Hearing Loss With Congenital Cytomegalovirus Infection

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abstract

OBJECTIVE: In this study, we determined the prevalence of hearing loss in 157 children with proven congenital cytomegalovirus (cCMV) infection. We looked at possible risk determinants for developing hearing loss and proposed recommendations for screening and follow-up in the newborn.

METHODS: In a prospective 22-year study, 157 children with proven cCMV infection were evaluated for sensorineural hearing loss (SNHL). The development of SNHL was correlated with the type of maternal infection (primary versus nonprimary), the gestational age of maternal primary infection, imaging findings at birth, and the presence of symptomatic or asymptomatic infection in the newborn.

RESULTS: Of all children, 12.7% had SNHL, and 5.7% needed hearing amplification because of SNHL. Improvement, progression, and fluctuations of hearing thresholds were seen in 45%, 53.8%, and 5.7% of the children, respectively. Hearing loss was more common in the case of a symptomatic infection at birth ($P = .017$), after a maternal primary infection in the first trimester of pregnancy ($P = .029$), and in the presence of abnormalities on a neonatal brain ultrasound and/or MRI ($P < .001$).

CONCLUSION SNHL is a common sequela in children with cCMV infection. Risk factors for SNHL were primary maternal infections before the 14th week of pregnancy, the presence of a disseminated infection at birth, and imaging abnormalities in the newborn. These children may benefit from a more thorough investigation for SNHL than children who do not present with those risk factors.

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Prof. Dr. I. Foulon conceptualized and designed the study and drafted the initial manuscript; Dr. Y. De Brucker performed the retrospective analysis of the imaging results, helped with the acquisition of data, and reviewed the manuscript; Prof. Dr. R. Buyl aided in the statistical analysis and reviewed the manuscript; Mrs. E. Lichtert performed the audiometric testing, reviewed the manuscript, and helped with the acquisition of data; Dr. K. Verbruggen, Prof. Dr. D. Piérard, Dr. FA Camfferman, and Prof. Dr. L. Gucciardo helped with the acquisition of data and reviewed the manuscript; Prof. Dr. F. Gordts reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Hearing loss is 1 of the most common sequelae in children with a congenital cytomegalovirus infection.

WHAT THIS STUDY ADDS: Incidences of hearing loss and the need for hearing rehabilitation in children with congenital cytomegalovirus infection are discussed. We describe risk indicators for late-onset hearing loss.

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Congenital cytomegalovirus (cCMV) infection is the most common fetal viral infection and is the leading cause of nonhereditary sensorineural hearing loss (SNHL) in the developed world.[1] Despite the high incidence of cCMV infection (0.53%),[1,2] screening for a cytomegalovirus infection during pregnancy and neonatal screening at birth are not recommended.[3] However, asymptomatic children can develop sequelae, with SNHL as the most present feature. The risk of developing hearing loss in children with an asymptomatic infection is between 5% and 20%.[1,4–6] In ∼10% of the children, the infection is symptomatic at birth. The risk for developing SNHL in those symptomatic children is much higher (30%–65%).[4–7]

In this prospective study, we determined the incidence of SNHL in 157 children with proven cCMV infection. We searched for risk determinants for developing hearing loss and propose recommendations for screening and follow-up in the newborn.

METHODS

The study protocol was approved by the Committee of Medical Ethics of the Universitair Ziekenhuis Brussel (2004/098). This is a prospective study that covers the period between 1995 and 2017.

Subjects

A total of 173 children with a cCMV infection managed in the ear, nose, and throat department of the Universitair Ziekenhuis Brussel were included in the study. These children were consecutive live-born infants born in the Universitair Ziekenhuis Brussel and detected through an ongoing screening program. Of these children, 60 were already described in a previously published article[1] in 2008. This screening program, designed as previously described,[8] consisted of virological screening (saliva or urine cytomegalovirus culture) in all live-born infants within 5 days after birth.

Type of Maternal Cytomegalovirus Infection

As part of standard prenatal care, women managed at the prenatal consultation were screened for cytomegalovirus antibodies at the first prenatal consultation and at birth. This allowed us to determine for each congenitally infected child the type of maternal cytomegalovirus infection. An infection was considered primary when a maternal seroconversion in cytomegalovirus immunoglobulin G (IgG) occurred during pregnancy or when the serological results were highly suggestive of a primary cytomegalovirus infection (high immunoglobulin M antibodies and low IgG antibodies in the first trimester of pregnancy followed by a rise in IgG antibodies and a decrease in immunoglobulin M antibodies). An infection was considered nonprimary when a congenitally infected neonate was born to a mother showing immunity for cytomegalovirus infection in a serum sample obtained before conception or when the serum sample obtained in the first trimester of pregnancy had high IgG avidity antibody.

