Long-term audiological follow-up of children with congenital cytomegalovirus

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Abstract. Long-term audiological follow-up of children with congenital cytomegalovirus.

Objective: To evaluate the audiological outcome of children with congenital cytomegalovirus infection.

Methodology: In a prospective study, the hearing of 98 congenitally cytomegalovirus-infected children born between January 2003 and July 2009 was systematically evaluated until the age of six using the Flemish CMV protocol. Symptomatic children with hearing loss at birth were treated with ganciclovir, if parents consented.

Results: Seventy children passed initial screening, 28 had unilateral or bilateral hearing loss. In the normal hearing group, one asymptomatic and two symptomatic children developed late-onset hearing loss. Eight children in the group with hearing loss at birth received ganciclovir. Nine symptomatic and 11 asymptomatic children did not receive ganciclovir.

In the treated group, 37.5% of the children had stable hearing loss, and 37.5% had progressive and/or fluctuating hearing loss. First progression or fluctuation always occurred after the age of one year. The hearing threshold improved in 25.0%. The improvement took place during or shortly after treatment. Hearing loss remained stable in 33.3% of the untreated symptomatic children, while progression or fluctuation occurred in 55.5%. In the asymptomatic group, hearing loss was most commonly stable (63.6%). The first change in the hearing threshold was almost always detected before the age of one year in both untreated groups.

Conclusions: Hearing loss caused by congenital cytomegalovirus infection cannot be defined unequivocally either with respect to the level of hearing loss or its evolution over time. Treating symptomatic children with ganciclovir leads to a better prognosis during the first year of life, after which progression or fluctuation again becomes more likely. However, overall, progression is more common in the untreated symptomatic group. Asymptomatic children with SNHL are more likely to have a stable hearing status.
Material and methods

Subjects
The study population consisted of 98 children, 62 boys and 36 girls, born between January 2003 and July 2009. Children were included in the study when there was a suspicion of maternal CMV infection and cCMV was confirmed in the blood or urine of the newborn immediately after birth.

Audiological Assessment
In 2003, a number of hospitals in Belgium, including the University Hospitals of Leuven, set up a protocol for the audiological follow-up of children with CMV seroconversion during pregnancy. This protocol is referred to as the “Flemish CMV protocol”.

The protocol requires every newborn to undergo hearing screening within one month after birth. Auditory steady state responses (ASSR) or an auditory brainstem response (ABR) test as well as transient evoked oto-acoustic emissions (TEOAEs) are measured and high-frequency tympanometry is performed within 10 days after the refer. All subjects undergo an additional ABR at the age of three months.

At the University Hospitals of Leuven, Master software8 is used for the recording of the ASSR. Hearing thresholds at 0.5, 1, 2 en 4 kHz are determined using the protocol described by Luts et al.9 TEOAEs are measured using the Otodynamics ILOv6 system. TEOAEs are considered to be present in case of an overall reproducibility of 70% or more in combination with a signal-to-noise ratio of 6 dB or more in at least three consecutive frequency bands. High-frequency tympanometry is performed using a GN Otometrics Madsen Otoflex 100 system. Diagnostic ABR is recorded with a Bio-logic Navigator® Pro brainstem evoked system. Clicks of 100µs in duration are presented at a rate of 31 per second with alternating polarity using TDH-39 headphones. Electrodes are placed at the forehead and the mastoids. At each presentation level, 2000 sweeps are averaged. The presence of a response is determined by the visual inspection of the ABR waveforms. The threshold is defined as the lowest level at which wave V is detected and replicated.

In cases of hearing loss, early intervention at an audiological centre is initiated and ABR is repeated at the age of six months under general anaesthesia after paracenthesis when uncertainty persists about the hearing thresholds.

In cases of normal hearing, the protocol requires children without other lesions caused by the CMV infection to undergo hearing tests at 9 months, 12 months, 18 months, 24 months and then annually until the age of 6. In cases of other CMV-related lesions, an additional ABR is proposed at the age of 6 months. However, in view of the need for anaesthesia, at the University Hospitals in Leuven, this test is performed only to confirm progression or when grommets need to be placed in the presence of glue. All subjects included in the study were monitored in accordance with the Flemish CMV protocol. They underwent at least two audiological evaluations at different ages.

