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Hearing outcome in congenitally CMV infected children in Finland – Results from follow-up after three years age

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ABSTRACT

Objectives: Cytomegalovirus (CMV) is the most common congenital infection affecting about 0.6% of all newborns in developed countries. Vertical transmission to fetus can take place either after maternal primary or non-primary CMV infection during pregnancy. It is the most common infectious agent for sensorineural hearing loss (SNHL) in young children. The hearing loss after congenital CMV (cCMV) may be present at birth, or may develop after months or even years. In this study, we evaluated hearing outcome at 3–4 years of age in children (n 32) with cCMV identified in universal saliva CMV-PCR-based screening.

Methods: Study population consisted of mainly asymptomatic children (median age 3.1 years) with cCMV identified in newborn CMV screening. The type of maternal CMV infection (primary or non-primary) was determined by analyzing CMV antibodies (IgM, IgG and IgG avidity) from preserved maternal serum samples drawn in the end of first trimester of pregnancy. Hearing was evaluated with pure tone audiometry (PTA), or transient-evoked otoacoustic emission (TEOAE) and sound field audiometry (SF).

Results: Unilateral hearing loss occurred in 5/32 (16%) of the children with cCMV. None of the subjects in our cohort had bilateral hearing loss. Hearing loss occurred in 3/15 (20%) of children who were born to mothers with non-primary CMV infection during pregnancy, and in 2/10 (20%) of children whose mother had had a primary CMV infection during the 2–3 trimester. None of the additional 6 children, whose mother had primary infection in the first trimester, had hearing loss by age of 3–4 years. Two children with normal hearing at 1 years age had developed unilateral hearing loss by the age of three.

Conclusions: Unilateral hearing loss was relatively common among the mainly asymptomatic children with cCMV identified in screening. Long-term follow up of children with cCMV is essential to identify the children with late-onset hearing loss.

1. Introduction

Cytomegalovirus (CMV) is a common congenital infection affecting 0.6–0.7% of all newborns [1,2]. It is the most common non-hereditary cause for sensorineural hearing loss (SNHL) in children [3–5]. Infection of the fetus can occur both following primary maternal infection, when the mother acquires CMV for the first time during pregnancy or non-primary infection, which could be the result of a reactivation of latent CMV infection, or a re-infection with a new strain of CMV in seroimmune women. Historically, it has been assumed that mainly maternal primary infections cause harm to the infant [6]. However, recent studies have shown that long term sequelae occur both after maternal primary and non-primary infections [7].

Only about 10% of the infants with congenital CMV infection (cCMV) have symptoms at birth such as growth retardation, microcephaly, petechial rash, hepatosplenomegaly, retinitis, thrombocytopenia, or hepatitis [8–10]. Most, about 90% of affected infants are asymptomatic at birth. About half of the symptomatic infants will have some long-term

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sequelae due to the congenital infection [2]. Although the outcomes in asymptomatic infection are better, 10–15% of asymptomatic infants will develop sequelae, mostly SNHL [2]. In addition to hearing loss, cCMV may lead to neurodevelopmental impairment and visual abnormalities [1,2].

Symptomatic infection and long-term sequelae seem to be equally common among children infected after maternal primary and non-primary infections [7]. Hearing loss has been reported on average in 11% of children with cCMV after maternal primary-infection and 14% after maternal non-primary-infection [7].

Congenital CMV infection accounts for about 9–21% of SNHL in pediatric population [11,12]. According to a systematic review, hearing loss occurred in 12.6% of children with cCMV identified in universal screening [5]. Hearing loss occurred in 9.9% of the children with asymptomatic infection and in 33% of children with symptomatic infection [5]. The hearing impairment can be present at birth, but in a substantial number of children, it can develop after the first months or even years of life. In a review of both screening studies and clinical cohorts, the hearing loss was late-onset in 18.1% of symptomatic and 9% of asymptomatic children [5]. Another review focusing on only asymptomatic cCMV found a cumulative incidence of SNHL 7%–11% in studies with more than 5 years follow up [3].

