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Hearing Loss and Congenital CMV Infection: A Systematic Review

abstract



BACKGROUND AND OBJECTIVE: Hearing loss caused by congenital cytomegalovirus (cCMV) infection was first observed in 1964. Today cCMV is the most common cause of nonhereditary sensorineural hearing loss in childhood. Our objective was to provide an overview of the prevalence of cCMV-related hearing loss, to better define the nature of cCMV-associated hearing loss, and to investigate the importance of cCMV infection in hearing-impaired children.

METHODS: Two reviewers independently used Medline and manual searches of references from eligible studies and review articles to select cohort studies on children with cCMV infection with audiological follow-up and extracted data on population characteristics and hearing outcomes.

RESULTS: Thirty-seven studies were included: 10 population-based natural history studies, 14 longitudinal cohort studies, and 13 retrospective studies. The prevalence of cCMV in developed countries is 0.58% (95% confidence interval, 0.41–0.79). Among these newborns 12.6% (95% confidence interval, 10.2–16.5) will experience hearing loss: 1 out of 3 symptomatic children and 1 out of 10 asymptomatic children. Among symptomatic children, the majority have bilateral loss; among asymptomatic children, unilateral loss predominates. In both groups the hearing loss is mainly severe to profound. Hearing loss can have a delayed onset, and it is unstable, with fluctuations and progression. Among hearing-impaired children, cCMV is the causative agent in 10% to 20%. Despite strict selection criteria, some heterogeneity was found between selected studies.

CONCLUSIONS: This systematic review underscores the importance of cCMV as a cause of sensorineural hearing loss in childhood. *Pediatrics* 2014;134:972–982

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KEY WORDS

cytomegalovirus, congenital infection, hearing, auditory, prevalence, symptomatic infection, systematic review

ABBREVIATIONS

cCMV—congenital cytomegalovirus
CI—confidence interval
DBS—dried blood spots
PCR—polymerase chain reaction
SNHL—sensorineural hearing loss
UNHS—universal neonatal hearing screening

Dr Goderis designed this review, performed the literature search, drafted the initial manuscript, and improved revised versions; Drs De Leenheer, Smets, Van Hoecke, and Keymeulen revised the analysis and interpretation of data and critically reviewed the manuscript; Dr Dhooge conceptualized this review, coordinated and supervised the process, approved the literature search and selection, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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The first article on hearing loss by congenital cytomegalovirus (cCMV) infection was published in 1964 by Medearis et al.¹ Over the past 50 years, numerous studies explored the relationship between cCMV infection and hearing loss. Today cCMV is acknowledged as the most common nongenetic cause of childhood sensorineural hearing loss (SNHL) and an important cause of neurodevelopmental delay.^{2–7}

Worldwide, cCMV infection affects 0.2% to 2.5% of all live-born neonates.^{8–11} In industrialized countries, the average prevalence of cCMV infection is 0.64% to 0.70%.^{4,12} The incidence of cCMV infection is highest in developing countries, 1% to 5% of all live births, and is probably driven by nonprimary maternal infections.¹³ The prevalence of cCMV infection increases with increasing maternal CMV seroprevalence. Most European countries have a maternal CMV seroprevalence ranging from 40% to 60%. In developing countries it is >90%.^{13,14} Maternal seroprevalence depends on age, socioeconomic status, and parity.^{15–17} But between industrialized countries there are clear differences in prevalence, probably because of race-bound predilection in addition to differences in sexual behavior, day care attendance, breastfeeding, and profession.^{18,19} Spreading of CMV occurs through close contact with infected body fluids. Children aged 1 to 2 years are the most important source of infection for women of reproductive age.^{20,21}

In seropositive mothers, reactivation of a latent virus or reinfection with a new CMV strain can cause cCMV disease as well, with or without permanent sequelae.^{22–30} The risk of vertical transmission seems to be higher in primary infections than in nonprimary infections. In a meta-analysis, Kenneson and Cannon¹² found rates of vertical transmission of 32% and 1.4% for primary and nonprimary infections, respectively. The rate of vertical transmission increases with older gestational age at infection,

but there is a significantly higher risk of fetal anomalies and symptomatic disease when maternal infection occurs during the preconceptional and periconceptional period and during the first trimester of pregnancy.^{31,32}