In the case of a primary infection during pregnancy, an estimation of the maternal trimester at which maternal infection occurred was performed. In the presence of a seroconversion, the timing of infection during pregnancy was based on the gestational age during pregnancy of the last negative serology result and the first positive serum sample and on the serological profile after seroconversion. When the serological profile in the first trimester of pregnancy was highly suggestive of a primary infection, the infection was designated as having taken place in the first trimester of pregnancy. The definition of trimester of pregnancy was based on American College of Obstetricians and Gynecologists guidelines.

Clinical Evaluation and Audiological Assessment

All congenitally infected neonates were examined at birth by a pediatrician. Signs of symptomatic infection (hepatosplenomegaly, petechiae, jaundice, or microcephaly) were recorded. Children with ≥1 sign were classified as having had a symptomatic infection.

All children were tested for SNHL until the age of 4 years according to an algorithm that was previously described.[9] All children received an otological examination by an ear, nose, and throat specialist, (high-frequency) tympanometry, auditory brainstem response, and distortion product otoacoustic emissions at birth. According to the presence of SNHL, children would follow different follow-up protocols. In the case of normal hearing at birth, follow-up is proposed at 5 and 12 months, then yearly until the age of 4. In the case of hearing loss at birth, more rigorous follow-up is needed.[9] During follow-up, different hearing tests are performed depending on the age of the child.[9]

Late-onset hearing loss was diagnosed when a child with a normal hearing at birth developed a hearing loss during follow-up. Progressive hearing loss occurred when children with an SNHL at birth had worsening of their hearing threshold during later visits. In contrast, improvement of hearing thresholds was also seen in children with hearing loss. Fluctuations (with improvement and worsening) were also recorded.

To determine the severity of SNHL, the classification from the International Bureau for Audiophonology[10] was used. In cases of bilateral SNHL, we used the result

of the better hearing ear to classify hearing loss.

Other risk factors of hearing loss were recorded according to the Joint Committee on Infant Hearing.[11]

Imaging

Children with proven cCMV infection underwent a brain ultrasound and/or MRI. The ultrasound of the brain was performed via a transfontanellar approach by using a pediatric ultrasound probe. The cranial ultrasound was done on different high-end sonographical devices with developments of the devices over the entire study period (1995–2017). MRI was performed on a 1.5 T Philips Intera or 3.0 T Philips Achieva MRI system (Best, Netherlands). No gadolinium contrast was administered. Imaging findings of cCMV infection were: intracranial calcifications, migrational abnormalities, white matter disease, periventricular cysts, cerebral atrophy, ventriculomegaly, ventricular adhesions, and lenticulostriate vasculopathy. Results from these imaging examinations were retrieved from the medical records of the children in a retrospective way. The radiologist who interpreted the imaging examinations was aware that those children had a cCMV infection but had no access to the results of the hearing test.

Statistics

Descriptive statistics of patient characteristics and possible predictors are presented as frequencies (n) and percentages (%). To test the relationship between possible predictors (cCMV, type of infection, maternal infection, time of infection [first, second, or third trimester], and SNHL), a χ^2 test or Fisher's exact test was used when appropriate. All tests were performed at a significance level of $P < .05$. The analyses were executed by using IBM SPSS software version 25 (IBM SPSS Statistics, IBM Corporation).