Treatment with ganciclovir was offered to all children with cCMV with both hearing loss and other CMV-induced lesions (central nervous system or ophthalmological). Parents were informed about the proposed ganciclovir therapy prior to birth. The newborns underwent hearing and visual screening, as well as brain echography or MRI in the first days after birth. This made it possible to start ganciclovir treatment quickly when necessary. Some parents refused therapy because of the side-effects associated with ganciclovir.

In the current article, children with neurological or ophthalmological lesions due to cCMV are referred to as symptomatic and children without such lesions are referred to as asymptomatic regardless of their hearing abilities.

Classification of Hearing Loss
The definition of normal hearing varied depending on the age of the subject. Normal hearing was defined as a pass on initial hearing screening or an ABR threshold at birth of 35 dBnHL or better. When hearing status was evaluated by visual reinforcement audiometry or play audiometry, hearing impairment was considered to be present when the pure tone average (PTA) of the response thresholds was more than 30 dBHHL. When results were unreliable, OAEs were measured. Hearing was considered to be normal if OAEs were present. When testing took place with headphones or insert phones, 20 dBHHL or less was adopted as the pass criterion.

Hearing loss was classified using the BIAP criteria (International Bureau for Audiophonology:...
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recommendation 02/1bis, May 1997): normal hearing was defined as hearing thresholds of 0 to 20 dBHL, mild hearing loss as hearing thresholds of 21 to 45 dBHL, moderate loss as 46 to 70 dBHL, severe loss as 71 to 90 dBHL and profound loss as thresholds exceeding 90 dBHL. In cases of bilateral loss, the degree of hearing loss in the better ear was used.

Progressive hearing loss was defined as a sensorineural decrease in hearing of more than 15 dB at one or more frequencies. Fluctuating hearing loss was defined as a decrease in hearing of more than 15 dB at one or more frequencies followed by an improvement of more than 15 dB. Recuperation was defined as a lasting increase in hearing of more than 15 dB at one or more frequencies. Consequently, not all subjects with a ‘recuperation’ of their hearing loss had normal hearing afterwards. In cases where a combination of various types of development was determined at the ear level, the predominant pattern of development of hearing sensitivity was used for classification purposes. Temporary hearing loss and changes in hearing threshold caused by middle ear infection were not taken into account.

Analysis of the results

Follow-up PTA measurements were available for a maximum of nine points in time (3m, 6m or 9m, 12m, 18m, 2yrs, 3yrs, 4yrs, 5yrs, 6yrs). The number of follow-up measurements depended on the date of inclusion in the study. PTA development was evaluated both at the patient level and the ear level. In the analysis of the children with hearing loss, development patterns in three groups were compared: children (or ears) with other lesions treated with ganciclovir, children (or ears) with other lesions not treated with ganciclovir and asymptomatic children (or ears).

Results

During the study recruitment period, 98 children entered the protocol at the University Hospitals Leuven. The average follow-up time until March 2013 was 5.4 years ± 1.9 years. The protocol requires every child to be monitored until the age of six. For seven children only, the results were incomplete because follow-up was terminated early. Some of these children went to another medical centre and, in some cases, parents refused further follow-up despite detailed information. Table 1 presents an overview of the number of children in follow-up at each test point.

Of 98 children, 24 children were born with a symptomatic CMV infection and 74 children were born with an asymptomatic CMV infection. Seventy (70/98) children passed initial hearing screening. Seven children in this group (10%) suffered from brain and/or visual disorders and 63 (90%) did not have lesions of this kind. Twenty-eight (28/98) children did not pass hearing screening (hearing loss >35 dBHL). Seventeen (61%) children with a hearing loss suffered from other CMV-related lesions.

Three children in the group of children with normal hearing at birth developed a late-onset hearing loss. In two symptomatic children, hearing loss was detected within five months after birth. One child had a severe and moderate hearing loss, which recuperated partially to moderate and mild hearing loss. Afterwards, hearing loss was stable. The second child had a progressive unilateral hearing loss. The affected ear was completely deaf in the final test. In the asymptomatic group, only one child developed a hearing loss at one single frequency (4 kHz) at the age of 2 years and 9 months. The hearing loss was progressive: the hearing threshold at 4 kHz increased from 40 to 60 dBHL at the age of 3 years and 8 months. Until that time, the hearing threshold at 8 kHz had never been determined. More extensive testing of hearing at the age of 4 years and 9 months showed that

<table>
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</table>

Table 1

Number and percentage of children in follow-up at each test point
hearing sensitivity at 8 kHz in the affected ear had also declined (65 dB HL).