The diagnosis of cCMV is based on detecting infectious virus, viral antigens or viral DNA in urine or saliva within the first three weeks of life [13]. Perinatal and postnatal infections are common and in contrast to congenital infections, are not associated with long-term morbidity [14]. Since the detection of virus after the first three weeks of life cannot differentiate between congenital and postnatal infection, retrospective diagnosis of cCMV is challenging. In some research settings, the polymerase chain reaction (PCR) testing of preserved dried blood spots or umbilical cord samples has been used for retrospective diagnosis [11,15]. The total disease burden and natural course of cCMV can only be evaluated from prospective screening studies, since most of the infected children are asymptomatic.

The aim of our study was to evaluate the long term hearing outcome at 3–4 years of age in cCMV children identified on newborn CMV screening. We also assessed whether children were infected either after maternal primary or non-primary CMV infection to see if there were any differencies among these groups [16].

2. Materials and methods

2.1. Study population

Study population consisted of 32 children with cCMV identified in a large newborn CMV screening study [16]. Informed consent was obtained from the parents for the enrollment in the screening and the study protocol was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa. The screening was performed in Helsinki area hospitals between September 2012 and January 2015.

After screening 19 868 infants using saliva CMV PCR test collected during the first week of life, we identified 40 children with cCMV [16,17]. The positive screening sample was confirmed by testing urine CMV culture and a new saliva CMV PCR by the age of 3 months. The findings from the clinical follow up of this cohort at 18 months age have been published [16]. As reported, all children with cCMV had passed neonatal hearing screening, which in our clinic means having normal otoacustic emission screening test result in one ear. None of the children in the original cohort required hearing rehabilitation by the age of 18 months [16]. Hearing testing results at 3–4 years of age were available for 32 of the study cohort. Three of these 32 children had symptomatic CMV infection. Two children were categorized as symptomatic based on calcifications on cranial ultrasound and one child had microcephaly (−3.3 SD). None of the children had apparent manifestations of congenital infection evaluated by a pediatrician during the first day or two of life before the child was discharged from the maternity hospital. At the age of three months all cCMV positive children were examined by a pediatrician and an ophthalmologist, and the cranial ultrasound was performed. None of the children received antiviral treatment, since the cCMV infection could be confirmed only after one month's age.

The type of maternal infection (primary/non-primary) had been assessed based on the anti CMV antibodies from the serum samples drawn in the early pregnancy before the gestational week 15 + 1, as described earlier [16]. Commercial assays (Architect CMV IgG, CMV IgM, and CMV IgG Avidity, Abbot Diagnostics) were used according to the manufacturer instructions [18,19].

2.2. Hearing assessments

Hearing was assessed with pure tone audiometry (PTA) using calibrated headphones whenever possible. The child is asked to respond to the frequency-specific pure tone stimuli, and responses from individual ears to tones from 250 to 4000 Hz were assessed (ISO 389-1). No masking sound stimuli were used to block the bone conduction to the opposite ear. Hearing thresholds $\leq$20 dB HL at frequencies 500, 1000, 2000 and 4000 Hz were considered normal hearing.

If the child is not cooperative for PTA testing, the hearing was assessed with transient-evoked otoacoustic emission (TEOAE) combined with sound field (SF) audiometry (ISO 389-7) (Interacoustics). TEOAE provides information on the function of the outer hair cells. An acoustic response produced by the hair cells to a sound stimulus can be measured separately from each ear. At least three different frequencies have to give over 6 dB signal to noise ratio responses to pass TOAE and fewer responses was considered TEOAE failure. SF measures behavioral response to the frequency-modulated tones, given through loudspeakers, of both ears simultaneously. Behavioral response to mean threshold of 20 dB or less between 500 and 4000 Hz in SF together with normal TEOAE responses from both ears were considered normal hearing.

The hearing assessment for all the children was performed in the same acoustically suitable soundproof room and two experienced pediatric audiologists did hearing testing. An otorhinolaryngologist also examined all the children. Otoscopy was done by the otorhinolaryngologist on the same day after the audiometry testing. In case of otitis media or glue ear, the child was re-tested after the resolution of middle ear effusion. Tympanometry was performed when there was suspicion of middle ear effusion or uncertain finding on otoscopy.

3. Results

3.1. Hearing outcome at 3–4 years age

The median age at the final hearing assessment was 3.1 years (range, 2.83 to 4.33). PTA was performed in 16 children, and in 15 children the hearing evaluation was based on TEOAE tested both ears combined with SF assessment. In one child, the assessment was based on SF only due to limited cooperation.

