Hearing in Children with Congenital Cytomegalovirus Infection: Results of a Longitudinal Study

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Objectives To evaluate hearing outcome, to characterize the nature of symptomatic and asymptomatic congenital cytomegalovirus (cCMV) infection and associated hearing loss, and to compare results with data from previous studies.

Study design A prospective multicenter registry was set up in 2007. Six centers participated in the development of a standardized protocol for diagnosis, treatment, and follow-up. Data were gathered in an online registry. Children (n = 379) with a documented cCMV infection and at least 2 separate audiologic evaluations were included. Audiometric results from a multicenter cohort study of children with cCMV infection with longitudinal observation were examined.

Results Results from 123 children with a symptomatic and 256 children with an asymptomatic cCMV infection were analyzed. In the group with symptomatic cCMV, 63% had hearing loss, compared with 8% in the group with asymptomatic cCMV. Delayed-onset hearing loss occurred in 10.6% of symptomatic cCMV and in 7.8% of asymptomatic cCMV. In the group with symptomatic cCMV, 29.3% of children used some kind of hearing amplification; 1.6% in the group with asymptomatic cCMV used hearing amplification.

Conclusions Symptomatic and asymptomatic cCMV infections are a major cause of hearing loss in childhood. Reliable estimates of the long-term outcome of cCMV infection are mandatory to increase vigilance, especially among pregnant women and to draw attention to preventive measures, vaccine development, and prenatal and postnatal therapy. Universal screening of newborns for cCMV infection should be initiated and combined with longitudinal audiometric follow-up. *(J Pediatr 2016;172:110-5)*.

Congenital cytomegalovirus (cCMV) infection is the most common congenital infection worldwide and the most important cause of nonhereditary sensorineural hearing loss in the developed world. The overall prevalence of cCMV infection among newborns is 0.58%-0.70% in industrialized countries.[1-3] Approximately 10% of infected newborns are symptomatic at birth. The outcome of these infants is poor, and most survivors suffer from severe neurologic sequelae[2-6]; however, the majority of children with cCMV infection are asymptomatic at birth. These children usually are not diagnosed with cCMV infection because of the lack of universal screening for cCMV at birth and during pregnancy. Some of the patients with clinically asymptomatic cCMV, however, develop late sequelae, with sensorineural hearing loss as the most common feature.[7-11] Because the majority of the group with asymptomatic cCMV remains undiagnosed, the precise extent and nature of the hearing loss in this large group is still unknown. The aim of this study is to evaluate hearing outcome and characterize the nature of cCMV-associated hearing loss in a contemporary population with cCMV.

Methods

In January 2007, a prospective multicenter registry was set up in Flanders by the Flemish Society of Pediatrics' Neonatology and Perinatal Epidemiology Working Group. Pediatricians and otorhinolaryngologists at 6 centers participated in the development

AABR	Automated auditory brainstem response
ABR	Auditory brainstem response
cCMV	Congenital cytomegalovirus
CMV	Cytomegalovirus
dB HL	Decibels hearing level
dB nHL	Decibels normal hearing level
DBS	Dried blood spot
MEE	Middle ear effusion
PCR	Polymerase chain reaction
TEOAE	Transient-evoked otoacoustic emission
UNHS	Universal neonatal hearing screening

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of a standardized protocol for diagnosis, treatment, and follow-up of children with cCMV. Data were gathered prospectively in an online registry. Children were followed until 6 years of age.

In this prospective study, 379 children, born between January 2007 and July 2014, were included. The inclusion criteria for this study were children with a documented cCMV infection with at least 2 separate audiologic evaluations.

Six centers in Flanders participated in registration: Ghent University Hospital (n = 164), Antwerp University Hospital (n = 50), Leuven University Hospital (n = 93), Sint Augustinus Hospital Antwerp (n = 35), Sint Jan Hospital Bruges (n = 26), and Middelheim Hospital Antwerp (n = 11). The registration was approved by the Ethic Committee and was enlisted at the Privacy commission. Neonates with proven cCMV infection were included, after written informed consent from the parents was obtained.

