Hearing and neurodevelopmental outcomes for children with asymptomatic congenital cytomegalovirus infection: a systematic review

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SUMMARY

Introduction: Congenital CMV is one of the commonest congenital infections and a recognised cause of sensorineural hearing loss and neurodevelopmental impairment. Ninety percent are clinically inapparent at birth but are reported to be at risk of developing such abnormalities throughout childhood, the extent of which requires further elucidation.

Methods: A systematic literature review was conducted using Medline and Embase databases, manual citation review, and personal libraries for articles reporting primary data on hearing and neurodevelopmental outcomes for children with asymptomatic congenital CMV. PROSPERO registration number CRD42015025407.

Results: Thirty-seven of 480 articles identified between 1969 and 2016 met the eligibility criteria. Twenty-nine of these contributed primary data on hearing outcomes and 20 on neurodevelopmental outcomes (12 of the 37 studies contributed data on both). Cumulative incidence of sensorineural hearing loss with follow up to at least 5 years was 7-11%, which is more than healthy controls but less than children with symptomatic congenital CMV (34-41%). The onset, course, and severity of hearing loss was variable with no reliable virological prognostic marker. In comparison to controls, children with asymptomatic congenital CMV did not perform worse than controls in neurodevelopmental assessments, and performed better than children with symptomatic congenital CMV.

Conclusions: Studies show children with asymptomatic congenital CMV are at increased risk of developing hearing loss, but perform equally well on neurodevelopmental assessments when compared to healthy controls. There is no reliable virological marker to determine

which infants will develop sequelae. Regular follow-up until school entry is supported by the literature.

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ABBREVIATIONS

AcCMV = asymptomatic CMV

cCMV = congenital CMV

dB = decibels

DBS = dried blood spot

DQ = developmental quotient

ge = genomic equivalents

IQ = intelligence quotient

ScCMV = symptomatic CMV

SNHL = sensorineural hearing loss

INTRODUCTION

Congenital CMV (cCMV) is one of the commonest congenital infections, with a birth prevalence of 0.64%, and can result from maternal primary infection, re-infection, or re-activation during pregnancy.¹ Currently there is no effective method to prevent transmission of CMV from mother to the fetus or antenatal treatment strategies to mitigate the impact of congenital CMV infection.² Approximately 10% of infected neonates will be clinically apparent at birth, which can manifest as jaundice, petechiae, hepatosplenomegaly, thrombocytopenia, chorioretinitis, intrauterine growth restriction, microcephaly, seizures, or intracranial calcification³. It is estimated that 40%-58% of such children with symptomatic cCMV (ScCMV) experience long-term sequelae, in particular hearing and neurodevelopmental impairment.⁴ Currently, cCMV is the most frequent non-genetic cause of sensorineural hearing loss (SNHL).⁴⁻⁷

For the 90% of infected newborns who have clinically inapparent disease, their long-term outcomes are less clear. This is in part due to a lack of routine newborn screening for congenital CMV in a population where most infections will be asymptomatic and therefore not identified. Additionally, testing for CMV in infants with SNHL is not routine or universal practice, further contributing to lack of cCMV identification. The growing body of literature on asymptomatic cCMV (AcCMV) has identified long-term sequelae, primarily SNHL and neurodevelopmental impairment, in children who were asymptomatic at birth.⁸ However, the extent of these abnormalities remains uncertain.

As the majority of children with cCMV are asymptomatic at birth, AcCMV contributes significantly more than ScCMV to the overall burden of cCMV disease in childhood.⁸ An

appreciation of the natural history of AcCMV is therefore important for counselling, optimal clinical follow-up, and assessment of disease burden;⁹ as well as provide rationale for school hearing screening programs. We systematically reviewed the literature aiming to assess the extent of hearing loss and abnormal neurodevelopmental outcomes for children with AcCMV.

METHOD

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA Statement, 2009),¹⁰ and registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42015025407).

Search strategy

The search was conducted on 19 September 2016. The Medline database (1946 to present with daily update) was searched using the following strategy: (“congenital” and “cytomegalovirus infections or cytomegalovirus”) and (“asymptomatic infections or asymptomatic diseases” or “hearing or hearing loss or hearing tests or sensorineural hearing loss” or “cognition or cognitive disorders” or “child development” or “developmental disabilities” or “follow-up studies”). The Embase database (1974 to 16 September 2016) was searched using the following strategy: (“congenital infection” and “cytomegalovirus infection or cytomegalovirus”) and (“asymptomatic infection or asymptomatic disease” or “hearing impairment or hearing or hearing test” or “cognition assessment or cognition” or “nervous system development or brain development or psychomotor development or mental

development assessment or development or child development or mental development or language development or motor development or postnatal development or cognitive development or developmental disorder” or “follow up”). Two investigators independently reviewed all titles and abstracts and those considered to meet eligibility based on pre-determined inclusion and exclusion criteria underwent full text assessment. This was supplemented by manually searching citations in key reviews and articles undergoing full text assessment, as well as personal libraries. The two investigators reached consensus for the inclusion or exclusion of each article, with a third investigator consulted in the event of a consensus initially not being reached.