Confirmed unilateral hearing loss was seen in 57.1% of the referrals after neonatal hearing screening and bilateral hearing loss in 42.9%, resulting in a total of 40 affected ears. A classification of severity shows that 43.8% of the group of children with unilateral hearing loss had profound hearing loss, 18.8% severe hearing loss, 31.2% moderate hearing loss and only 6.2% mild hearing loss (Table 2). More than 60% of the children had severe or profound hearing loss in their affected ear. More than 60% of the children referred with bilateral loss were born deaf, while 33.4% of the subjects suffered from a mild or moderate hearing loss in their better ear.

Seventeen of the 28 children with a hearing loss presented with a symptomatic infection. Eight of them received ganciclovir therapy starting in the first month after birth. The parents of the other nine symptomatic infected children refused therapy. An evaluation of the evolution of the hearing loss shows that 37.5% (3/8) of the treatment group had stable hearing (Figure 1). One child had a bilateral mild hearing loss, one child had a bilateral profound hearing loss and one child had a unilateral profound hearing loss.

There was partial or complete recovery of the hearing loss in 25% (2/8) of the children. The improvement took place during, or shortly after, therapy. The hearing threshold recovered completely in one child, who presented with a moderate unilateral hearing loss. The second child had a bilateral profound hearing loss, as well as visual and neurological deficits. The hearing threshold of one ear improved partially, from profound to severe hearing loss.

There was a progressive hearing loss in one ear and a fluctuating hearing loss in the other ear in 25% (2/8) of the children. In one child with a bilateral moderate hearing loss at birth, one ear recovered completely. At the age of 1 year 1 month, however, the hearing loss worsened in the other ear, resulting in complete deafness. From the age of 4 onwards, there was a fluctuating hearing loss at the higher frequencies in the initially better ear. Hearing loss varied from moderate to severe. At that time, CMV in urine tested negatively and the child received therapy with cortisone for three months. Hearing loss has been stable since. The second child underwent almost the same changes in hearing status. This child had an initially unilateral moderate hearing loss. After treatment with ganciclovir, hearing loss was stable. At the age of 18 months, the hearing loss evolved into deafness. At the age of 4, the hearing of this child deteriorated in the initially normal hearing ear. Hearing loss was moderate and fluctuated over time. Cortisone was administered for 10 days in response to fluctuations but without effect on the hearing threshold.

The last child in the treatment group had a bilateral fluctuating hearing loss. This child had a unilateral profound hearing loss at birth. After treatment with ganciclovir, hearing thresholds initially remained stable. At the age of 13 months, the ABR thresholds were 85 dBnHL for the left ear and 80 dBnHL for the right ear. During the next 18 months, hearing thresholds gradually improved again until hearing became normal. At the age of 2.5 years, hearing deteriorated again. The ABR thresholds were 70 and 80 dBnHL for the left and right ears respectively. To date, these hearing thresholds have remained stable. The child is now 7 years old.

In the symptomatic group with untreated children, hearing loss was bilaterally stable in 33.3% (3/9) of the cases. Two children had a unilateral profound hearing loss and one child had a bilateral profound hearing loss. In one child (11.1%), there was bilateral recuperation of the hearing loss. However, it should be noted that this child received immunoglobulins for the cCMV at another hospital because of the determination of a bilateral moderate hearing loss and diffuse alterations of the white substance with periventricular and cerebellar haemosiderin deposits immediately after birth. Stable hearing status in one ear and a progressive hearing loss in the other ear were found in 33.3% (3/9) of the children. Two children were deaf in the ear with stable hearing; the third child had normal hearing in

| Table 2 | Degree of SNHL for cCMV-infected children born with a hearing loss |
|---|---|---|---|---|
| At birth | unilateral n = 16 | bilateral n = 12 | | 
| n | % | n | % | 
| Mild | 1 | 6.2 | 2 | 16.7 |
| Moderate | 5 | 31.2 | 2 | 16.7 |
| Severe | 3 | 18.8 | 0 | 0 |
| Profound | 7 | 43.8 | 8 | 66.6 |
that ear. In all three ears with a progressive hearing loss, the loss was profound at the final audiological evaluation. One child had a bilateral progressive hearing loss, and one child had a bilateral fluctuating hearing loss. Hearing thresholds varied from normal hearing to profound hearing loss.