At enrollment, data were collected on the prenatal period, diagnosis, symptoms at birth, results of additional investigations, and therapy. Long-term data were collected on neuromotor skills, hearing, and vision. The audiologic follow-up results are presented. Results mainly are presented in terms of patients rather than ears, to be able to provide prognostic rates for counseling parents of children with cCMV infection. Some results are displayed for the number of ears, to show the biological impact of the infection along with the functional impact.

The Working Group developed guidelines for therapy.[12] Antiviral treatment is recommended in all newborns with cCMV infection who are classified as symptomatic after neonatal evaluation with the exception of children with isolated bilateral deafness. In this scenario, the preferred treatment is cochlear implantation because the expected improvement is too small to obtain functional hearing. In all other children with symptomatic cCMV, treatment is discussed with the parents with consideration of possible harms and benefits of therapy.

Diagnosis of cCMV Infection

Diagnosis is made by virus isolation or polymerase chain reaction (PCR) on a urine sample taken within the first 2 weeks of life. Most children are included at birth through routine clinical management, such as a known seroconversion of the mother during pregnancy or suspected symptoms at birth. Some children are included because of a failed universal neonatal hearing screening (UNHS) with automated auditory brainstem responses (AABRs), by which every newborn in Flanders is tested within the first weeks after birth. If hearing loss is confirmed by formal auditory brainstem response (ABR) testing, an etiologic evaluation is performed, including PCR testing for cytomegalovirus (CMV) of the dried blood spot (DBS) and, if positive, cCMV infection is diagnosed. A few children are diagnosed retrospectively by PCR on DBS because of delayed-onset hearing loss occurring after the UNHS.

Definition of Symptomatic and Asymptomatic cCMV

In the registry, a child is classified as symptomatic when ≥1 significant abnormalities are found after neonatal investigations: physical examination, central nervous system imaging, hearing tests, fundoscopy, and blood tests. Patients with a late diagnosis of cCMV as the result of delayed-onset hearing loss are considered asymptomatic, because, as a result of the lack of symptoms at birth, there had been no reason to screen for cCMV infection.

Audiologic Assessment

Audiologic testing is performed according to a protocol (**Figure 1**; available at www.jpeds.com). Audiologic evaluation consists of evaluation of the middle ear function by otomicroscopical inspection and otoadmittance measurements. The tympanometric probe tone frequency is 1000 Hz in children <9 months of age and 226 Hz in children ≥9 months of age. In children <6 months, hearing generally is assessed by means of diagnostic ABR during natural sleep. In some cases ABR is performed at a later age under general anesthesia after insertion of ventilation tubes in children showing protracted middle ear effusion (MEE), recurrent acute otitis media, or in cases with equivocal hearing results. Older children are tested by age-appropriate tone audiometry.

In the analysis of monaural results, either a click ABR threshold or a pure tone average (average hearing sensitivity at 500, 1000, 2000, and 4000 Hz, International Bureau for Audiophonologie index) was used. Transient-evoked otoacoustic emissions (TEOAEs) also are evaluated in the case of ventilated middle ears.[13] In this age category (0-6 years), MEE is common. In cases of MEE, the aim is to test after eradication of middle ear disease. All thresholds obtained from ears with a possible transient conductive hearing loss or from unreliable measurements are omitted in the analysis. If antiviral treatment is administered, an ABR test is performed before and after therapy. The neonatal hearing results are based on AABR if hearing is normal, because AABR is known to have a high sensitivity and specificity.[14] In infants with an abnormal AABR, a diagnostic ABR is performed within the first month after birth, combined with otomicroscopy and otoadmittance to rule out MEE. These results also are included in the neonatal hearing results.

Classification of Hearing Loss

The threshold obtained by ABR is the lowest intensity at which wave V can be detected and replicated. A neonatal ABR is considered normal with a click-threshold of 40 Decibels normal hearing level (dB nHL) in combination with present TEOAEs. In all later ABR measurements, hearing sensitivity is classified as normal when the click-threshold is ≤30 dB nHL. A threshold between 31 and 45 dB nHL is classified as mild, between 46 and 70 dB nHL as moderate, between 71 to 90 dB nHL as severe, and ≥91 dB nHL as profound hearing loss.[15] The classification of the pure tone