Inclusion criteria

Articles published in the English language reporting primary data on SNHL and/or neurodevelopmental outcomes for children with AcCMV were included in the review. No eligibility restrictions were placed on follow-up duration or protocols. For articles arising from the same study cohort, the article with the longest follow-up period that met the eligibility criteria was included. For studies arising from overlapping cohorts, each individual study was assessed and included if it had a unique study design or reported on unique statistical analyses for either SNHL or neurodevelopmental outcomes.

Exclusion criteria

Articles were not eligible if the abstract did not report primary data on SNHL or neurodevelopmental outcomes for children with AcCMV and were excluded prior to full text assessment. Case reports, case series, and review articles were excluded on the basis of low

quality or non-primary evidence. Following full text assessment, articles were excluded if they: (1) did not present primary data on SNHL or neurodevelopmental outcomes for children with AcCMV; (2) did not stratify outcomes exclusively for children with AcCMV; (3) were retrospective analyses in a cohort of children with either hearing loss or neurodevelopmental delay; or (4) had insufficient follow-up information.

Quality assessment and risk of bias

Study quality was assessed according to the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence¹¹ and rated on a scale of 1 to 5, with 1 reflecting the highest and 5 the poorest quality of evidence. Risk of bias was addressed through the inclusion and exclusion criteria, and at the study level for eligible studies during data extraction. Selection bias was minimised by excluding retrospective studies in cohorts of children with the outcome of interest (SNHL and/or neurodevelopmental delay) as well as case reports and case series. During data extraction from eligible studies, subjects with AcCMV who had received antiviral therapy or hearing augmentation were excluded from contributing to the results derived from the respective study. Where possible, acknowledgement of the nature of antenatal infection (primary or non-primary) is made to identify subsets of AcCMV subjects whose outcomes may not be necessarily generalizable to other AcCMV subsets. Furthermore, studies that explicitly included the absence of SNHL as part of the diagnostic criteria for AcCMV, and therefore minimised SNHL as a confounding factor for neurodevelopmental performance, were extracted as a subset of studies.

Definitions

The accepted diagnostic criteria for cCMV included confirmation of CMV via virus isolation (culture) or PCR in saliva and/or urine up to 3 weeks of age, or detection of CMV via PCR on dried blood spot (DBS). AcCMV was defined as cCMV without any of the following symptoms or signs attributable to cCMV during the first 30 days of life: conjugated hyperbilirubinemia, petechiae, hepatosplenomegaly, thrombocytopenia, chorioretinitis, intrauterine growth restriction, microcephaly, seizures, or intracranial calcifications. SNHL during the newborn period was not considered part of the diagnostic criteria for ScCMV, as it was not uniformly reported nor consistently considered a feature of ScCMV across the studies. SNHL was defined as hearing loss beyond a threshold of 20 decibels (dB), with the exclusion of conductive hearing impairment. Neurodevelopmental impairment was defined as below average performance on neurological, cognitive or developmental assessment tools as determined by investigators.

RESULTS

Literature search

A total of 480 articles published between 1969 and 2016 were identified from the primary and secondary searches. The primary database search retrieved 291 articles from Medline and 172 articles from Embase. The secondary search identified an additional 9 articles from citations and 8 articles from personal libraries. After removing 49 duplicates, the remaining 431 articles had their titles and abstracts reviewed. Ninety-six articles met criteria for full text assessment, and of these, 37 articles were eligible for inclusion. Twenty-nine articles reported unique primary data on hearing outcomes and 20 articles reported unique primary data on

neurodevelopmental outcomes for children diagnosed with AcCMV (Figure 1). Twelve articles reported unique primary data on both hearing and neurodevelopmental outcomes.

Hearing outcome

The characteristics and findings of the 29 eligible studies reporting primary data on hearing outcomes are summarised in Table 1. There were multiple studies derived from overlapping cohorts in Alabama (United States),^{6,12-16} Texas (United States),^{17,18} Brussels (Belgium),^{19,20} Bologna (Italy),^{21,22} and Flanders (Belgium).²³⁻²⁵ Depending on the child's age, hearing evaluations consisted of auditory brainstem response, otoacoustic emissions, immittance measures of middle ear function, behavioural audiometry, pure-tone audiometry, speech audiometry, and auditory steady state response. Twenty-seven studies reported cumulative incidence data over varying follow-up periods. Studies from two major cohorts, Alabama and Belgium, provided the most robust cumulative incidence data. From the overlapping Alabama cohorts, Dahle et al¹³ (651 subjects), Fowler et al 1999⁶ (335 subjects), Fowler et al 1997¹² (307 subjects), and Rosenthal et al¹⁵ (420 subjects), reported a SNHL cumulative incidence of 7.4% over a median 5 years follow-up, 11.3% over 6 years of follow-up, 7.2% up to 7 years of follow-up, and 6.9% up to 8 years of follow-up respectively. In the Flanders cohort, Goderis et al 2016²⁵ (256 patients) reported a SNHL cumulative incidence of 8.2% up to 6 years of follow-up. When comparing AcCMV with healthy controls, Fowler et al 1997¹² reported no cases of SNHL among 277 controls compared to 22/307 (7.2%) in the AcCMV group up to 7 years. In comparison to children with ScCMV, Dahle et al¹³ found SNHL in 40.7% of their ScCMV group compared to 7.4% in the AcCMV group over a median of 5 years; Fowler et al 1999⁶ reported SNHL in 36.4% of ScCMV subjects at 6 years compared