None of the 32 children had bilateral hearing loss. Five children (16%) had unilateral hearing loss with a mean threshold ranging from 27 to 68 dB HL. Ear status in otomicroscopy and pneumatic otoscopy examined by otorhinolaryngologist in the same day was normal in all children with hearing loss. Patient 1 had normal tympanometry, patients 2–5 did not undergo tympanometry. The hearing test results are presented in Fig. 1. Unilateral hearing loss presented in 1/3 (33%) of symptomatic and 4/29 (14%) of asymptomatic children. The previous hearing examinations were performed at 3 months, 10–12 months and 18 months age and the summary of the latest hearing results at 3–4 years age of these children are presented in Table 1. Patient 1 had abnormal TEOAE in right ear detected first at 3 months and persisted at 10 months and 18 months of age. Patients 2 and 3 had normal TEOAE at 3 months and 10 months of age but no reliable assessment at 18 months of age due to insufficient cooperation. Patient 4 had abnormal TEOAE in both ears

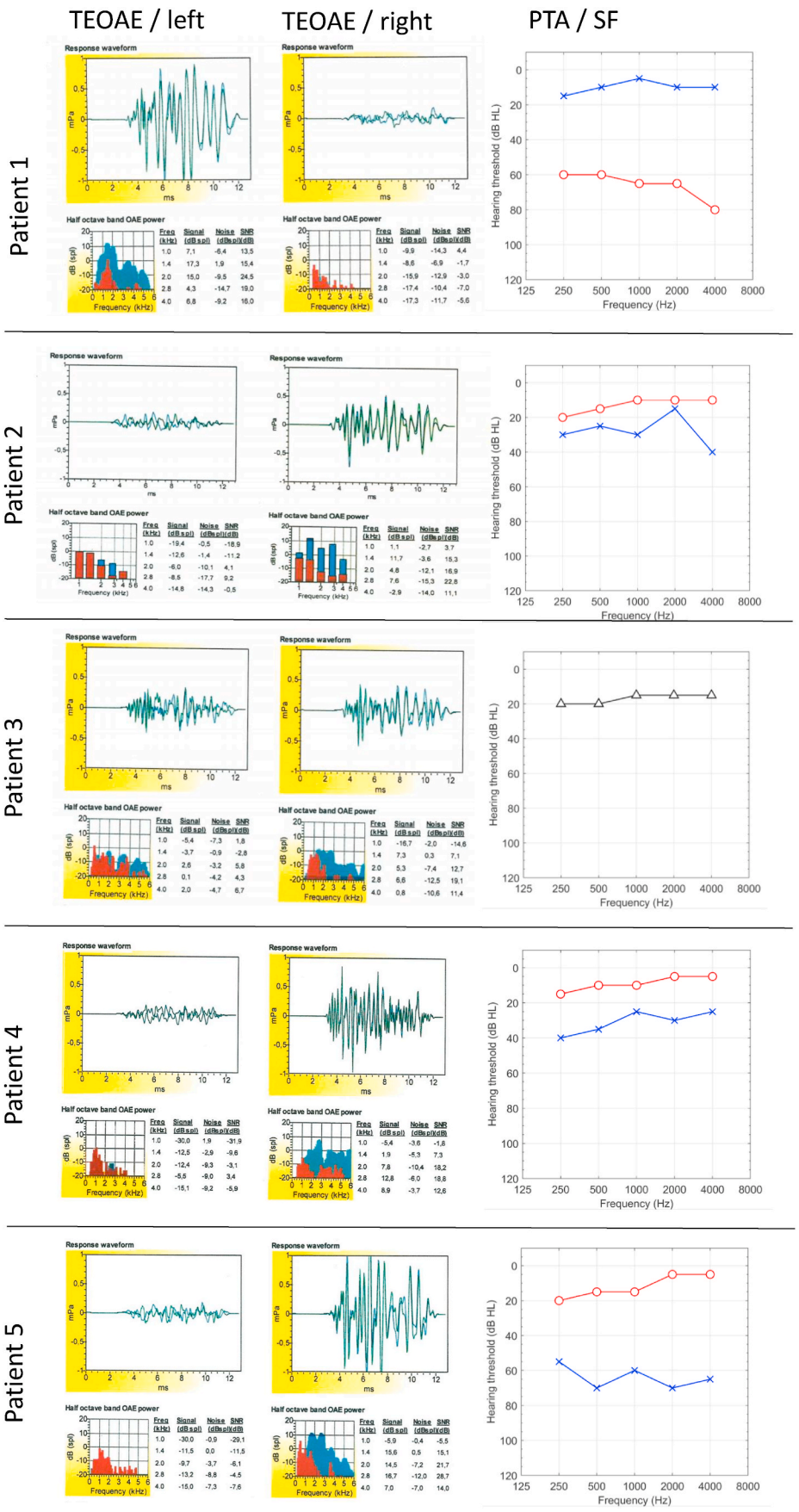

Fig. 1. Hearing test results at 3–4 years age. TEOAE = transient-evoked otoacoustic emission, PTA = pure tone audiometry, SF = sound field audiometry, X = left ear in PTA, O = right ear in PTA, Δ = combined hearing in SF.

Table 1
The previous hearing results of the 5 subjects with abnormalities in the hearing follow-up at 3–4 years age.

symptomatic/ asymptomatic Type of maternal infection	Previous hearing assessments TEOAE (dx/sin)			Hearing assessment at 3–4 years age		
	3 month	10–12 month	18 month	PTA (dx/ sin) (dB HL)	TEOAE (dx/sin)	Sound Field (dB HL)
Patient 1 symptomatic non-prim	fail/ pass	fail/ pass	fail/ pass	68/9	fail/pass	
Patient 2 asymptomatic prim in 2–3. trim	pass/ pass	pass/ pass	–	11/ 27	pass/fail	
Patient 3 asymptomatic non-prim	pass/ pass	pass/ pass	–	–	pass/fail	16
Patient 4 asymptomatic non-prim	fail/ fail	pass/ fail	pass/ fail	7/29	Not performed	
