Does normal fetal brain ultrasound predict normal neurodevelopmental outcome in congenital cytomegalovirus infection?

Natalie Farkas1†, Chen Hoffmann2,3†, Liat Ben-Sira3,4, Dorit Lev3,5, Avraham Schweiger1,6, Dvora Kidron3,7, Tally Lerman-Sagie3,8 and Gustavo Malinger3,9*

1The Academic College of Tel-Aviv-Yafo, Tel-Aviv, Israel
2Neuroradiology Unit, Chaim Sheba Medical Center, Tel Hashomer, Israel
3Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel
4Pediatric Radiology Unit, Tel-Aviv Medical Center, Tel-Aviv, Israel
5Genetics Institute, The Edith Wolfson Medical Center, Holon, Israel
6Leowenstein Rehabilitation Center, Raanana, Israel
7Department of Pathology, Pinhas Sapir Medical Center, Kfar Saba, Israel
8Pediatric Neurology Unit, The Edith Wolfson Medical Center, Holon, Israel
9Department of Obstetrics and Gynecology, The Edith Wolfson Medical Center, Holon, Israel

Objective We evaluated the neuropsychological outcome of children with proven congenital cytomegalovirus (CMV) infection and normal consecutive fetal neurosonographic examinations.

Methods We retrospectively reviewed laboratory and imaging findings of children with congenital CMV infection. The study group consisted of children with a positive polymerase chain reaction (PCR) in amniotic fluid and virus isolation in urine in the first week of life, and normal fetal ultrasonographic (US) examination findings, including a normal multiplanar neurosonographic evaluation. Patients with abnormal magnetic resonance (MR) findings were not excluded. The study and control groups were evaluated for cognitive, language, and motor development at one follow-up examination conducted at 11–81 months of age.

Results Children with congenital CMV infection and normal fetal brain findings in the US examination did not differ from the control group in terms of cognitive, language, motor, emotional–behavioral, and executive functioning. There were no differences between congenitally infected children who had a normal fetal brain MR examination and children whose fetal brain MR examination raised suspicion of a possible brain insult.

Conclusions Normal neurosonographic examinations during pregnancy appear to predict a normal early neurodevelopmental outcome in fetuses with congenital CMV infection. Outcome did not correlate with suspected abnormal white matter on fetal MR imaging. Copyright © 2011 John Wiley & Sons, Ltd.

Key words: cytomegalovirus; prenatal diagnosis; ultrasound; MRI; neurodevelopmental outcome

INTRODUCTION

Cytomegalovirus (CMV) is the largest member of the virus family Herpesviridae that infects almost all humans at some point in their lives (Ross and Boppana, 2004). Congenital CMV infection is most likely to occur following primary infection during pregnancy, and it is less common in cases of reactivation of the disease or infection by a different CMV strain (Boppana et al., 1999; Enders et al., 2001). The prevalence of congenital CMV infection varies between 0.15 and 2.2% (Ross and Boppana, 2004; Ross et al., 2006; Malm et al., 2007). While most infants born with congenital CMV infection are asymptomatic, 10–15% show clinical findings at birth (Ross and Boppana, 2004).

It is generally agreed that congenital CMV infection, whether it is symptomatic or not, is a major risk factor for perceptual deficits. However, its influence on children’s future neuropsychological functioning is less well established. Symptomatic congenital CMV infection is a major risk factor for poor developmental outcome (Williamson et al., 1982; Conboy et al., 1986) but the available data regarding neuropsychological outcome for asymptomatic children is inconsistent (Conboy et al., 1986; Ivarsson et al., 1997; Kadowen et al., 1998; Temple et al., 2000; Zhang et al., 2007). Several studies based on imaging techniques have shown that the presence of microcephaly at birth and/or intracranial pathologies is associated with a very high risk of neurological abnormalities and mental retardation (Boppana and Fowler, 1997; Noyola et al., 2001; Ancora et al., 2007). Imaging studies from prenatally diagnosed children are scant and contradictory. Some studies have shown that the presence of abnormal brain findings in the US examination is highly suggestive of a poor neurodevelopmental outcome (Lipitz et al., 1997; Malinger et al., 2003b; Benoist et al., 2008a). Other studies found that
the US examination could not identify all the fetuses at risk for severe neurodevelopmental sequelae (Liesnard et al., 2000; Enders et al., 2001; Lipitz et al., 2002; Guerra et al., 2008).