to 11.3% of AcCMV subjects; and Rosenthal et al¹⁵ reported SNHL in 33.7% of their ScCMV group up to 8 years of follow-up compared to 6.9% in the AcCMV group. The remaining studies with cumulative incidence data^{14,17,19-24,26-41} involved relatively smaller cohorts (8-89 children) with variable study designs. The cumulative incidence of SNHL in these studies ranged from 0-25% over varying time periods (Figure 2).

The SNHL reported in these studies was variable in onset, severity, and course. Median age of delayed onset SNHL calculated in 2 prospective studies from the Alabama cohorts was 27 months¹² and 44 months,¹³ while Goderis et al²⁵ reported a mean age of 20 months. The oldest subject with late onset SNHL was aged 15.2 years at diagnosis.¹³ The severity of SNHL ranged from mild to profound; however hearing assessments and decibel thresholds for classification of SNHL severity was not consistent across the studies. Where reported, the range of lower limits for SNHL categories included: mild 20-30 dB, moderate 30-45 dB, severe 60-70 dB, and profound 80-90 dB hearing loss. The course of SNHL was assessed in 6 studies,^{12,13,20,23,33,34} where SNHL was reported as stable, fluctuating, resolving or progressive. Fluctuating SNHL was reported in 16% to 54%^{12,13,20,34} of study subjects; progressive SNHL varied from 1.6% to 54%;^{12,13,20,23,34} and improving SNHL ranged from 7% to 48%.^{13,33,34} However, the duration of follow-up, as well as dB thresholds and definitions for the course of SNHL (eg. stable, fluctuating, improving, and progressive) in these studies differed. Some studies based the course of SNHL on changes (or lack thereof) in hearing loss categories over serial audiology assessments, whilst other studies specified dB variations (ranging from >5-15) as evidence of fluctuation, improvement, or progression. In addition, Dahle et al¹³ who reported the highest proportions for fluctuating and progressive

SNHL, categorised threshold variations for each audiometric frequency, therefore making it possible to assign a subject to more than one category of SNHL course. This could subsequently overestimate the relative proportions of the different courses of SNHL.

Neurodevelopmental outcome

Table 2 summarises the characteristics and findings of the 20 articles reporting primary data on neurodevelopmental outcomes. There were multiple studies derived from overlapping cohorts in Alabama (United States),⁴²⁻⁴⁴ Texas (United States),^{18,30} and Bologna (Italy).^{21,22} The specific age-appropriate neurodevelopmental assessments varied across the studies, and included neurological and developmental clinical examination, developmental profile, Bayley's Scales of Infant Development, Griffiths Mental Development Scales, Stanford-Binet Intelligence Scale, Wechsler Intelligence Scale for Children, Wechsler Preschool and Primary Scale of Intelligence, Bender-Gestalt Test, Vineland Adaptive Behaviour Scales, Vineland Social Maturity Scale, Kaufman Assessment Battery for Children, Brunet-Lezine Scale, Wide Range Assessment Test, Milani-Comparetti neuroevolutive assessment, Brazelton behavioural assessment, Prechtl general movement assessment, Gesell Developmental Schedule, Peabody Developmental Motor Scales, Alberta Infant Motor Scales, Ghent Developmental Balance Test, Amiel-Tison and Gosselin assessment, and NEPSY (A Developmental Neuropsychological Assessment). The cumulative incidence of neurodevelopmental impairment in patients with AcCMV was reported in 9 studies and varied from 0% to 9.1%.^{19,21,22,28,31,32,40,41,45} Of the larger prospective studies, Zavattoni et al⁴⁰ reported 5/89 (5.6%) AcCMV cases developed neurocognitive impairment over a 6 year follow-up period; Ancora et al²² reported a normal developmental quotient (DQ) and motor

examination in all of their AcCMV cases over an average follow-up period of 3.5 years; Lanari et al²¹ reported neurodevelopmental sequelae in 1/35 (2.9%) of their AcCMV cohort over a mean follow-up period of 18 months; Forner et al⁴¹ reported neurodevelopmental impairment in 3/33 (9.1%) of their AcCMV cases over 6 years; and Ahlfors et al 1983²⁸ reported 1/28 (3.6%) AcCMV cases developed neurodevelopmental impairment with up to 7 years of follow-up.

