Cranial Ultrasound Scanning and Prediction of Outcome in Newborns with Congenital Cytomegalovirus Infection

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Objective To report the accuracy of ultrasound scanning (US) in predicting neurodevelopmental and sensorineural outcome in patients with congenital cytomegalovirus (CMV) infection.

Study design Fifty-seven neonates with congenital CMV infection underwent brain US and were observed prospectively for motor skills, developmental quotient, and hearing function.

Results Abnormal results on US were found in 12 of 57 neonates. US lesions were more frequent in newborns with clinical and laboratory signs of congenital CMV infection at birth (10/18; P < .001). At least 1 sequela developed in all neonates with symptoms who had abnormal US results, whereas none of the neonates with symptoms who had normal US results had long-term sequelae (P < .001). In the population without symptoms, sensorineural hearing loss developed in 3 of 37 (8.1%) neonates with normal US results, whereas severe sequelae developed in 1 of 2 neonates with abnormal US results.

Conclusions A good correlation was found between cerebral US abnormalities and the prediction of outcome in newborns who were congenitally infected with CMV and had symptoms at birth. US could be performed as the first neuroimaging study in these newborns. Data are insufficient to permit any suggestions for the population without symptoms. (J Pediatr 2007;150:157-61)

Congenital cytomegalovirus (CMV) infection can cause a wide spectrum of brain damage related to inflammatory and teratogenic effects, including meningoencephalitis, calcifications, microcephaly, disturbance of neuronal migration, germinal matrix cysts, ventriculomegaly, and cerebellar hypoplasia.1 Computed tomography (CT), magnetic resonance imaging (MRI), and cerebral ultrasound scanning (US) are well-documented means for detecting brain lesions and other anomalies of the central nervous system (CNS).2-5 CT has been used to detect CNS lesions, predicting neurodevelopmental outcome,3,6 and to identify infants at risk of impaired hearing and those who could benefit from ganciclovir treatment.7,8 US is the safest means to image the neonatal brain and, unlike CT, is readily available at the bedside. The use of US to predict the neurodevelopmental and sensorineural outcome of congenital CMV infection has not been reported.

We undertook a systematic prospective US study of all neonates in whom congenital CMV infection was diagnosed, correlating cerebral US features with neurodevelopmental and sensorineural sequelae.

METHODS

Between January 1997 and September 2003, 57 newborns in whom congenital CMV infection was diagnosed were referred to our tertiary care hospital, where we have set up a multidisciplinary team specializing in the treatment of patients with congenital CMV infection.

Congenital CMV infection was diagnosed on the basis of isolation of the virus from urine within the first 2 weeks of life in neonates born from mothers with a suspected or
ascertained CMV infection during pregnancy.\textsuperscript{9} Virus isolation was performed in cell cultures with the "shell vial" procedure.\textsuperscript{10} Newborns congenitally infected with CMV were defined as symptomatic when they had clinical signs, laboratory signs, or both at birth, including intrauterine growth retardation, microcephaly, seizures, chorioretinitis, hepatosplenomegaly, petechiae, elevated serum transaminase levels, neutropenia, and thrombocytopenia. US was obtained by using an Esaote AU5 with a 7.5-MHz sector probe transducer. Cranial US was performed in all cases within the first week of life and repeated at 1 and 3 months of age when results were negative. Neonates with abnormal US findings were re-examined weekly with US during the first month of life and then monthly until they were 6 months old. Two independent investigators (G.A. and F.S.), who were blinded to clinical findings, reviewed all scans and obtained the same results for the presence of lesions related to CMV congenital infection. US results were classified as normal or abnormal. Pathologic scans were defined as having periventricular/parenchymal calcifications, ventriculomegaly, cysts, cerebellar lesions (hyper-echogenicity, hypoplasia), or "candlestick" lenticulostriate vasculopathy (LSV).\textsuperscript{1,4,5} Ventricular size was measured at the midbody of the lateral ventricles on a sagittal view. Ventriculomegaly was classified as mild, moderate, or severe, according to Allan.\textsuperscript{11} Scans showing only mild ventriculomegaly (ie, ventricular size between 3 and 5 mm) were not considered pathologic. In addition, isolated LSV (ie, increased echogenicity at the level of vessels in the basal ganglia and thalamus) was not considered pathologic. LSV is not a specific marker of pathologic findings and outcome.