Approximately 10% to 15% of children with cCMV are symptomatic at birth. Outcomes for these infants are poor, and most survivors suffer from severe neurologic sequelae.^{4,33–35} The overall mortality rate is <5%.^{10,27,35,36} The majority of children with cCMV are asymptomatic and therefore not diagnosed at birth. However, 7% to 15% of clinically asymptomatic patients may develop late sequelae, including SNHL, which is by far the most common sequela.^{5,37–39}

Because the majority of children are asymptomatic at birth and because there is no systematic newborn screening, the impact of cCMV is ill defined. Population-based natural history studies that accurately estimate the prevalence of disease and morbidity burden are scarce, but the economic burden is estimated to be similar to that for congenital rubella before the introduction of vaccination.^{13,40,41} Because SNHL is the most common sequela of cCMV infection, it is a major contributor to disease burden. Reliable estimates of the hearing loss caused by cCMV are needed to increase vigilance among health care workers and the public.

Retrospective studies performed on a population of deaf children report frequencies of cCMV-related hearing loss ranging from 2% to 18%.^{42–45} However, it is assumed that the importance of asymptomatic cCMV as a cause of hearing loss may be higher than currently believed.^{3,46,47}

This systematic review provides an overview of the prevalence of cCMV-related hearing loss based on the literature of the past 50 years and aims at better defining the nature of cCMV-associated hearing loss and the importance of cCMV among patients with childhood hearing loss.

METHODS

A systematic literature search was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.⁴⁸ The Medline database was searched for relevant articles published from inception to December 2013. In order to find all articles about hearing loss and cCMV infection, we used the following subject headings: congenital cytomegalovirus AND (hearing OR deafness OR auditory), combined with the results for perinatal cytomegalovirus AND (hearing OR deafness OR auditory) in all fields. This resulted in 476 citations, of which titles and abstracts were read by 2 reviewers independently. A manual search of reference lists of the retrieved articles resulted in 8 additional articles. Duplicates and non-English articles were excluded, because omission of non-English articles has been shown to have minimal impact on the results. Also, nonrelevant papers, defined as not focusing on the topic as indicated by the abstract, were excluded. A total of 101 articles were read in detail and narrowed to 37 relevant studies (Fig 1). Variable definitions of symptomatic cCMV are found in the literature. The most common definition of symptomatic disease is the presence of ≥ 1 of the following symptoms at birth: petechiae, jaundice with conjugated hyperbilirubinemia, hepatosplenomegaly, thrombocytopenia, chorioretinitis, seizures, microcephaly, and intracranial calcifications.^{3,4,28,34,49} Only studies that mentioned ≥ 3 of these symptoms were included. If there was no description or definition, studies were nevertheless included if there was a reference to an article with a similar definition. Diagnosis of cCMV had to be confirmed by virus isolation or polymerase chain reaction (PCR) of CMV in urine or saliva, collected within 3 weeks of birth to distinguish it from postnatally acquired infections.^{18,50}