Eleven studies compared neurodevelopmental outcomes in AcCMV to controls. Eight of these reported no difference in performance on neurodevelopmental assessments between AcCMV cases and controls,^{24,26,29,30,38,42,43,46} whilst Lanari et al²¹ reported neurodevelopmental impairment in only 1/35 (2.9%) of AcCMV cases compared to 0/16 controls over an average 18 month follow-up period. The remaining two studies reported worse performance on neurodevelopmental assessments for AcCMV cases compared to controls.^{44,47} However, in the study by Temple et al,⁴⁴ the difference reported at 4-6 years of age was not evident for patients >6 years. Zhang et al⁴⁷ reported similar rates of mental retardation (DQ/IQ <70) for AcCMV cases and controls, but poorer verbal IQ scores in AcCMV children. However, hearing assessments were not reported in this cohort, thus SNHL was not excluded as a confounder and explanation for poorer verbal IQ in this AcCMV group. Five studies assessed neurodevelopmental outcomes for AcCMV compared to ScCMV. Children with ScCMV performed consistently worse on neurodevelopmental assessments than those with AcCMV, with all 5 studies demonstrating poorer neurodevelopmental outcomes for ScCMV cohorts compared to AcCMV cohorts.^{21,28,31,40,46}

The cumulative incidence for neurodevelopmental impairment in the ScCMV cohorts for these studies ranged from 30.7% to 66.7%.

AcCMV without SNHL

Five articles included SNHL in the neonatal period as part of the diagnostic criteria for ScCMV. Thus, from these studies, SNHL and neurodevelopmental outcomes in a group categorised as AcCMV without SNHL (in the newborn period) could be determined. In this subset of studies, the cumulative incidence (follow-up period in parentheses) of delayed onset SNHL was reported as 2.9% (mean 18 months),²¹ 5.6% (up to 6 years),⁴⁰ 8.2% (over 6 years),²⁵ 13.2% (up to 2 years)²⁴ and 24.2% (over 6 years).⁴¹ From a neurodevelopmental perspective, the cumulative incidence was reported as 2.9% (mean 18 months),²¹ 5.6% (up to 6 years),⁴⁰ and 9.1% (over 6 years).⁴¹ De Kegel et al²⁴ reported no difference in psychomotor performance between AcCMV cases and controls at 2 years. The studies reporting highest cumulative incidence values for SNHL and neurodevelopmental impairment were derived from cohorts of children born to mothers with primary CMV infection during pregnancy,^{40,41} and may therefore not be representative of the AcCMV population in general but indicate a higher risk sub-group of children with AcCMV. In addition, Conboy et al⁴² and Temple et al⁴⁴ compared neurodevelopmental outcomes for children with AcCMV without SNHL to controls. Conboy et al⁴² found no difference in cognitive performance between children aged 6.5-12.5 years, while Temple et al⁴⁴ did demonstrate poorer cognitive and motor performance for children with AcCMV compared to controls in the 4-6 year age group but no differences in the >6 year age group. However both of these studies enrolled older children and did not

report hearing status at birth. Therefore it is uncertain if these study cohorts faithfully represent AcCMV cohorts without SNHL.

Virological prognostic markers

Six studies included assessment of virological markers to predict which children with AcCMV will develop sequelae. Noyola et al¹⁸ reported that children with AcCMV who had shorter duration of urinary CMV excretion (<4 years) were more likely to develop SNHL (34.2% vs 8.5%). This was postulated to be due to better immune control of viral replication, and resultant immune activation within the hearing apparatus. In overlapping Alabama cohorts: Boppana et al¹⁴ found that children with SNHL as the only manifestation of AcCMV had higher CMV viral loads (urine and/or blood) during early infancy than children with AcCMV and normal hearing; Ross et al¹⁶ reported no positive predictive value between SNHL and CMV viral load in blood during infancy and early childhood, but found that children with AcCMV and levels of CMV viremia $\leq 3,500$ genomic equivalents (ge)/mL had a negative predictive value of 94-100% for developing SNHL; and Rosenthal et al¹⁵ demonstrated an association between older age at CMV viraemia in urine and delayed onset SNHL, however this was not analysed exclusively for the AcCMV cohort. Together, these Alabama studies suggest a direct cytopathic effect of CMV as the pathogenic mechanism for SNHL. In addition, Forner et al⁴¹ calculated viremia thresholds of $\geq 12,000$ copies/mL and $\geq 17,000$ copies/mL at birth as predictive of developing any CMV-related sequelae or SNHL respectively; and Lanari et al²¹ reported a correlation between neonatal CMV viral load or antigenemia and the development of sequelae, however this result was not stratified by AcCMV versus ScCMV cases.