TABLE 1 Characteristics of the Population

Characteristics	Children (cCMV)
Subjects, *N*	157
Asymptomatic, *n* (%)	146 (93%)
Symptomatic, *n* (%)	9 (5.7)
Unknown, *n* (%)	2 (1.3)
Maternal cytomegalovirus infection	
Primary infection, *n* (%)	76 (48.4)
Nonprimary infection, *n* (%)	42 (26.8)
Unknown, *n* (%)	39 (24.8)
SNHL, *n* (%)	20 (12.7)
Unilateral, *n* (%)	11 (7.0)
Bilateral, *n* (%)	9 (5.7)
Hearing amplification, *n* (%)	9 (5.7)
Progression, *n* (%)	7 (53.8)
Late-onset hearing loss, *n* (%)	7 (4.5)
Unilateral, *n* (%)	5 (3.2)
Bilateral, *n* (%)	2 (1.3)

RESULTS

Subjects

Of the 173 children with a cCMV infection managed in our department, 13 were lost to follow-up and 3 died of the consequences of a symptomatic cCMV infection before hearing evaluation was performed. The remaining 157 children were enrolled in the study. A symptomatic infection was diagnosed in 9 children (5.7%), and an asymptomatic infection was diagnosed in 146 children (93%). For 2 children, no clinical information at birth was available. In Table 1, the characteristics of the population are shown.

Information About Maternal Cytomegalovirus Infections

Of the 157 children, 76 (48.4%) were born after a maternal primary infection, and 42 children (26.8%) were born after a maternal nonprimary infection. In 39 (24.8%) cases, the type of infection could not be determined. Among the 76 cases of maternal primary infection, the cytomegalovirus infection was estimated to have occurred in the first, second, and third trimester of pregnancy in 17, 33, and 22 children, respectively. In 4 children, it was not possible to determine timing of primary maternal infection.

Hearing Loss

Hearing loss was diagnosed in 20 children (12.7%). Of these children, 9 (5.7%) needed rehabilitation for their SNHL. The average time for follow-up was 41.4 months; the median was 31 months. All children received a hearing test within 2 weeks after birth.

In Table 2, the severity of hearing loss in these children is presented. A symptomatic infection has a statistically higher risk for developing SNHL (44.4%) compared with an asymptomatic infection (11.0%; $P = .017$).

Hearing loss was detected in children born after a maternal primary infection (11.8%) as well as after a maternal nonprimary infection (4.8%; $P = .32$). When the type of maternal infection was unknown, SNHL occurred in 23.1% of children ($P = .045$). The 2 children who developed hearing loss after a maternal nonprimary infection both had bilateral SNHL (severe and profound).

A primary cytomegalovirus infection during the first trimester of pregnancy resulted in hearing loss in 5 out of 17 children (29.4%), of which all were severe to profound (Table 3). In the case of an infection in the second trimester of pregnancy, 3 children developed hearing loss, of which 1 child developed a severe unilateral hearing loss after bacterial meningitis. Two children had

TABLE 2 Severity of SNHL in Children With cCMV Infection (Total Group, 157 Children)

Severity of SNHL	*n* (%)
Mild (21–40 dB)	2 (1.3)
Moderate (41–70 dB)	3 (1.9)
Severe (71–90 dB)	3 (1.9)
Very severe (91–119 dB)	2 (1.3)
Profound (>120 dB)	10 (6.4)
Total	20 (12.7)

TABLE 3 Hearing Loss According to the Trimester of Maternal Primary Infection

Severity of SNHL	Trimester of Primary Maternal infection			
	First (n = 17)	Second (n = 33)	Third (n = 22)	Total (N = 72)[a]
Mild (21–40 dB)	0	1	1	2
Moderate (41–70 dB)	0	1	0	1
Severe (71–90 dB)	1	1	0	2
Very severe (91–119 dB)	1	0	0	1
Profound (>120 dB)	3	0	0	3
Total, n (%)	5 (29.4)	3 (9.1)	1 (4.5)	9 (12.5)

[a] In 4 cases, the time of infection could not be determined.

unilateral mild or moderate SNHL. The mother of this last child had her primary infection at ~15 weeks' gestation. In the case of infection in the third trimester of pregnancy, 1 child developed hearing loss; this child developed a mixed hearing loss (not specific for cCMV) at the age of 19 years. When infection took place in the first trimester of pregnancy, there was a statistically higher incidence of SNHL compared with a cytomegalovirus infection later in pregnancy (P = .029).

Characteristics of Hearing Loss

Among the 157 children with normal hearing thresholds at first visit, 7 developed late-onset hearing loss (4.5%). Three children with late-onset hearing loss had other important risk factors for hearing loss: 1 child had a familial risk factor for hearing loss (first degree) and another child had hearing loss after bacterial meningitis. One child developed a mixed hearing loss (not specific for cCMV infection) at the age of 19 years. If we exclude these 3 children from the group of children with late-onset hearing loss, the risk for late-onset SNHL is even lower (2.5%). Of the 20 children with SNHL, improvement in hearing thresholds was observed in 9 (45%).