Patient 5 asymptomatic prim in 2–3. trim	pass/ fail	pass/ fail	–	10/ 66	pass/fail	

Non-prim = non-primary, prim = primary, trim = trimester, TEOAE = transient-evoked otoacoustic emission, PTA = pure tone audiometry, dB HL = decibels hearing level, dx = right ear, sin = left ear.

at 3 months of age. Follow up visits at 7 months, 12 months, and 18 months of age showed normal TEOAE in the right ear and abnormal in the left ear. Patient 5 had abnormal TEOAE in the left ear at 3 months and 10 months of age but testing could not be completed at the 18-month assessment visit because of lack of cooperation.

Hearing was normal in 27 children at 3–4 years of age. Twelve children had mean hearing thresholds 20 dB or less in PTA. Fourteen children had mean hearing thresholds 20 dB HL or less in SF combined with normal TEOAE in both ears. One child with mean hearing threshold of 16 dB HL in SF and insufficient co-operation for TEOAE and was regarded as having normal hearing; however unilateral hearing loss cannot be ruled out in this case.

3.2. Hearing loss and type of maternal infection

The type of maternal infection could be ascertained in the mothers of 31 children. Unilateral hearing loss was detected in 3/15 (20%) of children born to mothers with non-primary infection and in 2/10 (20%) of children born following primary maternal infection in the 2–3 trimester. None of the six children born to mothers with primary infection documented in the 1st trimester had hearing loss at 3–4 year assessment. In one child with normal hearing, the type of maternal infection could not be defined.

4. Discussion

Prospective follow-up of a cohort of 32 children with cCMV consisting mostly of children with asymptomatic cCMV identified on newborn CMV screening was carried out to determine hearing outcomes at 3–4 years of age. Our findings show that 5/32 (16%) children had hearing loss, which was unilateral in all children. None of the children had bilateral hearing loss.