DISCUSSION

Approximately 1 in 150 children globally are born with congenital CMV, 10% of whom will be symptomatic with sequelae, leaving the majority who are asymptomatic at birth with uncertainty about their long term outcome. Children with asymptomatic congenital CMV are the major contributor to the overall disease burden associated with cCMV,⁸ making this a significant childhood priority. Our systematic review determined that: (i) children with AcCMV are at increased risk of SNHL throughout early childhood with 7%-11 % developing SNHL; (ii) SNHL in these children may fluctuate, progress, or resolve in up to half; (iii) the extent to which children with AcCMV have neurodevelopmental impairment is less clear, though they perform similarly on neurodevelopmental assessments when compared to healthy controls; and (iv) there is no virological marker to predict who will develop sequelae.

Synthesis of the studies on outcomes for children with AcCMV was limited by the heterogeneity of study designs; differences in hearing and neurodevelopmental evaluations; the lack of uniform definitions for SNHL and AcCMV (particularly with regards to SNHL); and variable duration of follow-up. Early studies were more likely to be subject to the absence of hearing documentation in the newborn period as universal newborn hearing is a relatively recent public health initiative. In addition, hearing loss as a confounding variable was not always reported in the studies investigating neurodevelopment, making it difficult to exclude the contribution of co-existing hearing loss to adverse neurodevelopmental outcomes. Despite these limitations there are consistencies in the findings. The risk of SNHL for children with AcCMV (7%-11%) is greater than that for healthy controls but less than those with ScCMV (34%-41%). The course of SNHL may fluctuate, progress, or resolve in

up to a half of such patients. These results are in keeping with a recent meta-analysis by Goderis et al 2014,³ which found an overall incidence of SNHL of approximately 10% in children with AcCMV compared to approximately 30% of children with ScCMV. However, based on the current evidence, it is difficult to predict which children will experience SNHL, and similarly difficult to predict the onset, severity or course of SNHL for these children.

The absence of increased neurodevelopmental sequelae for children with AcCMV is supported by 8 studies reporting similar performance in neurodevelopmental assessments compared to controls.^{24,26,29,30,38,42,43,46,48} Two other comparative studies had either not adequately excluded hearing loss as a confounder for language delay⁴⁷ or demonstrated neurodevelopmental impairment that did not persist into an older age group.⁴⁴ Only one study compared the cumulative incidence of neurodevelopmental impairment in AcCMV cases with controls, reporting 2.9% and zero respectively.²¹ These results are reflected in a review by Cannon et al⁴⁹ who estimated similar rates of cognitive deficits for children with AcCMV and the general population (4.7% and 3.8% respectively). In addition, Townsend et al,⁵⁰ reporting on two contemporaneous studies in the United Kingdom and Sweden, demonstrated no differences in cognitive performance between children with AcCMV or 'mildly symptomatic cCMV' and controls at 5 years of age (London cohort) or at 7 years of age (Malmo cohort). Similarly, an early report on congenital CMV children (who were mostly asymptomatic at birth) with neurodevelopmental follow up at 3 and 5 years, found no difference in IQ scores between infected children and controls.⁵¹ Of note, in uncontrolled series of children with AcCMV without hearing loss, the highest cumulative incidence for neurodevelopmental impairment was reported for cohorts of AcCMV children born to

mothers who had primary CMV infection during pregnancy.^{40,41} This may indicate a subgroup of children with AcCMV who are at higher risk for sequelae, which needs to be further investigated.

The pathogenic mechanisms for long-term sequelae of AcCMV infection remain controversial. The two leading hypotheses include direct cytopathic effects of CMV and host immune response. The results from Noyola et al¹⁸ suggest an immunogenic phenomenon in the development of delayed SNHL, whereas the results from Boppana et al,¹⁴ Ross et al,¹⁶ Rosenthal et al,¹⁵ Forner et al,⁴¹ and Lanari et al²¹ point toward a direct cytopathic effect of CMV. This has implications for counselling parents of children with AcCMV and the potential role of antiviral therapy. These results are based on small numbers of a subset of AcCMV cases. Prioritising asymptomatic children for treatment at the present time is therefore not possible as there are still no surrogate markers to predict which children will go on to develop abnormalities, and who may benefit from antiviral therapy. Investigation in larger cohorts across a range of maternal CMV status is required before determining the applicability of such surrogate markers.

Robust prospective long-term longitudinal observational studies are needed to better describe the outcomes for children with AcCMV, particularly with respect to neurodevelopment. The evolution of and inconsistency in the definition of AcCMV infection with respect to the presence or absence of SNHL at birth, and lack of uniformity in classifications of SNHL and neurodevelopmental assessments make interpretation or comparisons difficult. Consensus on the definitions, and measurement of neurodevelopmental outcomes with adequate exclusion of confounding hearing loss would enable more accurate evaluation of outcomes. In addition,

stratifying outcomes for children with AcCMV based on the type maternal antenatal infection (primary or non-primary) may identify specific risk profiles for the different sub-groups.