The present study was designed to evaluate the neuropsychological outcome of children with congenital CMV infection and normal consecutive neurosonographic fetal examinations. In addition, we investigated whether MR provided additional information on these infants.

METHODS

Study population

We retrospectively reviewed files of patients with congenital CMV infection that were referred to the Fetal Neurology Clinic of Wolfson Medical Center, Holon, or underwent fetal MR examinations at the Neuroradiology Units of Sheba Medical Center, Tel Hashomer, and at Tel-Aviv Sourasky Medical Center, Israel, during a period of 7 years, from January 2001 to September 2007.

The women were referred for prenatal diagnosis for suspected CMV infection following seroconversion. The suspected time of infection was calculated based on the study of available serum samples obtained at different gestational ages either for the follow-up of seronegative patients or from stored serum samples obtained during first or second trimester triple test studies.

Vertical transmission of infection to the fetus was evaluated by polymerase chain reaction (PCR) amplification of cytomegalovirus DNA in amniotic fluid samples and/or by isolation of virus from urine collected during the first week of life.

Fetal ultrasound studies included biometry and a structured search for anomalies with particular emphasis on those characteristic of CMV infection: presence of ventriculomegaly, periventricular hyperechogenicity with or without cysts, brain calcifications, intraventricular adhesions, malformations of cortical development, callosal or cerebellar insults, brain atrophy, or hemorrhage (Malinger et al., 2003b). Multiplanar fetal neurosonography was performed using a unified protocol as previously described (Malinger et al., 2003a, 2006). The patients were initially evaluated by US examination following seroconversion and at 3- to 4-week intervals until 35–38 weeks of pregnancy. Brain MR examinations performed at 32–36 weeks of pregnancy were available in some, but not all, of the cases. MR scans were obtained using a protocol previously described (Grossman et al., 2006).

A total of 109 women were identified (Figure 1). PCR amplification tests were available for 91 cases; 22 (24.2%) were negative and 69 (75.8%) were positive. Among the fetuses with positive PCR amniocentesis, 37 had normal neurosonographic examinations while 32 had US signs of CMV infection. The remaining 18 cases had normal findings in the US examinations, chose not to perform amniocentesis, and the virus was isolated from the newborn’s urine.

Termination of pregnancy was offered according to the Israeli law in all cases with abnormal findings; nevertheless, eight couples opted to continue pregnancy.

After counseling, four couples with normal brain findings in the US examination but an abnormal finding in magnetic resonance imaging (MRI) decided to terminate pregnancy. Another couple opted for termination due to the development of severe hepatomegaly at 34 weeks of pregnancy. We reviewed the autopsy results in two of these cases. Forty couples, including 8 with abnormal US findings, decided to continue the pregnancy. Eight families with normal findings in the US examinations were lost to follow up, and three refused to participate.

The remaining 21 children were included in the study group, all of them with normal findings in the US examinations. MRI was available for 16 children and found to be normal in 11 and abnormal in 5.

Four children with congenital CMV infection were treated by intravenous ganciclovir followed by oral valganciclovir during the first months of life.

The control group (n = 21) included age- and gender-matched, randomly selected children whose mothers had a normal prenatal findings in the US examination and no clinical evidence of CMV infection. Fetal MRI was not performed on patients in the control group.