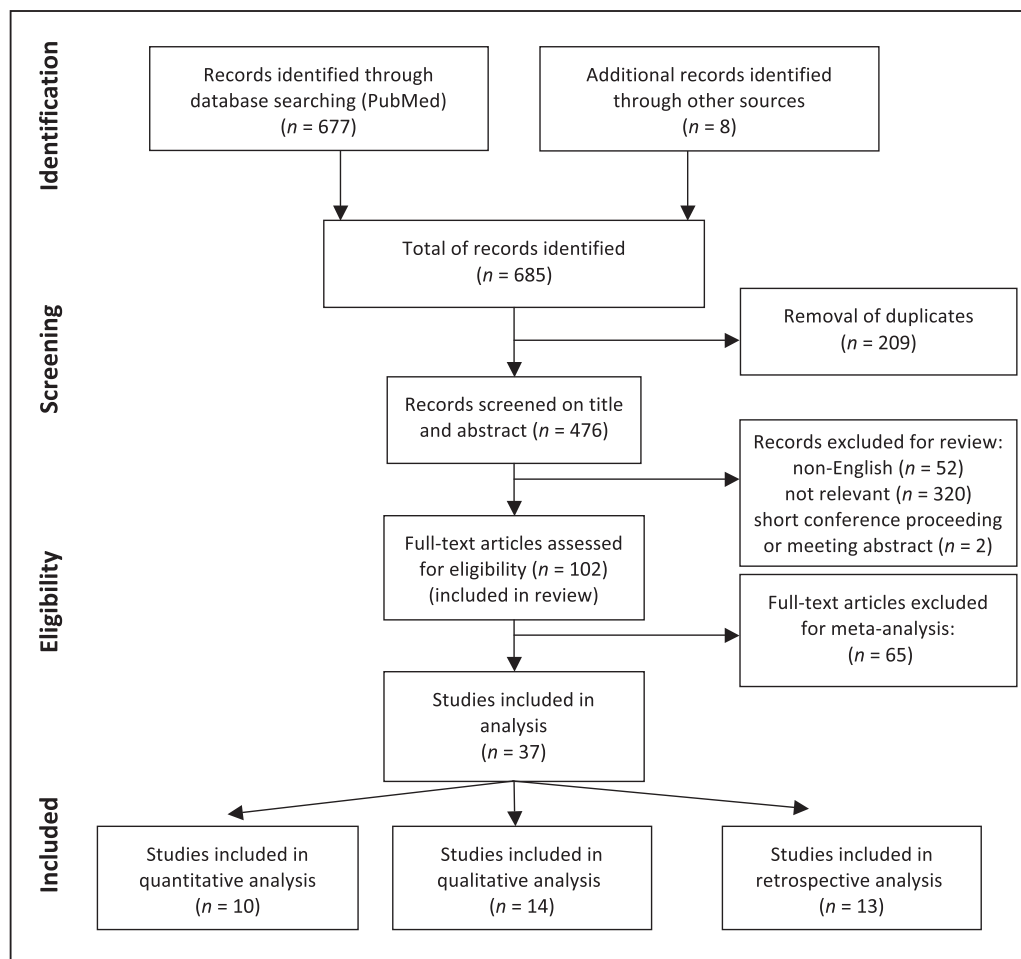


FIGURE 1
PRISMA flowchart of literature search.

Only articles with data from primary sources were included. In case of multiple reports from 1 research group, the most recent or the most detailed report was chosen. Methods for hearing evaluations were not standardized across the studies, nor were follow-up protocols. Only studies where transient middle ear pathology was excluded by otoscopy, admittance measurements, and absence of air–bone gap were included. Hearing loss includes both unilateral and bilateral SNHL, with thresholds >20 dB. Individual study quality was assessed through evaluation of study design, number of evaluations, length of follow-up, outcome measurement method, and reporting of confounding factors for hearing loss. Selected articles were divided according to 3 different approaches.

Quantitative Approach

To determine the prevalence of cCMV-associated hearing loss on a population level, we selected studies where cCMV infection was diagnosed through universal newborn screening for cCMV. The following articles were included: original peer-reviewed articles where screening for cCMV was done in all newborns during a given period and studies where the diagnosis of cCMV was made by **virus isolation or PCR of CMV in urine or saliva, collected within 3 weeks of birth**. Studies with cases identified by immunoglobulin M detection in blood samples were not included because such assays lack sensitivity.^{27,51,52} The use of the aforementioned definition of symptomatic cCMV was required. We were especially interested in studies

with a longitudinal prospective design. Data on the number of symptomatic and asymptomatic patients and the associated hearing loss had to be available. Studies with children treated with ganciclovir or valganciclovir were excluded to determine the exact number of affected children in the natural course of infection.