In conclusion, we can, with reasonable confidence, counsel parents of a child deemed to have asymptomatic congenital CMV that there is about a 1 in 10 risk of their child developing hearing impairment throughout early childhood. We can caution that this will fluctuate, progress, or improve in up to half. Neurodevelopment appears to be on par with children without cCMV, but further longitudinal studies are suggested. However, we are unable to predict which individuals will experience such sequelae, nor their severity or course. Long term follow-up to at least school entry for both hearing and neurodevelopment is supported by the literature.

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REFERENCES

1. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol.* 2007;17(4):253-276.
2. McCarthy FP, Giles ML, Rowlands S, Purcell KJ, Jones CA. Antenatal interventions for preventing the transmission of cytomegalovirus (CMV) from the mother to fetus during pregnancy and adverse outcomes in the congenitally infected infant. *Cochrane Database Syst Rev.* 2011(3):Cd008371.

3. Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooge I. Hearing loss and congenital CMV infection: a systematic review. *Pediatrics*. 2014;134(5):972-982.
4. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol*. 2007;17(5):355-363.
5. Grosse SD, Ross DS, Dollard SC. Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: a quantitative assessment. *J Clin Virol*. 2008;41(2):57-62.
6. Fowler KB, Dahle AJ, Boppana SB, Pass RF. Newborn hearing screening: will children with hearing loss caused by congenital cytomegalovirus infection be missed? *J Pediatr*. 1999;135(1):60-64.
7. Dahl HH, Ching TY, Hutchison W, Hou S, Seeto M, Sjahalam-King J. Etiology and audiological outcomes at 3 years for 364 children in Australia. *PloS One*. 2013;8(3):e59624.
8. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. *Clin Microbiol Rev*. 2013;26(1):86-102.
9. Gantt S, Dionne F, Kozak FK, et al. Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection. *JAMA Pediatr*. 2016;170(12):1179-1180.

10. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
11. Group OLoEW. "The Oxford 2011 Levels of Evidence". *Oxford Centre for Evidence-Based Medicine* <http://www.cebm.net/ocebm-levels-of-evidence>. Accessed May 2nd, 2017.
12. Fowler KB, McCollister FP, Dahle AJ, Boppana S, Britt WJ, Pass RF. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. *J Pediatr*. 1997;130(4):624-630.
13. Dahle AJ, Fowler KB, Wright JD, Boppana SB, Britt WJ, Pass RF. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. *J Am Acad Audiol*. 2000;11(5):283-290.
14. Boppana SB, Fowler KB, Pass RF, et al. Congenital cytomegalovirus infection: association between virus burden in infancy and hearing loss. *J Pediatr*. 2005;146(6):817-823.
15. Rosenthal LS, Fowler KB, Boppana SB, et al. Cytomegalovirus shedding and delayed sensorineural hearing loss: results from longitudinal follow-up of children with congenital infection. *Pediatr Infect Dis J*. 2009;28(6):515-520.
16. Ross SA, Novak Z, Fowler KB, Arora N, Britt WJ, Boppana SB. Cytomegalovirus blood viral load and hearing loss in young children with congenital infection. *Pediatr Infect Dis J*. 2009;28(7):588-592.

17. Williamson WD, Demmler GJ, Percy AK, Catlin FI. Progressive hearing loss in infants with asymptomatic congenital cytomegalovirus infection. *Pediatrics*. 1992;90(6):862-866.
18. Noyola DE, Demmler GJ, Williamson WD, et al. Cytomegalovirus urinary excretion and long term outcome in children with congenital cytomegalovirus infection. Congenital CMV Longitudinal Study Group. *Pediatr Infect Dis J*. 2000;19(6):505-510.
19. Casteels A, Naessens A, Gordts F, De Catte L, Bougateg A, Foulon W. Neonatal screening for congenital cytomegalovirus infections. *J Perinat Med*. 1999;27(2):116-121.
20. Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. A 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection. *J Pediatr*. 2008;153(1):84-88.
21. Lanari M, Lazzarotto T, Venturi V, et al. Neonatal cytomegalovirus blood load and risk of sequelae in symptomatic and asymptomatic congenitally infected newborns. *Pediatrics*. 2006;117(1):e76-83.
22. Ancora G, Lanari M, Lazzarotto T, et al. Cranial ultrasound scanning and prediction of outcome in newborns with congenital cytomegalovirus infection. *J Pediatr*. 2007;150(2):157-161.
23. Royackers L, Rector E, Verhaert N, Desloovere C. Long-term audiological follow-up of children with congenital cytomegalovirus. *B-ENT*. 2013;Suppl 21:57-64.