Test procedures

After approval of the Institutional Review Boards, a written and oral explanation about the study was given

Referred patients

<table>
<thead>
<tr>
<th>PCR data available</th>
<th>Abnormal US</th>
<th>Normal US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>22</td>
<td>69</td>
</tr>
<tr>
<td>Positive</td>
<td>37</td>
<td>5</td>
</tr>
</tbody>
</table>

Termination of pregnancy (TOP) delivered (Delivered) and refused (Refused).

Test procedures

After approval of the Institutional Review Boards, a written and oral explanation about the study was given...
to the parents of the children, and a written consent form was obtained. Past medical history and developmental milestones of the child were retrospectively obtained as well as family history and demographic features. Age-appropriate neuropsychological and behavioral tests were performed at the Pediatric Neurology Clinic of the Wolfson Medical Center or at the participant’s home. This evaluation provided a Full-Scale IQ/DQ assessment, and children’s performance was also evaluated across a wide range of cognitive domains, including executive functioning, language, motor abilities and behavior. Neuropsychological evaluation was not blind, as the examiner was the same person who contacted the families of both the study and control groups.

Assessment instruments

On the basis of the children’s age, two different batteries were administered: the younger sub-group consisted of children aged 11–42 months and the older sub-group of children aged 43–83 months.

The younger sub-group was assessed with the Bayley Scale of Infant and Toddler Development, Third Edition (BSID-III) (Bayley, 2006). The older sub-group was assessed with the Kaufman Assessment Battery for Children (K-ABC) (Kaufman and Kaufman, 1983), the Peabody Picture Vocabulary Test, Fourth Edition (PPVT-IV) (Dunn and Dunn, 2007), and the Wide Range Assessment of Visual Motor Abilities (WRA VMA)-Pegboard subtest (Adams and Sheslow, 1995).

Parents of the older sub-group completed the age-appropriate version of the Child Behavior Checklist (CBCL/1.5-5; CBCL/6-18) (Achenbach and Rescorla, 2000, 2001), a questionnaire that obtains information regarding behavioral/emotional problems.

In addition, the age-appropriate version of the Behavior Rating Inventory of Executive Function (BRIEF-P, BRIEF) (Gioia et al., 2000, 2002) was completed by the parents of the children in both age groups.

Finally, all the parents were administered an additional demographic questionnaire concerning personal information, including: educational background, income level, and health status of family members.

Statistical analyses

Analyses of the outcome data were carried out using SPSS 16.0 (Softonic, Cerdanyola del Vallés, Spain) statistical analysis software. As most of the aforementioned neuropsychological tests and questionnaires do not have Israeli normative data, we used the control group to validate all test results. Analysis was performed for each age group separately as well as for the two groups combined. To compare between the experimental and the control groups as a whole, regardless of different age groups, test scores were converted into age-appropriate z-scores ($M = 0$, $SD = 1$), creating three composite variables: (1) cognitive score, comprising the total K-ABC score and the Bayley’s cognitive score; (2) receptive language score, comprising the PPVT score and the Bayley’s receptive language score; and (3) fine motor score, comprising the Pegboard score and the Bayley’s fine motor score. As the tests that were used in this study are standardized and provide age-corrected standard scores, the raw scores were first converted into the age-corrected $z$-scores, and then averaged across the relevant scales to provide the three index scores.

Multivariate analysis of variance (Wilks’ lambda MANOVA) was performed to examine differences between the experimental and the control groups in terms of cognitive, language, motor, behavioral, and executive functioning. MANOVA was also performed to examine differences between children who had abnormal MRI findings compared with children with normal MRI imaging during pregnancy. These analyses were performed in order to compare group means across the dependent variables simultaneously, but also each variable separately. Tests were considered significant at $p < 0.05$.

RESULTS

Forty-two infants and children were evaluated in the present study (20 boys and 22 girls). The mean subject age at examination was 34.4 months (range 11–83 months). Each group consisted of 7 older children and 14 infants. The children were evaluated only once.