Qualitative Approach

To determine the nature of cCMV-associated hearing loss, we selected cohort studies with a longitudinal audiological follow-up. Those studies include children detected by systematic cCMV screening or diagnosed because of known seroconversion of the mother, or children with clinical signs suggestive of the disease. We selected all studies that

conducted longitudinal testing in a group of ≥ 20 children with cCMV infection. The use of the aforementioned definition of symptomatic cCMV was mandatory. Children had to have ≥ 2 audiological evaluations during follow-up. In such studies an overrepresentation of symptomatic children is expected, so to stratify the results according to symptomatic or asymptomatic cCMV infection, we needed data on the number of symptomatic and asymptomatic patients and the associated hearing loss. Concerning the different characteristics of cCMV-related hearing loss, we used the studies with the most complete information on that specific parameter. An additional goal was to determine the relationship between primary and non-primary (reactivation or reinfection) infection and hearing loss.

Retrospective Approach

A method for retrospective diagnosis of cCMV was introduced in 1994 by Shibata et al.⁵³ They detected CMV DNA by means of PCR on neonatal dried blood spots (DBS). Since then several studies tested and adapted this method, with sensitivity ranging from 71% to 100% and specificities of 99% to 100%.⁵⁴ A recent study found much lower sensitivities, near 34%, when DBS were used as screening test.⁵⁵ However, it is the only way to detect a cCMV infection retrospectively. Detection of CMV DNA can vary depending on the method of DNA extraction from the cards, the amplification method, and the part of the CMV genome being detected.^{56–58} It may also be influenced by the time and conditions in which the cards have been stored. Cross-contamination of adjacent stored cards has been reported.^{54,59–61}

To understand the importance of cCMV as a cause of childhood hearing loss, we reviewed studies that conducted retrospective testing in a group of hearing-impaired children. Requirements were testing by real-time PCR for quantitative

analysis of CMV DNA on DBS or on dried umbilical cords. A distinction was made between studies that excluded other risk factors for hearing loss and those that did not.

Statistical Analysis

We performed a meta-analysis by using a random effects model of DerSimonian and Laird to calculate estimated proportions. R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to make calculations. For each inquiry a confidence interval (CI) was calculated and a forest plot was developed. I^2 is a measure of heterogeneity; it indicates the percentage of variance attributable to study heterogeneity rather than chance. The P value reflects the significance of the heterogeneity. The study was conducted in accordance with the instructions of the PRISMA statement for reporting systematic reviews and of the Meta-analysis of Observational Studies in Epidemiology group for reporting meta-analyses of observational studies.^{48,62}

RESULTS

Quantitative Approach

Ten studies were selected according to the aforementioned protocol. An overview of the studies is shown in the Supplemental Information. We found an overall prevalence of cCMV infection of 0.58%. The proportions for symptomatic and asymptomatic infected children were 9.8% and 90.2%, respectively. Hearing loss occurred in 32.8% of symptomatic cases, compared with 9.9% of asymptomatic children. The overall rate of hearing loss in cCMV infection was 12.6%. The overall rate of hearing loss by cCMV infection in the population was estimated to be 0.5 in 1000 children. Table 1 includes an overview of the estimated proportions.

Qualitative Approach

Fourteen longitudinal cohort studies of children with cCMV infection that

focused on hearing were included (Supplemental Information). In those studies, symptomatic children were overrepresented, so we stratified the results according to symptomatic or asymptomatic cCMV infection. In symptomatic cCMV infection hearing loss was bilateral in 71.2% and unilateral in 28.8% of cases. The majority of hearing loss was severe to profound, with 65.1% of bilateral hearing loss severe to profound, necessitating hearing amplification and rehabilitation. Of all symptomatic children with hearing loss, 18.1% had a delayed onset. Approximately 1 in 6 symptomatic children with hearing loss exhibited progressive hearing loss, and 1 in 5 symptomatic children with hearing loss experienced fluctuations. In the asymptomatic group, hearing loss was unilateral in 57%. The majority of hearing loss was also severe to profound, but the percentage of children with bilateral severe to profound hearing loss was less than in the symptomatic group. However, in 42.6% of the hearing-impaired asymptomatic children, hearing loss necessitated hearing amplification and rehabilitation. Of all asymptomatic children with hearing loss, 9% had a delayed onset. Approximately 1 in 5 asymptomatic children with hearing loss exhibited progressive hearing loss, and 1 in 4 asymptomatic children with hearing loss experienced fluctuations.