24. De Kegel A, Maes L, Dhooge I, van Hoecke H, De Leenheer E, Van Waelvelde H. Early motor development of children with a congenital cytomegalovirus infection. *Res Dev Disabil.* 2016;48:253-261.
25. Goderis J, Keymeulen A, Smets K, et al. Hearing in Children with Congenital Cytomegalovirus Infection: Results of a Longitudinal Study. *J Pediatr.* 2016;172:110-115.
26. Reynolds DW, Stagno S, Stubbs KG, et al. Inapparent congenital cytomegalovirus infection with elevated cord IgM levels. Casual relation with auditory and mental deficiency. *N Engl J Med.* 1974;290(6):291-296.
27. Stagno S, Reynolds DW, Amos CS, et al. Auditory and visual defects resulting from symptomatic and subclinical congenital cytomegaloviral and toxoplasma infections. *Pediatrics.* 1977;59(5):669-678.
28. Ahlfors K, Forsgren M, Ivarsson SA, Harris S, Svanberg L. Congenital cytomegalovirus infection: on the relation between type and time of maternal infection and infant's symptoms. *Scand J Infect Dis.* 1983;15(2):129-138.
29. Kumar ML, Nankervis GA, Jacobs IB, et al. Congenital and postnatally acquired cytomegalovirus infections: long-term follow-up. *J Pediatr.* 1984;104(5):674-679.
30. Williamson WD, Percy AK, Yow MD, et al. Asymptomatic congenital cytomegalovirus infection. Audiologic, neuroradiologic, and neurodevelopmental abnormalities during the first year. *Am J Dis Child.* 1990;144(12):1365-1368.
31. Barbi M, Binda S, Primache V, Clerici D. Congenital cytomegalovirus infection in a northern Italian region. NEOCMV Group. *Euro J Epidemiol.* 1998;14(8):791-796.

32. Numazaki K, Fujikawa T. Chronological changes of incidence and prognosis of children with asymptomatic congenital cytomegalovirus infection in Sapporo, Japan. *BMC Infect Dis.* 2004;4:22.
33. Barbi M, Binda S, Caroppo S, et al. Multicity Italian study of congenital cytomegalovirus infection. *Pediatr Infect Dis J.* 2006;25(2):156-159.
34. Iwasaki S, Yamashita M, Maeda M, Misawa K, Mineta H. Audiological outcome of infants with congenital cytomegalovirus infection in a prospective study. *Audiol Neurotol.* 2007;12(1):31-36.
35. Dar L, Pati SK, Patro AR, et al. Congenital cytomegalovirus infection in a highly seropositive semi-urban population in India. *Pediatr Infect Dis J.* 2008;27(9):841-843.
36. Engman ML, Malm G, Engstrom L, et al. Congenital CMV infection: prevalence in newborns and the impact on hearing deficit. *Scand J Infect Dis.* 2008;40(11-12):935-942.
37. Lackner A, Acham A, Alborn T, et al. Effect on hearing of ganciclovir therapy for asymptomatic congenital cytomegalovirus infection: four to 10 year follow up. *J Laryngol Otol.* 2009;123(4):391-396.
38. Shan R, Wang X, Fu P. Growth and development of infants with asymptomatic congenital cytomegalovirus infection. *Yonsei Med J.* 2009;50(5):667-671.
39. Yamamoto AY, Mussi-Pinhata MM, Isaac Mde L, et al. Congenital cytomegalovirus infection as a cause of sensorineural hearing loss in a highly immune population. *The Pediatr Infect Dis J.* 2011;30(12):1043-1046.

40. Zavattoni M, Lombardi G, Rognoni V, et al. Maternal, fetal, and neonatal parameters for prognosis and counseling of HCMV congenital infection. *J Med Virol.* 2014;86(12):2163-2170.
41. Forner G, Abate D, Mengoli C, Palu G, Gussetti N. High Cytomegalovirus (CMV) DNAemia Predicts CMV Sequelae in Asymptomatic Congenitally Infected Newborns Born to Women With Primary Infection During Pregnancy. *J Infect Dis.* 2015;212(1):67-71.
42. Conboy TJ, Pass RF, Stagno S, et al. Intellectual development in school-aged children with asymptomatic congenital cytomegalovirus infection. *Pediatrics.* 1986;77(6):801-806.
43. Kashden J, Frison S, Fowler K, Pass RF, Boll TJ. Intellectual assessment of children with asymptomatic congenital cytomegalovirus infection. *J Dev Behav Pediatr.* 1998;19(4):254-259.
44. Temple RO, Pass RF, Boll TJ. Neuropsychological functioning in patients with asymptomatic congenital cytomegalovirus infection. *J Dev Behav Pediatr.* 2000;21(6):417-422.
45. Sohn YM, Park KI, Lee C, Han DG, Lee WY. Congenital cytomegalovirus infection in Korean population with very high prevalence of maternal immunity. *J Korean Med Sci.* 1992;7(1):47-51.
46. Pearl KN, Preece PM, Ades A, Peckham CS. Neurodevelopmental assessment after congenital cytomegalovirus infection. *Arch Dis Child.* 1986;61(4):323-326.