Eleven children in our study group presented with hearing loss at birth as the only symptom of the infection. Ganciclovir was therefore not offered to these children.

The hearing status in 63.6% (7/11) of these children was stable. Four children were bilaterally deaf at birth. Three children had unilateral deafness and normal hearing in the other ear. Complete recuperation of their unilateral moderate hearing loss was seen in 18.2% (2/11) of these children. Another 18.2% (2/11) had bilateral progressive hearing loss. One child with a unilateral mild hearing loss at birth developed a profound hearing loss in that ear and a moderate hearing loss in the other ear. The other child had a unilateral severe hearing loss which evolved into a profound hearing loss. In addition, the initially normal hearing ear developed a moderate hearing loss.

**Ear-specific analysis**

Table 3 is an overview of the evolution of the hearing status at ear level. Sixteen ears received ganciclovir therapy. In 50% (8/16) of the cases, no differences in hearing status were seen. Four ears with stable hearing were deaf. Hearing was normal or the hearing loss was mild in the other four ears. Hearing loss was progressive or fluctuating in six (6/16) ears, despite the therapy. In all cases, progression and fluctuation started after the age of 1 year. Permanent improvement in hearing thresholds was seen in two ears in the treatment group. The improvement took place during or shortly after therapy (Figure 2).

An evaluation of the ears of the symptomatic untreated children shows that hearing status was stable in 50% (9/18) of these ears. Five ears were
Hearing loss was progressive in four ears. Two ears with normal hearing at birth developed a moderate and mild hearing loss before the age of 1. One ear with a mild hearing loss and one ear with a severe hearing loss evolved into complete deafness by the age of 1 year. In two ears, initial hearing loss (mild and moderate) had recovered completely at 3 and 7 months respectively.

### Discussion

Analysis of the audiologic results of cCMV infected children with hearing loss at birth shows that the degree of hearing loss varies from mild to profound. In our study, 10.7% (3/28) and 25% completely deaf since birth, one ear had a severe hearing loss and three ears had normal hearing. In five ears, the hearing loss progressed. In three ears, progression occurred within the first year after birth. In one child, both ears had a progressive hearing loss from the age of 2 years onwards. In another child, the hearing loss was fluctuating in both ears. Fluctuation occurred first at the age of 6 months. The two ears that recuperated were the ears of the child treated with immunoglobulins (see analysis at patient level). Recuperation was first observed at the age of 5 months.

Hearing was stable in sixteen of the 22 ears (72.7%) in the asymptomatic group. Eleven of these ears were deaf; hearing was normal in five.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic - ganciclovir n = 16</th>
<th>Symptomatic - No ganciclovir n = 18</th>
<th>Asymptomatic n = 22</th>
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</thead>
<tbody>
<tr>
<td>Stable</td>
<td>n = 8 50.0</td>
<td>n = 9 50.0</td>
<td>n = 16 72.7</td>
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<tr>
<td>Progression</td>
<td>2 12.5</td>
<td>5 27.8</td>
<td>4 18.2</td>
</tr>
<tr>
<td>Fluctuation</td>
<td>4 25.0</td>
<td>2 11.1</td>
<td>0 0</td>
</tr>
<tr>
<td>Recuperation</td>
<td>2 12.5</td>
<td>2 11.1</td>
<td>2 9.1</td>
</tr>
</tbody>
</table>

progress = progr., fluctuation = fluct., recuperation = recup.

### Figure 2

Onset of the first change in hearing status at the ear level in symptomatic children treated with ganciclovir (sympt - ganc), symptomatic children not treated with ganciclovir (sympt - no ganc) and asymptomatic children (asympt).
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(7/28) of the children had mild and moderate hearing loss respectively at birth. Although these milder hearing losses do occur, 64.3% (18/28) of our population had severe or profound deafness at birth in the affected ear(s). Long-term follow-up shows that, at the final audiological testing, just as many or even more children had a severe or profound hearing loss. Severe to profound hearing loss in at least one ear was seen in 75.5% (13/17) of the symptomatic and 81.8% (9/11) of the asymptomatic children. These data closely match those of Dhale et al.,11 who conclude that about 74% of the symptomatic children and 68% of the asymptomatic children had these degrees of hearing loss. Although the prevalence of SNHL in children with an asymptomatic CMV infection is much lower than in symptomatic children, the SNHL is equally severe.