To evaluate the impact of maternal seroimmunity on hearing status, we selected 3 additional studies that reported the amount of hearing loss in relation to type of infection (primary or nonprimary). Hearing loss occurred in 12.1% of the primary infections and in 11.8% of the nonprimary infections. A summary of the qualitative approach is found in Tables 2 and 3.

Retrospective Approach

Thirteen studies were selected for a retrospective approach (Supplemental

TABLE 1 Results of the Quantitative Approach^{3,8,23,27,40,51,63–66}

	Estimated Proportion, %	95% CI	I^2 , %	P of Heterogeneity
Prevalence of cCMV in population	0.58	0.41–0.79	94.3	<.0001
Proportion of symptomatic cCMV	9.8	5.8–14.6	70	.0004
Proportion of asymptomatic cCMV	90.2	85.4–94.2	70	.0004
Proportion of symptomatic cCMV with hearing loss	32.8	23.2–43.2	0	.6423
Proportion of asymptomatic cCMV with hearing loss	9.9	6.3–14.2	46.9	.0495
Proportion of cCMV with hearing loss(10% \times 90%)+(30% \times 10%)	12.6	9.4–16.3	26.7	.198
Prevalence of hearing loss by cCMV in population	0.05	0.03–0.09	79.6	<.0001

Information). In the first analysis, all selected retrospective studies were included. In the next 2 analyses the distinction was made between studies that excluded children with other risk factors for hearing loss (eg, known hereditary and environmental causes) and studies that did not. In the group of hearing-impaired children the prevalence of cCMV-related hearing loss was ~8% (Table 4). In the group of hearing-impaired children with hearing loss from unknown origin where known risk factors for hearing loss were excluded, the prevalence of hearing loss by cCMV was ~20%.

Quality of Studies

The majority of studies included in the quantitative and qualitative approach had a prospective study design. The number of hearing evaluations in studies used in the quantitative approach was low in comparison to studies in the qualitative approach. Also, the follow-up was longer in the studies included in the qualitative approach. Methods of outcome measurement seemed not to differ greatly between the studies. Only a few studies reported other risk factors for hearing loss.

DISCUSSION

This systematic review estimates the prevalence and nature of the hearing loss attributable to cCMV infection, based on a meta-analysis of a number of selected articles. We found an overall prevalence of cCMV infection of 0.58% in industrialized countries. This is consistent with the 0.64% found in a previous meta-analysis by Kenneson and Cannon.¹² Globally significant differences in epidemiology exist between and within countries. In developing nations with highly seropositive populations, prevalence ranges between 1% and 6%.⁸⁶ This correlation is explained by the fact that cCMV birth prevalence increases with maternal seroprevalence. A high seroprevalence means that there are more pregnant women at risk for reactivation or reinfection next to a higher prevalence of risk behavior and a higher rate of exposure to CMV. The increased rate of nonprimary infections leads to a higher birth prevalence on population level, despite the lower risk of vertical transmission.^{12,30} The risk of symptomatic infection and permanent sequelae is higher among infants whose mothers

experienced a primary infection, but disabilities have also been observed as a result of nonprimary infection.^{27,87,88} Percentages of newborns with symptomatic disease or long-term sequelae after nonprimary infection vary between 1% and 10%.^{28,29,89} Data are currently insufficient to estimate the exact proportion of cCMV-disabled children attributable to nonprimary infection.⁸⁸