Eleven of the 11 surviving neonates with abnormal US results, MRI, or both was performed in all surviving infants with abnormal US results. MRI was performed in 2 cases during the neonatal period and in 6 cases between 4 and 12 months of age. CT was done in the first trimester of fetal life.

Informed consent was obtained from the parents or legal guardians of the infants studied.

Data were recorded in an Excel database and analyzed with the SPSS 5.0 software (SPSS, Chicago, IL). The chi-square statistic was used to test the relationship between US findings and outcome.

**RESULTS**

Twelve of 57 (21.0%) neonates referred to our institution with a diagnosis of congenital CMV infection showed cerebral US abnormalities typical of congenital CMV infection. Eighteen of 57 (31.6%) showed clinical or laboratory signs of congenital infection at birth. US lesions were more frequent in newborns with clinical and laboratory signs of congenital CMV infection at birth (10/18) than in newborns who had no symptoms at birth (2/39; \( P = .000 \)). Clinical data for patients with normal and abnormal US results are reported in Table I. In most cases, US showed a varying combination of calcifications, ventriculomegaly, cysts, cerebellar anomalies, and LSV. Lesions were detected at the first US examination and remained stable in all cases, with the exception of a periventricular cyst that enlarged during the first week of life. No infant with normal US results at birth developed lesion(s) at subsequent evaluations. Further investigations were performed in the 11 surviving infants with pathologic US findings: 3 underwent CT, 4 underwent MRI, and 4 underwent both CT and MRI. CT results confirmed US findings in all cases, and no additional abnormalities were detected. Although the MRI missed calcifications in 2 cases, it disclosed additional findings in 6 cases compared with US, including migrational disorders, leukodystrophy, and delayed myelination. In 1 case, US missed a temporal horn cyst, 5 mm in diameter, that was evident on MRI.

Follow-up data until patients were a minimum of 12 months old (mean age ± SD at last follow-up visit, 42.3 ± 11.3 months) were available for 56 of 57 patients; 1 infant died in the neonatal period of aortic thrombosis.\textsuperscript{21} Of the 11 surviving neonates with abnormal US results, only 1, who had moderate ventriculomegaly and a hyper-echoic lesion at the level of the germinal matrix that evolved into a cyst, had a normal outcome at follow-up. Strabismus development of the infants with a 3-axis grid including neurovegetative, motor, and relational/behavioral items combining the Milani-Comparetti neuroevolutive assessment.\textsuperscript{18} Brazelton behavioral assessment,\textsuperscript{19} and Prechtl general movement assessment.\textsuperscript{20} This comprehensive assessment method allowed detection of suspicion for abnormal psychomotor development, to permit early referral (before 4-6 months of age) for rehabilitation. Motor delay was defined as functional deficits in motor skills and unachieved developmental milestones requiring rehabilitation.

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developed in 1 infant whose US and CT scans showed a single calcification at the caudate level, and SNHL and strabismus developed in another infant with US and CT signs of multiple calcifications and ventriculomegaly. The other 8 infants, who had a varying combination of ventriculomegaly, diffuse calcifications, cerebellar hypoplasia, and periventricular cysts at birth, had poor psychomotor development (DQ median, 76.8; range, 67-79) associated with SNHL in 5 cases and motor delay in 6 cases (the latter were those with additional MRI findings compared with US; Table II).

Forty-two of 45 patients without cerebral US abnormalities had normal psychomotor and sensorineural outcomes; hypacusia developed in 3 children, mild and unilateral in 1 case and bilateral in the other 2 (Table II).