Table 1 illustrates the similarity between the study and control groups. Evaluation of the gestational age at infection was available in 17 cases, with a mean gestational age of 18.65 (range 7–31) weeks.

MRI examinations of the fetal brain, performed between 32 and 36 weeks of pregnancy, were performed in 16 patients of the study population and raised the suspicion of possible brain pathology in five (31.25%), including abnormal periventricular or temporal white matter (three), mild unilateral ventriculomegaly (one), enlarged temporal horns (one), periventricular temporal cysts (two), large cavum septi pellucidi (one) (Figure 2). These patients decided to continue the pregnancy.

In addition to the 21 children who participated in the current study, there were another four fetuses with abnormalities observed only on MRI but not on US examination, and the parents decided to terminate the pregnancy. Postmortem examination performed in two of these fetuses showed microglial nodules consistent with an inflammatory reaction without the presence of inclusion bodies in one, and no brain pathology in the other. Two families refused autopsy.

All but one child were asymptomatic at birth. Postnatal brain US examination was normal in all the children. One infant was diagnosed at birth as having bilateral sensorineural hearing loss, and had a cochlear implant transplanted at the age of 1 year. This infant had both normal fetal brain US and MRI examinations, and his development was found to be otherwise normal.

Children with congenital CMV infection and normal fetal brain US studies did not differ from the control
Table 1—Demographic features of children with congenital cytomegalovirus (CMV) infection and control children

<table>
<thead>
<tr>
<th>Demographic features</th>
<th>CMV children</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (47.6%)</td>
<td>10 (47.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (52.4%)</td>
<td>11 (52.4%)</td>
</tr>
<tr>
<td>Age (months)(^a)</td>
<td>34.41 ± 16.68</td>
<td>34.61 ± 16.39</td>
</tr>
<tr>
<td>Parental education(^b)</td>
<td>15.3 ± 2.4</td>
<td>15.1 ± 2.8</td>
</tr>
<tr>
<td>Length of pregnancy (weeks)</td>
<td>39.28 ± 1.8</td>
<td>39.50 ± 1.96</td>
</tr>
<tr>
<td>Child’s weight at birth (g)</td>
<td>3285.65 ± 499.79</td>
<td>3123.35 ± 572.80</td>
</tr>
<tr>
<td>Family’s level of income(^c)</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>

\(^a\) Data are presented as mean ± SD. \(^t\)-test for all independent samples was not significant.
\(^b\) Parental education is presented as the average of the number of years both parents studied.
\(^c\) Family’s level of income is presented as mean rank. Mann–Whitney non-parametric test was not significant (Mann–Whitney \(U = 190, p = 0.767\)).

Figure 2—(a) Transvaginal sagittal plane at 36 weeks of gestation showing normal echogenicity in the temporal lobe. The ultrasonographic (US) examination was performed following the abnormal magnetic resonance imaging (MRI). SSFSE T2 axial image at the level of the temporal lobes (b) demonstrates increased signal intensities in the anterior part of both lobes, in comparison to the white matter in the other parts of the image. SSFSE T2 coronal (c) and sagittal (d) also confirms the hyperintense signal in the anterior part of the temporal lobes.

In the younger sub-group, scores were slightly, but not significantly, higher for the congenital CMV infection group relative to the control group. Both groups scored higher than the standardization sample, but it could be an artifact stemming from the use of the Hebrew translation of the BSID-III. In contrast, in the older group, scores were slightly, but not significantly, higher for the control group relative to the study group. There was no difference between the groups in terms of emotional-behavioral and executive functioning.

We examined the difference between congenitally infected children who had a normal fetal brain MRI and those whose fetal brain MRI raised the suspicion of possible brain pathology (Table 3). No differences were found between the two groups in cognitive, language, and motor functioning. Analysis of the differences
in both hands.

Multivariate analysis of the variance was not significant.