The overall incidence of hearing loss in cCMV is 12.6%. One in 3 symptomatic children will experience loss, in comparison with 1 in 10 asymptomatic children. Extrapolation of these results to the population level shows that of every 10 000 children born each year, 5 will have cCMV-related hearing loss. In combination with birth rate statistics in Europe, this means that each year 2600 live-born children will experience immediate or delayed hearing impairment caused by cCMV. In the United States, the number is 1975 children per year. The results in the quantitative approach all have a strikingly high heterogeneity, which in most of the cases was significant. So despite our strict selection criteria, the results should be interpreted with caution. The majority of symptomatic children had bilateral hearing loss. In the asymptomatic group unilateral losses predominated. Presumably, a large number of unilateral hearing losses, often diagnosed at school age, are attributable to a missed asymptomatic cCMV infection. The challenge is to confirm the diagnosis

TABLE 2 Nature of Hearing Loss Stratified by Symptomatic or Asymptomatic Infection^{8,24,25,27–29,34,40,67–72}

Hearing Loss Characteristics	Symptomatic at Birth		Asymptomatic at Birth	
	Estimated Proportion, %	95% CI, I^2 , P of Heterogeneity	Estimated Proportion, %	95% CI, I^2 , P of Heterogeneity
Bilateral hearing loss	71.2	64.2–77.8, 0%, .8944	43.1	28.2–58.6, 39.8%, .1024
Unilateral hearing loss	28.8	22.2–35.9, 0%, .8944	56.9	41.4–71.8, 39.8%, .1024
Severe to profound hearing loss	76.8	70.1–83, 0%, .5044	77.7	59.6–91.6, 52.9%, .038
Bilateral severe to profound hearing loss	65.1	54.2–75.2, 0%, .4937	42.6	20.2–66.7, 49%, .0673
Delayed hearing loss	18.1	5.9–36.2, 65.4%, .0051	9	0.8–24.5, 64.8%, .0058
Progressive hearing loss	17.7	3.5–39.4, 80.5%, <.0001	20.3	5.3–41.8, 73.1%, .0002
Fluctuating hearing loss	21.5	9.3–37, 55.6%, .0272	24	2.1–59.6, 86.3%, <.0001

TABLE 3 Hearing Loss According to Type of Infection^{24,25,27–29,40,71,72}

Type of Infection	Estimated Proportion, %	95% CI	I^2 , %	P of Heterogeneity
Hearing loss in case of primary infection	12.1	8.6–16	18.8	.2814
Hearing loss in case of nonprimary infection	11.8	7.5–16.8	21.7	.2568

La transmission en cas de 1° infection est plus grande mais le nombre de réactivation est plus grand. A la fin on aura autant d'enfant en nombre sourd en raison d'une primo ou réinfection même si le risque est différent

	Estimated Proportion, %	95% CI	I^2 , %	P of Heterogeneity
Hearing loss by cCMV among hearing impaired ^{73–85}	10.4	8–13	54.1	.0103
Exclusion of other risk factors for hearing loss ^{73–76}	19.8	14.6–25.7	0	.5601
No exclusion of other risk factors for hearing loss ^{77–83}	8.2	6.5–10	0	.7938

retrospectively by PCR on DBS. In both groups, 3 in 4 children with hearing loss had a severe to profound hearing loss in ≥ 1 ear. In the symptomatic group 65% had a disabling bilateral severe to profound hearing loss with the need for hearing amplification and rehabilitation. In the asymptomatic group, 42.6% of hearing-impaired children had bilateral severe to profound hearing loss.