It is not only the degree of hearing loss that cannot be determined unequivocally; the same applies to the evolution of the hearing loss. Fluctuation, progression and recuperation were particularly apparent in children with an asymptomatic infection.11-12 Dahle et al.11 found that 54% of the asymptomatic and 54% of the symptomatic children had a fluctuating hearing threshold at one or more frequencies. Hearing loss was also progressive in 54% of the asymptomatic group. This was true of only 29% of the symptomatic children. Hearing recovered in 48% of the asymptomatic and 21% of the symptomatic children. Comparison of the ears in our three groups (sympt-ganc / sympt-no ganc / asymt) shows that the ears with a stable hearing status dominate in all groups, accounting for 50%, 50% and 72.7% respectively. Hearing was either normal or completely lost in nearly all of these ears. Progressive hearing loss is much more common in the symptomatic untreated group (27.8%) than in the treated group (12.5%). On the other hand, fluctuation is more prevalent in the treated group (25%) than in the untreated group (11%). Hearing did not fluctuate in any of the ears in the asymptomatic group. The number of ears in which there was a permanent recuperation of the hearing loss was almost the same in all three groups. The discrepancies between our results and the results of Dahle et al.11 and Foulon et al.12 are – at least partially – due to our inclusion criteria. Many asymptomatic children without hearing loss at birth were simply not included in our study because there was no diagnosis of cCMV. On the other hand, Dahle et al.11 evaluated the evolution of hearing threshold for each frequency separately. As a result, one ear (or child) could be included in several categories. This approach results in higher percentages in the various categories.

In respect of the effect of the ganciclovir therapy, Kimberlin et al.13 concluded that ganciclovir therapy, when started in the neonatal period in symptomatic children, reduces the deterioration of hearing loss at 6 months and ‘may’ prevent deterioration above the age of 1 year. They found stable or improved hearing loss status in 84% of the treated children and in 59% of the untreated children between baseline and 6 months. None of the treated children had a fluctuating or progressive hearing loss between baseline and 6 months. After the age of 1 year, hearing status deteriorated or fluctuated in 21% of this group; this figure was 68% in the untreated children. In our study, which looked at a lower number of children, hearing status was stable or recuperation of the hearing loss was seen in all eight of the treated children before the age of 1 year. Any recuperation actually occurred in the first 6 months after birth. Only 44.4% (4/9) of the untreated symptomatic children showed stable hearing or a recuperation during their first year of life. After the age of 1 year, fluctuation or progression occurred in 37.5% (3/8) of the treated children. In the untreated group, fluctuation or progression occurred in 55.6% (5/9) of the children. In this last group, the first fluctuation was in each case noticed before the age of 1 year. Progression had already started before the age of 1 year in 75% of the children with a progressive hearing loss, and after the first birthday in 25% of the cases. The difference in the timing of the onset of the change in hearing status between the two symptomatic groups may be due to the fact that the therapy temporarily suppresses the virus. Discontinuation of the antiviral therapy may reactivate the virus. In recent years, some researchers have therefore recommended antiviral therapy lasting more than the present six weeks for symptomatic infected children with a view to sustaining the suppression of viral replication and slowing down immune response. This treatment consists of six weeks of intravenous treatment with ganciclovir, followed by oral valganciclovir until the age of 6 to 12 months. The initial results are encouraging.14-16 These researchers conclude that valganciclovir oral solution results in plasma concentrations of ganciclovir that are...
comparable to those observed with the administration of intravenous ganciclovir. They found no deterioration in hearing at or above the age of 1 year, and they have stated that the prolonged therapy is well-tolerated and safe. Although these results are positive, the studies have almost always looked at audiological follow-up until the age of 1 year, and never gone beyond the age of 2. In our study, we found changes in hearing status at later ages after six weeks of intravenous treatment as well. Further studies with longer audiological follow-up are recommended with a view to establishing the effect of the prolonged therapy.

Conclusions

Hearing loss caused by cCMV cannot be defined unequivocally either in respect of the degree of hearing loss or its evolution over time. Long-term audiological follow-up is therefore recommended. A six-week course of intravenous treatment for symptomatic children with SNHL leads to a better prognosis during the first year of life than in untreated symptomatic children. Thereafter, hearing loss progression or fluctuation becomes more likely but progression is more common overall in the untreated group. Asymptomatic children with SNHL are more likely to have stable hearing status.

References


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