Statistical analysis of data was performed separately for the 2 groups of patients with or without symptoms at birth. At least 1 sequela developed in all 10 newborns with symptoms who had abnormal US results or they died, whereas none of the 8 newborns with symptoms who had normal US results showed long term sequelae (P < .001). In the asymptomatic population, SNHL developed in 3 of 37 (8.1%) newborns with normal US results, whereas severe sequelae developed in 1 of the 2 newborns with abnormal US results (odds ratio [OR], 11.3; 95% CI, 1.0-141.6; P = .2). When data for infected newborns, with or without symptoms at birth, were pooled, at least 1 sequela developed in 91.7% of patients with abnormal results on US performed in the neonatal period or they died, compared with 6.7% of the group with normal US results (OR, 154; 95% CI, 17.3-1219.6; P < .001). The individual risk for each sequela is reported in Table III.

**DISCUSSION**

CMV infection is the most common intrauterine infection in developed countries, with a prevalence of 0.2% to 2.2% in live neonates. Cerebral lesions, including meningoencephalitis, calcifications, microcephaly, disturbance of neuronal migration, germinal matrix cysts, ventriculomegaly and cerebellar hypoplasia, may develop in patients who are congenitally infected. The severity of the neuropathologic findings at birth correlates with poor outcome, including hearing loss, mental retardation, cerebral palsy, seizures, and chorioretinitis.1

Early identification of neonates at risk is important to help healthcare providers counsel parents and give adequate treatment and follow-up care. Neonatal clinical signs correlate with neurologic outcome in congenital CMV infection: sequelae can develop in as many as 80% of infants with symptoms, whereas available data suggest that either audiologic or developmental problems develop in 5% to 15% of newborns without symptoms in the first year of life.22-26 These findings indicate that the presence of symptoms at birth does not necessarily differentiate children in whom sequelae will or will not develop. The addition of CT scans improves the prognostic accuracy in patients with clinical signs: as many as 90% of infected infants with symptoms who have cerebral lesions on CT examination have neurodevelopmental or sensorineural sequelae.3 CT may also reveal rarer anomalies in infected newborns without symptoms who have poor developmental performance.24

Although CT is the most widely used and accepted imaging technique for investigating the brain in neonates who are congenitally CMV infected, we aimed to find the least invasive prognostic indicator in this population.27 Most of the lesions related to fetal infection are readily disclosed by US, including calcifications, ventriculomegaly, cysts in the germinal matrix, and cerebellar atrophy.1,4,5 In addition, US is the safest imaging technique for the evaluation of the newborn brain. It is also useful as a screening tool, available at the bedside, and feasible even in the most critical situations, whereas CT is not usually available in neonatal intensive care units, and newborns must be transported. Further, US is the same imaging tool used in the perinatal period, making US-

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**Table I. Clinical data of neonates with congenital cytomegalovirus infection according to neural ultrasound scanning findings**

<table>
<thead>
<tr>
<th>Clinical and laboratory signs</th>
<th>Children with normal US results (n = 45)</th>
<th>Children with pathological US results (n = 12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>18/27</td>
<td>5/7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) gestational age in weeks</td>
<td>38.3 (2.5)</td>
<td>38.0 (2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) birth weight in grams</td>
<td>3054 (676)</td>
<td>2875 (767)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of neonates with symptoms at birth (%)</td>
<td>8 (18)</td>
<td>10 (83)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*NS: Not statistically significant.

*Elevated serum transaminase level, neutropenia, thrombocytopenia.
based prognostic data useful to physicians involved in prenatal care.

Postnatal cerebral US was performed in both patients with symptoms and patients without symptoms in our cohort because cerebral lesions have been detected even in patients without symptoms.24,25 All newborns with symptoms who had abnormal US results showed at least 1 sequela or died, whereas none of the newborns with symptoms who had normal US results had any long-term sequelae (P < .001).

These findings are in agreement with those reported by Boppana et al, who used cerebral CT scanning to establish prognosis in a population of neonates with symptoms.3 Our data indicate a good correlation between cerebral US abnormalities and the prediction of outcome in newborns with congenital CMV infection who have symptoms at birth, suggesting that US may be performed as the first diagnostic study to detect brain lesions in these patients.