Owing to the broad spectrum of the disease, the ideal management in cases of PCR-proven fetal infection is problematic.

Imaging studies in prenatally diagnosed children are limited, focusing mainly on fetuses with abnormal findings usually associated with poor outcome (Benoist et al., 2008b; Malinge and Lerman-Sagie, 2008). However, there is a lack of information regarding the prognosis of infected children with normal fetal brain US examinations. Previous studies found that US examination failed to detect some fetuses at risk (Liptitz et al., 2002; Guerra et al., 2008).

In our study, all congenitally infected newborns, except one who had congenital sensori neural hearing loss (SNHL), were asymptomatic at birth and had normal brain findings in the US examinations. Although the presence or absence of signs and symptoms in newborns is thought to be useful in predicting complications later in life, the studies concerning neuropsychological functioning of symptomatic and asymptomatic children resulted in mixed findings (Williamson et al., 1982; Conboy et al., 1986; Ivarsson et al., 1997; Kashden et al., 1998; Temple et al., 2000; Kylat et al., 2006; Dollard et al., 2007; Zhang et al., 2007).

Recently the use of fetal brain MRI has gained widespread acceptance based on the assumption that it can provide additional information for accurate prenatal diagnosis and counseling. However, the actual contribution to the prognosis of congenital CMV remains unclear (Benoist et al., 2008b).

In consistency with previous studies regarding MRI and dedicated neurosonography (Malinge et al., 2004), the present study found agreement in 11/16 (68.75%) patients between the interpretation of the dedicated neurosonographic examination and the MRI. However, in 5/16 (31.25%) of the cases, dedicated neurosonography was normal while brain MRI performed at 32–36 weeks of gestation raised suspicion for a possible pathology. No significant differences in cognitive, language, and motor functioning were noted between congenitally infected children with normal and abnormal fetal brain MRI.

It is difficult to explain why infected children with suspected normal fetal MRI do not differ from children with a normal scan in terms of neuropsychological functioning. One explanation might be that the MRI is highly sensitive and identifies minor changes in white matter signal that could represent a reversible inflammatory reaction, without affecting long term neurodevelopment.

Information regarding the sensitivity and specificity of MRI in detecting white matter abnormalities is still controversial. Picone et al. (2008) found abnormal white matter in five fetuses with a normal fetal brain finding in the US examination. The autopsy or development was abnormal in all of these patients. However, these fetuses had extracerebral signs of CMV infection identified by US examination. When both MRI and US examinations did not reveal abnormal cerebral and extracerebral findings, the outcome was always good. Benoist et al. (2008b) found abnormal white matter in two fetuses in which both US and MRI examinations raised the suspicion of brain pathology. In one fetus, the US finding was normal but the MRI raised the suspicion of microcephaly. No fetal brain abnormality was observed at

## DISCUSSION

CMV screening is not performed routinely in most countries and there is a lack of knowledge regarding the ideal management in cases of PCR-proven fetal infection. Owing to the broad spectrum of the disease, the prenatal management of pregnant women with fetal intrauterine CMV infection is problematic.

### Table 2—Neuropsychological test performance of children with congenital cytomegalovirus (CMV) infection and control children

<table>
<thead>
<tr>
<th></th>
<th>Younger sub-group</th>
<th>Older sub-group</th>
<th>Both sub-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMV</td>
<td>Control</td>
<td>CMV</td>
</tr>
<tr>
<td>Cognitive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.84</td>
<td>0.91</td>
<td>0.99</td>
</tr>
<tr>
<td>SD</td>
<td>0.91</td>
<td>0.88</td>
<td>0.92</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.34</td>
<td>1.03</td>
<td>0.78</td>
</tr>
<tr>
<td>SD</td>
<td>0.90</td>
<td>0.55</td>
<td>0.86</td>
</tr>
<tr>
<td>Motor a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.14</td>
<td>−0.07</td>
<td>0.57</td>
</tr>
<tr>
<td>SD</td>
<td>0.90</td>
<td>0.56</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Data are presented as z-score.

