal findings on brain ultrasound compatible with congenital CMV infection.

Infants with asymptomatic infection were followed up with BSER studies and a behavioural hearing test, as mentioned above. Those who had late deterioration were treated with ganciclovir/valganciclovir.

**Statistical analysis**

Comparison of hearing deterioration between treated and untreated cases was done using a standard χ² test with correction for continuity.

The study was approved by the institutional Helsinki committee.

**RESULTS**

During the study period, 92 infants diagnosed with congenital CMV infection were followed in our clinic. Seventy-five (81.5%) were infected after a primary maternal CMV infection during pregnancy, 6 (6.5%) had reactivation of maternal CMV infection and 11 infants (12%) had no data as to the mother’s infection. Most (88 of 92) were full-term infants (≥37 weeks).

**LSV and symptomatic congenital CMV infection**

In 50 infants (54.3%), LSV was detected on the initial brain ultrasound study (figure 2). Among these patients, in 21 of 50 (42%), other symptoms and ultrasonographic findings consistent with congenital CMV infection were detected (table 1).

Eleven infants (22%) had other symptoms and signs of CNS involvement on initial examination (table 1), and in 18 cases (36%), LSV was the only abnormal finding.

**LSV and asymptomatic congenital CMV infection**

Nine of these 18 infants were born between 2005 and 2008 and were diagnosed with asymptomatic congenital CMV infection. Two had mild splenomegaly. All these infants were born after a primary maternal CMV infection: in the first trimester (n=3), second trimester (n=4) and not known (n=2). Treatment with ganciclovir/valganciclovir was not started at birth. Follow-up consisted of routine BSER studies and clinical examination every 4 months. Hearing deterioration developed in all these infants between ages 4 and 34 months (median 6 months) (table 3).

No other signs or symptoms of congenital CMV infection were found. None of these infants had pathological hyperbilirubinaemia or exposure to ototoxic antibiotics.

Subsequent to these cases, we modified our therapy protocol and began treating congenital CMV infants with only LSV with ganciclovir, followed by valganciclovir or valganciclovir alone, during the neonatal period in doses previously described. Among the infants with only LSV (nine cases) born after the protocol change, mild splenomegaly was detected in four. Eight of them were born after a primary maternal CMV infection in the first trimester (n=2), second trimester (n=5) and not known (n=1); one infant was infected due to a reactivation of maternal CMV infection. They were all treated and maintained normal hearing on follow-up of 8–27 months (median 15 months). The differences in hearing deterioration rates between treated and untreated cases were statistically significant (p<0.01). Among 19 infants born with asymptomatic congenital CMV infection (including normal ultrasound) (figure 2), hearing deterioration was detected on follow-up of 11–54 months in 3 (15.8%), a significantly lower rate than in infants with only LSV (p<0.001).
Figure 2  Flowchart of study infants with congenital cytomegalovirus (CMV) infection. CNS, central nervous system; LSV, lenticulostriated vasculopathy.

Table 1  Infants with lenticulostriated vasculopathy and other symptoms and ultrasound findings of congenital cytomegalovirus infection (n=21)