Only 2 of 39 neonates who were infected but had no symptoms had cerebral US abnormalities in our study. The first was a term newborn with ventriculomegaly associated with a globular hyperechogenicity at the germinal matrix level. At the time of diagnosis, we were not able to differentiate between a germinal matrix hemorrhage and a microinfarction of the germinal matrix suggestive of CMV infection. The finding was classified as abnormal; the patient’s outcome was normal. Severe psychomotor and auditory deficits developed in the second newborn, who had ventriculomegaly, calcifications, and cysts. Adverse psychomotor outcome associated with SNHL occurred in 1 of 39 infants without symptoms (2.6%). US permitted identification of cerebral lesions, associated with poor outcome, early in this patient’s life. In the asymptomatic population, US failed to predict isolated SNHL in 3 patients. Our data are too limited to reach any conclusions on the usefulness of cerebral US in congenitally infected newborns without symptoms at birth.

Although we did not find changes in the course of time in calcifications, ventriculomegaly, cerebellar hypoplasia, and subependymal cysts, follow-up US can serve as a means to track porencephalic cysts or hemorrhages. None of the cases in which the first US results were negative showed further lesions at subsequent examinations, indicating that repeat US may not be warranted in these children.

MRI may be a particularly useful imaging modality for detecting white matter lesions or gyral abnormalities, which are relatively common in congenital CMV infection after the neonatal period.2,28,29 MRI also is considered to be the best neuroimaging technique for studying abnormalities of migration.30 US has a low sensitivity in detecting gyral abnormalities or myelinization deficits because the conic shape of US hinders exploration of the cortical surface and the grey and white matter are difficult to distinguish.31 MRI detected gyral and white matter disorders not disclosed by US in 6 of our cases. As a complementary examination, MRI may be best performed after the first 6 months of life to study the mye-

### Table II. Outcome in neonates with congenital cytomegalovirus infection according to neural ultrasound scanning findings and presence or absence of symptoms at birth

<table>
<thead>
<tr>
<th>Outcomes (n)</th>
<th>Normal US results (n = 45)</th>
<th>Pathologic US results (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptoms (n = 8)</td>
<td>No symptoms (n = 37)</td>
</tr>
<tr>
<td>Death</td>
<td>0/45</td>
<td>3/45 (6.7%)</td>
</tr>
<tr>
<td>DQ ≤85 and motor delay</td>
<td>0/45</td>
<td>6/11 (54.5%)</td>
</tr>
<tr>
<td>DQ ≤85 + SNHL</td>
<td>0/45</td>
<td>6/11 (54.5%)</td>
</tr>
<tr>
<td>DQ ≤85 + SNHL + motor delay</td>
<td>0/45</td>
<td>6/11 (54.5%)</td>
</tr>
<tr>
<td>SNHL + strabismus</td>
<td>0/45</td>
<td>6/11 (54.5%)</td>
</tr>
<tr>
<td>Isolated SNHL</td>
<td>3/45 (6.7%)</td>
<td>11/12 (91.7%)</td>
</tr>
<tr>
<td>Strabismus</td>
<td>1/45</td>
<td>3/45 (6.7%)</td>
</tr>
<tr>
<td>Normal</td>
<td>0/45</td>
<td>34/45 (75.6%)</td>
</tr>
</tbody>
</table>

PPV, Positive predictive value; NPV, negative predictive value; NE, could not be estimated.

*One newborn with pathological US results died during the neonatal period. Follow-up data were available for 11 of the 12 patients who lived.

### Table III. Value of cranial ultrasound scanning in predicting outcome in 57 patients with congenital cytomegalovirus infection

<table>
<thead>
<tr>
<th>Number (%) of newborns with poor outcome</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of newborns with poor outcome</td>
<td>Normal US results</td>
<td>Pathological US results*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DQ ≤85</td>
<td>0/45</td>
<td>8/11 (72.7%)</td>
<td>NE</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Motor delay</td>
<td>0/45</td>
<td>6/11 (54.5%)</td>
<td>NE</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SNHL</td>
<td>3/45 (6.7%)</td>
<td>11/12 (91.7%)</td>
<td>154 (17.3–1219.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*One newborn with pathological US results died during the neonatal period. Follow-up data were available for 11 of the 12 patients who lived.
linization pattern. It has yet to be defined whether and when MRI should be performed in infants with congenital CMV infection who have no symptoms.

REFERENCES