The hearing loss caused by cCMV infection has an exclusively sensorineural character. Its pathogenesis is poorly understood. Most studies describe **injuries to endolymphatic structures and the stria vascularis that may cause potassium imbalance and subsequent degeneration of the sensory structures**.^{90,91} Some authors attribute hearing loss to the **cytopathic effect of the virus itself** and the **host immune response** on inner ear structures.^{92–96} Regarding a possible **delayed onset** of hearing loss, percentages in the literature range from **0% to 50%**.^{3,24,27,66,67} We calculated $\sim 18\%$ in the symptomatic group and $\sim 9\%$ in the asymptomatic group, but in both groups there was significant heterogeneity between studies. This was also the case for progression and fluctuation of hearing loss. Part of the heterogeneity in delayed onset probably results from the fact that the first studies of cCMV and hearing loss date from the period before the implementation of universal neonatal hearing screening (UNHS), so that the onset of hearing loss could not be de-

termined exactly. Furthermore, in this population middle ear problems and testing difficulties are important confounders, despite the fact that we tried to control for these confounding factors when selecting articles. The mechanisms behind delayed onset, progression, and fluctuation have not been elucidated. Like other herpesviruses, CMV establishes latency after primary infection. **It is hypothesized that viral reactivation and localized host inflammatory responses to reactivation might play a role**.^{92–96}

Because of the high heterogeneity and low P values, the exact percentages for delayed onset, progression, and fluctuation are hard to define. It is important to inform the parents that hearing loss in cCMV can be delayed in onset and might progress and fluctuate over varying time frames. It is also important to realize that UNHS is not an absolute safeguard. This along with the unstable nature of the hearing loss makes longitudinal audiologic follow-up of children with cCMV infection mandatory. **Delayed-onset hearing loss usually occurs before 6 years of age, mainly in the first year after birth**, but hearing loss at older ages is reported occasionally.^{3,24,65,67,69,97,98} **Most authors suggest follow-up until the age of 6 years**.^{3,49,99,100} The risk of hearing loss does not vary between primary and nonprimary infections. **Nonprimary infections usually result in an asymptomatic infection. The incidence of hearing loss in the**

nonprimary group therefore is comparable to the incidence of hearing loss in the asymptomatic group.

In our meta-analysis, we found a high I^2 for each parameter of hearing loss we investigated, despite strict selection criteria for the inclusion of articles. The high rate for I^2 indicates that most of the variability across studies results from heterogeneity rather than chance. Using strict eligibility criteria for studies selected, we tried to obtain high study quality and low heterogeneity, but some limitations exist. Baseline measurements were not always provided, and time points for collecting outcomes and method of measuring outcomes differed between studies. Most striking was the variability in defining symptomatic cCMV, the main indicator of permanent disabilities. A clear definition is crucial if we want to analyze and compare the results of different studies. The global study quality of selected studies was deemed to be moderate to good. With this systematic selection, the most appropriate articles to represent hearing outcomes in cCMV infection were included.

Regarding the importance of cCMV-related hearing loss in the total population of children with SNHL, we calculated that 1 in 10 hearing-impaired children has cCMV-related hearing loss. When known risk factors or causes of hearing loss are excluded, cCMV is the cause of hearing loss in 1 out of 5 children. **Quantitative PCR assays have not been standardized across laboratories, which makes comparison of data from different studies difficult.** When relying on a DBS test, **we also have to consider that viral DNA levels are lower in peripheral neonatal blood than in urine or saliva**.^{98,101,102} It is possible that viremia had not yet occurred at the time of sampling.¹⁰³ Moreover, as mentioned earlier, **length of storage of the DBS might decrease the apparent viral load**.¹⁰⁴ **These factors might lead to**

underestimation of the role of cCMV.

Therefore, this retrospective approach suggests an important etiological role for cCMV in hearing loss in childhood.

We did not focus on risk factors for hearing loss in our systematic review. Much research has already been done on that subject, but it remains controversial. Symptomatic infection; disseminated disease, especially with petechiae and intrauterine growth retardation; and a high viral load at birth seem to be associated with hearing loss.^{75,105–107}

Identification of risk factors might be helpful for a more directed and rigorous follow-up of infants at risk for hearing loss. Furthermore, it might decrease the number of dropouts in longitudinal follow-up of asymptomatic infants. Accurate prospective longitudinal studies would also help reveal the full spectrum of cCMV disease and identify such risk factors.