<table>
<thead>
<tr>
<th>Additional ultrasound findings</th>
<th>Symptoms of congenital CMV</th>
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<tr>
<td></td>
<td>CNS</td>
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<tr>
<td>1  Calcification, PHE</td>
<td>Microcephaly</td>
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<tr>
<td>2  PHE</td>
<td>Microcephaly</td>
</tr>
<tr>
<td>3  Calcification, PHE</td>
<td>Microcephaly, SNHL</td>
</tr>
<tr>
<td>4  Calcification, ventriculomegaly</td>
<td>Microcephaly</td>
</tr>
<tr>
<td>5  Calcification</td>
<td>ND</td>
</tr>
<tr>
<td>6  PHE</td>
<td>Microcephaly</td>
</tr>
<tr>
<td>7  Venticulomegaly, pseudocysts</td>
<td>Microcephaly, SNHL</td>
</tr>
<tr>
<td>8  Ventricular septations</td>
<td>SNHL</td>
</tr>
<tr>
<td>9  Calcification, PHE</td>
<td>SNHL</td>
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<tr>
<td>10 PHE</td>
<td>Microcephaly</td>
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<tr>
<td>11 Calculation</td>
<td>ND</td>
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<td>12 Pseudocysts</td>
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<td>13Calcification, pseudocysts</td>
<td>Microcephaly, SNHL</td>
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<td>14Calcification, ventriculomegaly</td>
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<td>15Calcification, pseudocysts</td>
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<td>16Calcification</td>
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<td>17Pseudocysts</td>
<td>Microcephaly, chorioretinitis</td>
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<td>18Calcification</td>
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<td>20Pseudocysts</td>
<td>Microcephaly, chorioretinitis</td>
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<td>21Calcification</td>
<td>Microcephaly</td>
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CNS, central nervous system; IUGR, intrauterine growth restriction; ND, not detected; PHE, periventricular hyperechoicity; SNHL, sensorineural hearing loss.
DISCUSSION

In this large patient series, LSV was found in 54% of infants with congenital CMV infection. In nearly 36% of these cases, LSV was the only CMV-related pathological finding on initial examination after birth. Changing our policy to early treatment with antiviral therapy, based on the presence of LSV alone, had a possible effect in preventing hearing deterioration, which occurred in all untreated cases prior to modification of the treatment plan (table 5). The longer follow-up duration in the untreated babies increases their likelihood of late deterioration. However, even a few cases of very late hearing deterioration in the treated group will not significantly change the results. The results of the worst hearing test are presented in table 3 since most of these infants were treated as soon as the deterioration was detected and some improved (data not shown); this improvement in hearing may be due to either the natural history of the disease or the treatment. Hearing deterioration in the group with LSV without early treatment was also significantly higher than in the 19 infants born with an asymptomatic CMV infection (no LSV), all after a primary maternal infection (figure 2). Of these 19 infants, hearing deterioration was detected only in 3 cases (p<0.001).

Although this conclusion is limited by the small number of cases and a relatively short duration of follow-up for the treated infants, we believe that the difference is significant and reflects a strong causal association.

Other researchers have also suggested that LSV in infants with a congenital CMV infection may be considered a manifestation of CNS involvement. 18 19

The pathogenesis of hearing damage in children with a congenital CMV infection is unclear. Sensorineural impairment may be due to damage, both cytopathic and immune mediated, of the stria vasularis in the organ of Corti. The relationship between LSV and hearing damage is also unclear and found to be unexpectedly very high. However, we assume that LSV in infants with a congenital CMV infection and no other medical problems related to LSV findings may be a sign of CNS and inner ear involvement. Only petechiae and intrauterine growth retardation have previously been shown to independently predict hearing loss in children with symptomatic congenital CMV infection. 20

As mentioned previously, LSV was found to be associated with many other pathological conditions in neonates such as chromosomal aberrations, cardiac anomalies and complications due to prematurity. A large series of neonatal brain ultrasound studies demonstrated that LSV can be found in up to 5.8% of cases, 1 – 7 mostly taken from neonatal intensive care unit data, indicating either premature infants or those having severe medical problems. Analysis of the data from these studies revealed that most of these infants had serious underlying medical problems.

The incidence of LSV in these case series, in infants with no obvious medical problems, was approximately 0.8%. In many of the infants, a urine culture or serology for CMV was not taken. LSV was found to be very rare in a recently published study of brain ultrasound in normal full-term infants. 21 We therefore suggest that ultrasound findings of LSV in full-term infants with congenital CMV infection and no other underlying medical problem be assessed differently.

The main limitations of our study were the retrospective methodology, small number of infants, short-term follow-up and no controlled group of normal neonates who had undergone brain ultrasound. A prospective study following infants with congenital CMV infection and no other underlying medical problem is needed.

In conclusion, the results of this study indicate that LSV is a relatively common finding in infants with symptomatic congenital CMV infection and is a sign of CNS involvement. Moreover, LSV may serve as a marker of high risk for sensorineural hearing loss.

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Competing interests None.

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