Progression of hearing loss was observed in 7 children with hearing loss at birth (53.8%). In the whole group, fluctuations were seen in 9 children (5.7%). Seven children had >1 characteristic.

Imaging

A total of 140 children (89.2%) underwent imaging of the brain: 137 children underwent a brain ultrasound (of which 25 underwent an MRI as well), and 3 children underwent an MRI without a brain ultrasound. In Table 4, the results of brain imaging are shown. Chances of developing SNHL in the case of a normal imaging result (ultrasound and/or MRI) are 6.6%. In the case of an abnormal result (21 children), the risk of SNHL is 42.9% (P < .001). The sensitivity in detecting SNHL was 52.9% in the case of an abnormal imaging result, and the specificity was 90%. The risk of developing late-onset hearing loss after an abnormal imaging test was higher than in the case of a normal test result (14.3% vs 2.3%). Also, progression of SNHL occurred more often in the case of abnormal ultrasound and/or MRI results (28.6% vs 1.7%). Because of small numbers, a significance was not obtained. Ultrasound examination was found to be a good predictor of the risk of having SNHL. Brain imaging results were abnormal in 60%, 0%, and 5.3% of the children with a maternal infection in the first, second, and third trimester of pregnancy, respectively.

DISCUSSION

In our population, the incidence of SNHL in children with cCMV infection was 12.7%. This is in accordance with other studies[1,12,13] in which incidences of hearing loss between 12% and 20% were reported. A symptomatic infection is known to have a higher risk for developing SNHL.[1,4–6] This was confirmed in our study, with 44.4% of the included children who were symptomatic presenting with hearing loss. Children who had an infection after a maternal primary infection had a higher chance of developing SNHL than children who had an infection after a maternal nonprimary infection, although this was not statistically significant. This is in accordance with previous publications.[14] Although less frequent, hearing loss after a maternal nonprimary infection was also severe and profound in our group.

Despite high incidences of hearing loss, not all children need hearing rehabilitation. Some children have only mild or unilateral hearing loss. In these cases, children are followed but do not always need hearing amplification. It is interesting to note that the need for hearing rehabilitation is often not mentioned in the available literature. In our study, only 5.7% of all neonates who were congenitally infected needed hearing amplification (hearing aid or cochlear implantation). In children with a symptomatic infection, 44.4% required hearing rehabilitation compared with 3.4% in the group with an asymptomatic infection. In 1 study by Goderis et al,[4] the need for hearing amplification was 1.6% in children with an asymptomatic

TABLE 4 Hearing Loss According to Imaging Results of 140 Children

	Ultrasound (N = 137)		MRI (N = 28)	
	Normal	Abnormal	Normal	Abnormal
Total, n (%)	120 (87.6)	17 (12.4)	17 (60.7)	11 (39.3)
Normal hearing, n (%)	111 (92.5)	9 (52.9)	14 (82.4)	7 (63.6)
SNHL, n (%)	9 (7.5)	8 (47.1)	3 (17.6)	4 (36.4)

infection and 29.3% in the group with symptomatic infection. For this reason, we can assume that the economic and social impact of an asymptomatic cCMV infection might not be as high as presumed by the incidence of SNHL alone.

If neonatal screening for cCMV infection is implemented, it should be noted that many children with asymptomatic infections will be diagnosed. To prevent unnecessary hearing evaluations, risk indicators should be detected, and the way hearing follow-up is proposed should be changed. In a previous publication,[9] we proposed an algorithm for hearing follow-up. Moreover, several risk indicators were identified in this present study; therefore, we propose to update this algorithm to reduce the number of hearing tests and unnecessary concern in parents. Maternal infection during the first trimester of pregnancy is known to have a predictive value on adverse outcome in the children.[15–17] This can also be seen in our study: we detected a 29.4% risk for developing SNHL when maternal primary infection occurred in the first trimester of pregnancy. Only 1 child had a moderate hearing loss after a maternal primary infection in the second trimester of pregnancy that could truly be linked to a cCMV infection. Thereby, mothers who had a primary infection during the second or third trimester of pregnancy could be reassured because hearing loss was rarely seen in these children.