The absence of specific medical interventions for seronegative mothers and uncertainty about fetal prognosis has discouraged routine maternal antibody screening. To date, universal systematic screening of newborns for cCMV has not been implemented. Recent screening techniques such as PCR on urine, saliva, or blood are potentially simple, low-cost methods that could be used in future newborn screening programs.^{50,55,108} In our center an ongoing prospective study is comparing sensitivity and specificity between PCR on DBS and urine culture. At present urine or saliva culture, with or without PCR, remains the gold standard.

A systematic screening together with UNHS could identify the most suitable candidates for antiviral therapy. Currently, antiviral treatment with ganciclovir or valganciclovir is recommended only for symptomatic newborns with severe symptomatic focal organ disease or central nervous system involvement.^{109–112}

The remainder could be enrolled in a longitudinal follow-up program to detect delayed-onset or progressive hearing loss and other developmental delays. Early detection of hearing loss leads to early intervention and better patient outcomes.^{113,114}

Prevention strategies, such as CMV vaccination or passive immunization with hyperimmune globulin, are currently subjected to clinical trials but are not yet in clinical use. Preliminary results are promising, but currently there are insufficient data to support the use of prenatal interventions.^{115–117} Preconceptional seroimmunity provides only partial protection against newborn disease and adverse outcomes. Infected infants born to seroimmune mothers are not completely protected from SNHL, but their hearing loss is often milder and less frequently bilateral.^{425,28,29}

Increasing awareness of cCMV infection and implementing behavioral measures such as frequent hand-washing after exposure to young children's body fluids and avoiding intimate contact with young children for all prospective mothers remain the most important preventive strategies.

CONCLUSIONS

This systematic review confirms the important role of cCMV in childhood SNHL. However, because of the lack of systematic screening for cCMV in newborns and the characteristics of the disease, underestimation of its role in hearing loss is likely. Despite the threefold lower prevalence of hearing loss in asymptomatic cCMV, the numerous asymptomatic cases mean that this group is an important component of the group of hearing-impaired children. There is no pathognomonic configuration of hearing loss caused by cCMV. Rather, it is characterized by its unstable nature, with progression and fluctuations. Delayed-onset hearing loss is not uncommon. Long-term audiological follow-up for ≥ 6 years is strongly recommended. Systematic screening could identify the most suitable candidates for therapy, and the remainder could be enrolled in a longitudinal follow-up program to detect delayed-onset hearing loss.

Until a CMV vaccine becomes available, behavioral and educational interventions are the most effective strategy to prevent maternal CMV infection.^{118–120} The high incidence and the devastating morbidity associated with cCMV emphasize the importance of preventive measures and of clinical research on prenatal and postnatal interventions. There is still a lot of work to do, but with this systematic review we hope to increase awareness of the cCMV disease burden.

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HIDE AND SEEK: *When the kids were little, we used to play hide and seek all the time. There were innumerable hiding places around the house and yard, and we always had a great time. In the oceans, hide and seek has a different and much more serious context. Fish are hiding from other fish; if found, they are often eaten. Fish in coastal waters try to avoid this by using camouflage, blending into sand, rocks, and plants, or hiding among coral and kelp. However, in the middle of the ocean, there are no places to hide. Fish in these areas (particularly small fish) have to hide in plain sight.*

As reported in The New York Times (Science: August 19, 2014), some fish living in the middle of the ocean have evolved clever ways to go unseen. Their bodies have a density and refraction index that is so similar to their watery environment that light actually passes through them, making them almost invisible. One problem with this transparency is that there is no protection from the sun, which can not only burn the external structures but internal organs as well. Secretions – similar to suntan lotions – protect them from the sun, but then they are no longer invisible to predators that can detect ultraviolet light.

Terrestrial animals, of course, are unlikely to ever become transparent because they are so much denser than air and have a significantly different refraction index. As for me, I have no reason to become invisible. I want my family to be able to find me when I am home and I don't believe there are predators in my neighborhood that are trying to dine on me.

Noted by WVR, MD

Hearing Loss and Congenital CMV Infection: A Systematic Review
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