Motor scale for the older sub-group and both sub-groups is presented as the z-score of the average performance in both hands.

Table 3—Neuropsychological test performance of children with cytomegalovirus (CMV) and normal fetal brain magnetic resonance imaging (MRI) examination and children with CMV and abnormal fetal brain MRI

<table>
<thead>
<tr>
<th></th>
<th>Normal MRI (n = 11)</th>
<th>Abnormal MRI (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.88</td>
<td>0.99</td>
</tr>
<tr>
<td>SD</td>
<td>0.82</td>
<td>0.88</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.21</td>
<td>1.21</td>
</tr>
<tr>
<td>SD</td>
<td>1.21</td>
<td>1.21</td>
</tr>
<tr>
<td>Motor a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.79</td>
<td>0.24</td>
</tr>
<tr>
<td>SD</td>
<td>0.90</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Data are presented as z-scores.

Multivariate analysis of the variance was not significant.

Motor scale is presented as the z-score of the average performance in both hands.

between groups in terms of emotional-behavioral and executive functioning could not be carried out, as the number of children in each group was insufficient.

Comparison of the means revealed no differences between children who received and did not receive antiviral treatment, in terms of cognitive, language, and motor functioning.

The hypothesis of equal variance was verified for each independent variable in all of the analyses (Levene’s test of equality of error variances was insignificant: \( p > 0.05 \)).

### DISCUSSION

CMV screening is not performed routinely in most countries and there is a lack of knowledge regarding the ideal management in cases of PCR-proven fetal infection. Owing to the broad spectrum of the disease, the prenatal management of pregnant women with fetal intrauterine CMV infection is problematic.

Imaging studies in prenatally diagnosed children are limited, focusing mainly on fetuses with abnormal findings usually associated with poor outcome (Benoist et al., 2008b; Malinge and Lerman-Sagie, 2008). However, there is a lack of information regarding the prognosis of infected children with normal fetal brain US examinations. Previous studies found that US examination failed to detect some fetuses at risk (Liptitz et al., 2002; Guerra et al., 2008).

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postnatal transfontanellar ultrasound (TFU) examination in this patient. Normal prenatal TFU examination had the best negative predictive value (93.5%) and the authors concluded that isolated abnormalities suspected on MRI should be considered with great caution. The lack of correlation between minor MRI changes on prenatal scans and the postnatal neurologic clinical outcome, should not necessarily question the accuracy of the observed prenatal MRI changes, but rather the predictive value of those changes with respect to clinical outcome. Further studies are needed to clarify this relationship.

The finding that in an otherwise normal fetus, neurosonography can predict normal neurodevelopmental outcome is reassuring and extremely important for the families of thousands of children born each year with CMV infection. However, the relatively small sample size cannot rule out the possibility of an uncaptured effect and thus it should be viewed with caution. Nevertheless, the rigorous control procedure, thoroughness of the testing, and the strict objectivity of the measurements allow a reasonable degree of confidence in the results.

Caution is also needed as we cannot rule out entirely the possibility that neuropsychological or perceptual deficits will manifest later in life, as most of the children were evaluated at a young age. Therefore, repeat neuropsychological evaluations during school years may be appropriate.

CONCLUSIONS

Normal serial targeted transabdominal and transvaginal ultrasound examinations performed at 3- to 4-week intervals during pregnancy, and aimed at the visualization of specific and well-defined signs of brain abnormalities known to be associated with CMV infection, appear to predict good early neurodevelopmental outcome.

When the US finding is normal even if the MRI reveals abnormal white matter signal, the prognosis remains good. The nature and significance of these MRI abnormalities are not clear, but even if they do reflect actual brain pathology, the probability of neurodevelopmental impairment seems low.

REFERENCES