Of the 32 children in the study cohort, 3 were categorized as having symptomatic cCMV and 1 (33%) symptomatic child had hearing loss which is similar to published data [4,5]. Hearing loss has occurred in approximately 33–55% of children with symptomatic cCMV [4,5]. Two of the 3 children with symptomatic cCMV in our cohort had no abnormal clinical findings at birth but had abnormal cranial ultrasound imaging. The 3rd symptomatic child had microcephaly (−3.3 SD) at birth with normal hearing on follow-up. Only the child with microcephaly could have been identified as CMV positive without the screening, as the two additional children were categorized as symptomatic only based on imaging findings. Of the 29 children with asymptomatic cCMV, four (14%) had hearing loss, consistent with the previous reports, which have showed that 5–21% of asymptomatic children had SNHL [4,5]. It is surprising that none of the children had bilateral hearing loss. In systematic review, cCMV related hearing loss was bilateral in 71.2% of symptomatic and 43% of asymptomatic children [5].

All children in the cohort had passed the neonatal hearing screening as newborn. Three children, however, had abnormal TEOAE in one ear at 3–18 months of age. It is possible that these three children had unilateral hearing loss at birth because neonatal hearing screening included testing in only one ear. Two children with unilateral hearing loss at 3 years of age had had normal TEOAE at ten-month of age. Both these children had unsuccessful TEOAE testing at 18 months of age due to insufficient co-operation. Based on these evaluations, we can only surmise that the hearing loss developed between one and three years of age. Both children with suspected late-onset hearing loss had asymptomatic cCMV infection. In longitudinal studies of children with cCMV and hearing loss, the impairment has been late-onset in 9% of children with asymptomatic cCMV and in 18.1% of children with symptomatic cCMV [5]. In our cohort none of the children had bilateral hearing loss, which is unexpected. In previous literature, 43% of the children with asymptomatic cCMV and hearing loss had bilateral impairment [5]. The proportion of bilateral hearing loss has been even higher, 71.2%, in the cohorts of symptomatic cCMV with hearing loss [5].

The standard of care in Helsinki University Hospital does not include active hearing rehabilitation for children with unilateral hearing loss and in the neonatal hearing screening only one ear is screened. Normal hearing in one ear was considered sufficient for speech and cognitive development. However, recent studies have shown that unilateral hearing loss early in life can have detrimental effects on some areas of speech and language development and auditory listening. The children with unilateral hearing loss performed poorer than their peers [20,21]. There is also evidence that children with congenital unilateral severe to profound hearing loss benefit from cochlear implantation [22]. Speech recognition and localization in a noisy background was better in the children with implantation leading to significant improvement in learning abilities and academic performance [22]. Especially during the early grades, the learning environment in a classroom can be noisy. Therefore, the approach to rehabilitation of unilateral hearing loss will most likely include active intervention. In addition, it could be argued that neonatal hearing screening should include testing of both ears. One of the five university hospital districts in Finland is already screening both ears. Universal screening for cCMV could enable to identify the asymptomatic children in risk for late-onset hearing loss. The hearing loss in cCMV patient is often progressive, which underlines the importance of long-term follow up.

We were also able to determine the frequency of hearing loss in children with cCMV following primary and non-primary maternal CMV infections and the timing of maternal infection in women with primary infection during pregnancy. Hearing loss was detected in 2/16 (12.5%) children born to women with primary infection and 3/15 (20%) children born following non-primary maternal infection. It has been well-described that children with cCMV born to women with both primary and non-primary infections can develop SNHL [23,24]. In our cohort, surprisingly, all six children whose mothers had primary CMV infection during the first trimester had normal hearing. In such a small cohort (n 6) it can be also a coincidence. However, two children born to mothers with primary CMV infection after the 1st trimester had hearing loss. This is in contrast to the findings from previous study in Finland and a more recent study in France that showed no adverse sequelae in children with cCMV born to women with primary infection after the 1st trimester [25,

26]. Our findings highlight the need for long-term follow up of all children with cCMV, regardless of the timing of infection.