The true burden of late-onset hearing loss has long been overestimated. Most reports defined late-onset hearing loss as a percentage of all children with hearing loss.[6,18] By doing so, higher percentages of late-onset hearing loss are obtained, but they do not represent the risk of developing hearing loss in a group of children with normal hearing at birth. It is more interesting to define late-onset hearing loss as a percentage of children with no hearing loss at birth that will finally develop SNHL. In our study, 7 children had late-onset hearing loss. This is 4.5% of all children with normal hearing after birth and 2.5% if we exclude children with other important risk factors for hearing loss. This is in line with other studies, in which incidence between 1.3% and 10.6%[4,18,19] is mentioned. In the studies by Dahle et al[6] and Royackers et al,[19] late-onset hearing loss was mainly seen in children with a symptomatic infection (16%–17.4%). Most cases of late-onset hearing loss were diagnosed before the age of 24 months.[4] Because late-onset hearing loss is seldom seen after the age of 4, we propose to end the follow-up period at the age of 4. In our group, children who developed hearing loss after this age probably had another cause for their hearing loss. Work by Lanzieri et al[20] confirms that screening for hearing loss in children with cCMV infection and normal hearing at the age of 5 years old might not be of clinical importance because the risk of delayed-onset hearing loss at that age is not greater than in a control group.

On the other hand, specific subgroups should be screened more often. In our study, we showed that children born after a maternal primary infection in the first trimester of pregnancy, children with a symptomatic infection, and children with abnormalities revealed on brain ultrasounds or MRI are at higher risk for developing SNHL and late-onset hearing loss. For these children, we recommend $\geq$4 hearing tests during the first year of life and every 6 months after that until the age of 4, even if these children have no hearing loss at birth. The presence of a symptomatic infection, neurologic involvement, and ultrasound result abnormalities are known to be predictive of the development of hearing loss.[21–25]

Progression of SNHL in those children presenting with hearing loss at birth is not infrequent. In our study, we saw progression of SNHL in 53.8% of the children. This is in accordance with the literature,[20] in which progression of hearing loss is a frequently observed phenomenon. Even if it is mainly seen in children with a symptomatic infection,[4,6,12] it also occurs in children with an asymptomatic infection.[18,26] We therefore recommend managing all children with SNHL at birth more often and also longer than 4 years because in these children, progression of hearing loss can occur throughout adolescence.[20]

It is important to mention that in our group, there were a significant number of children with other etiologies of hearing loss, and the diagnosis of a cCMV infection should not exclude other etiologies.

A limitation of the study could be that all the children studied live in the Brussels area, and this might not be representative of Belgium. It is possible that the incidence of cCMV is different from the rest of Belgium and the proportion of maternal primary infection versus maternal nonprimary infection might not be comparable. Another limitation is the fact that only 28 children received MRI examination. It is possible that some children with normal ultrasound examination results could have shown abnormalities on MRI results.

The strength of this study resides in the inclusion of children through an ongoing study, in which all children born in our hospital were screened for a cCMV infection and pregnant women received serological screening as part of standard medical care. We believe that a serological algorithm during pregnancy could be of utmost importance for the prediction of sequelae in the offspring because mainly children with cytomegalovirus infections during the first trimester of pregnancy are at risk for SNHL.

Without maternal serological data, counseling during and after pregnancy will be more difficult. Therefore, a serological screening during pregnancy is mandatory. In a previous study,[8] it was demonstrated that serological screening in pregnant women is possible, and that this method allows for the detection of 82% of all cCMV infections.[8] Lastly, but not least, it is also assumed that with this method, children with the highest risk for developing sequelae (infections in the first trimester) would be detected. Other authors confirm that the serological profile during pregnancy, including the avidity index, can help in predicting infection and sequelae in the offspring.[27,28]

Because primary infections in the first trimester of pregnancy had the highest risk for SNHL, preventive measures to avoid cytomegalovirus infection during pregnancy should be implemented before conception.

CONCLUSIONS

The prevalence of SNHL in children with cCMV infection in our population is 12.7%. Children with a symptomatic infection, abnormal brain ultrasound or (MRI) examination results, or a maternal primary infection in the first trimester of pregnancy have higher risks for developing late-onset SNHL. We propose an audiological follow-up on the basis of these risk indicators.

ABBREVIATIONS

cCMV: congenital cytomegalovirus
IgG: immunoglobulin G
SNHL: sensorineural hearing loss

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