Another important factor that was not evaluated in this study is whether the asymptomatic children identified in neonatal screening could benefit from interventions. In addition to more thorough hearing follow up and possible hearing rehabilitation, treatment with ganciclovir or valganciclovir for moderately to severely symptomatic children with cCMV has improved the hearing and neurologic outcome [27,28]. The current data does not support antiviral treatment for asymptomatic infants [13,29]. However, the approach to children with isolated hearing loss is controversial. In 2017, two expert consensus recommendations on management of cCMV were published [13,29]. While one group did not recommend antiviral treatment for isolated hearing loss due to lack of evidence [29], the other group could not reach consensus [13]. In 2018, Pasternak et al. published a retrospective report of 59 children with isolated hearing loss, treated with antivirals for 12 months [30]. The hearing improved in 69% of the affected 80 ears [30]. The retrospective nature of the report and lack of control group make the conclusions on the effect of antivirals debatable. The natural course of hearing loss in cCMV can be progressive or fluctuating [5]. In another report on natural course of asymptomatic cCMV infection, 14/23 (61%) of the children with abnormal initial hearing assessment had normal hearing in subsequent assessments [31]. More research is needed to understand the possible benefit of antivirals in the mildly symptomatic children identified in the screening. Two ongoing randomised controlled trials (NCT03107871 and NCT01649869) are evaluating effectiveness of oral valganciclovir in children older than 1 month with hearing loss and cCMV. One non-randomized prospective study (NCT03301415) is evaluating whether valganciclovir, initiated during the first month of life, can prevent the late onset hearing loss in asymptomatic children with cCMV. The results of these studies will likely provide some answers in the future.

The strength of our study is the definition of long-term hearing outcome in a cohort of children with cCMV identified on universal newborn screening. Without the CMV screening study, the children with unilateral hearing loss could have been unrecognized. In addition, we were able to ascertain the type of maternal infection in most mothers of infected children. However, there are some limitations. The type of hearing loss could not be determined because of insufficient co-operation of young children and unsure results for measuring bone conduction thresholds. Also use of masking during hearing testing will confuse young children and is not used at this age group. Although the PTA testing is a reliable tool to determine hearing function in individual ears, only half of the children could be assessed with PTA due to insufficient co-operation. TEOAE is reliable but only measures outer hair cell function and the SF testing assesses the combined hearing and therefore providing the hearing function of the better ear. Normal SF combined with normal TEOAE results from both ears can reliably exclude hearing loss. However, abnormal TEOAE with normal SF cannot absolutely confirm diagnosis of unilateral hearing loss, as technical inaccuracies especially with insufficient co-operation may influence the result. In our cohort, 4/5 children with hearing loss had confirmed loss using the reliable PTA testing. One child had abnormal TEOAE in one ear with normal SF and further follow-up is necessary to confirm hearing loss. One child in our cohort had normal SF but TEOAE and PTA could not be completed because the lack of cooperation and this child was considered to have normal hearing. However, unilateral hearing loss cannot be excluded in this child. Another limitation of our study is the possibility of missing unilateral hearing loss in newborn hearing screening, as so far, the screening is passed if one ear gives normal hearing response.

The symptom based clinical diagnosis of cCMV infection seems to be rare in Finland because a retrospective study revealed only 29 children with symptomatic cCMV infection in all University hospitals in Finland years 2000–2012 [25]. In the large newborn screening study, the prevalence of cCMV infection is low at 0.2% in Finland [16]. However, a significant proportion of infected children developed hearing loss on follow-up at 3–4 years of age. At earlier follow up of the same cohort at 18 months of age, there were no significant differences in hearing outcomes between children with cCMV and the healthy controls [16]. Since cCMV-associated SNHL can be of late onset and develop after the first few years of life, the true prevalence and disease burden can only be estimated after careful long-term follow-up. We shall continue to follow-up these cCMV positive children and re-evaluate them at the age of six years.

In the original screening study we identified 40 cCMV positive children [16]. Only 32 of them accomplished the 3–4 year follow up. However, the risk for missing profound bilateral hearing losses among the eight children not attending to the 3–4 year follow-up is unlikely. In Finland, all children are systematically followed up in child health centers until 6 years of age. The children are referred to tertiary care hearing evaluation if there is any suspicion of hearing impairment. The children requiring hearing rehabilitation in the Helsinki area are taken care of in our clinic and there is no parallel system. However, mild and unilateral hearing losses in young children can be missed in primary care follow up.

5. Conclusions

In conclusion, hearing loss occurred in 16% of the children with cCMV after follow up until 3–4 years age. None of them had bilateral hearing loss. Two of these children had late-onset hearing loss. Adverse hearing outcome occurred both in children born to mothers with primary infection after the first trimester, and non-primary infection during pregnancy. Long-term follow up of the children with cCMV is essential, regardless of the timing of maternal infection.

Declaration of competing interest

None.

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