47. Zhang XW, Li F, Yu XW, Shi XW, Shi J, Zhang JP. Physical and intellectual development in children with asymptomatic congenital cytomegalovirus infection: a longitudinal cohort study in Qinba mountain area, China. *J Clin Virol.* 2007;40(3):180-185.
48. Kumar ML, Nankervis GA, Gold E. Inapparent congenital cytomegalovirus infection. A follow-up study. *N Engl J Med.* 1973;288(26):1370-1372.
49. Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? *Rev Med Virol.* 2014;24(5):291-307.
50. Townsend CL, Forsgren M, Ahlfors K, Ivarsson SA, Tookey PA, Peckham CS. Long-term outcomes of congenital cytomegalovirus infection in Sweden and the United Kingdom. *Clin Infect Dis.* 2013;56(9):1232-1239.
51. Saigal S, Lunyk O, Larke RP, Chernesky MA. The outcome in children with congenital cytomegalovirus infection. A longitudinal follow-up study. *Am J Dis Child.* 1982;136(10):896-901.

LIST OF TABLE AND FIGURE LEGENDS

Figure 1.

Table 1.

^aCategorized for different audiometric frequencies, therefore study subjects may have more than one type of threshold variation.

^bComparison with control group only for neurodevelopmental outcomes.

^cScCMV cases not included as a proportion received GCV and unsuitable for comparison with AcCMV cases.

ABR = auditory brainstem response

AcCMV = asymptomatic congenital cytomegalovirus

GCV = ganciclovir

OAE = otoacoustic emissions

NPV = negative predictive value

ScCMV = symptomatic congenital cytomegalovirus

SNHL = sensorineural hearing loss

Figure 2.

First author, year of publication (number of AcCMV cases)

Table 2.

^aIncludes 24 infants with SNHL.

AcCMV = asymptomatic congenital cytomegalovirus

DQ = developmental quotient

IQ = intelligence quotient

ScCMV = symptomatic congenital cytomegalovirus

SNHL = sensorineural hearing loss.

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Table 1. Characteristics and findings of eligible studies included in the systematic review for hearing outcomes.

First Author	Year	Study design	Participants	Length of follow-up	Quality of evidence (level)	Findings
Stagno ²⁷	1977	Prospective case-control	51 AcCMV 41 controls	Mean 54 months	3	7/51 (14%) AcCMV cases developed SNHL compared to 2/41 (5%) controls.
Ahlfors ²⁸	1983	Prospective cohort	28 AcCMV 14 ScCMV	Up to 7 years	3	2/28 (7.1%) AcCMV cases developed SNHL compared to 6/14 (42.9%) ScCMV cases.
Kumar ²⁹	1984	Prospective case-control	17 AcCMV 21 controls	Mean 7.6 years	3	4/17 (23.5%) AcCMV cases developed SNHL compared to 1/21 (4.8%) controls.
Williamson ¹⁷	1992	Prospective case-control	59 AcCMV 26 controls	Up to 3 years	4	8/59 (13.6%) AcCMV had congenital SNHL. 1/51 (2%) AcCMV developed late onset SNHL. 0/26 controls

							developed SNHL.
Fowler¹²	1997	Prospective case-control	307 AcCMV 277 controls	Up to 7 years	2	22/307 (7.2%) AcCMV with SNHL. 4/22 (18%) delayed onset SNHL (median 27 months). 11/22 (50%) progressive SNHL. 5/22 (23%) fluctuating SNHL. 0/277 controls developed SNHL.	
Barbi³¹	1998	Prospective cohort	12 AcCMV 3 ScCMV	Up to 2 years	4	0/12 AcCMV cases with SNHL compared to 1/3 (33.3%) ScCMV cases.	
Casteels¹⁹	1999	Prospective cohort	13 AcCMV	1 year	4	2/13 (15.4%) AcCMV cases developed SNHL.	
Fowler⁶	1999	Prospective cohort	335 AcCMV 53 ScCMV	Mean 55 months	2	Cumulative incidence SNHL: 1 month = 2.9% AcCMV, 16.5% ScCMV; 3 months = 4% AcCMV, 22.8% ScCMV; 6 years = 11.3% AcCMV, 36.4% ScCMV.	
Dahle¹³	2000	Prospective	651 AcCMV	Median 5 years	2	48/651 (7.4%) AcCMV developed SNHL. 18/48	

		cohort	209 ScCMV			(37.5%) delayed onset SNHL (median 44 months). 26/48 (54.2%) fluctuating SNHL ^a . 26/48 (54.2%) progressive SNHL ^a 23/48 (47.9%) improved SNHL ^a . 85/209 (40.7%) ScCMV developed SNHL.
Noyola ¹⁸	2000	Prospective cohort	58 AcCMV 12 ScCMV	≥6 years	3	SNHL more likely to occur with shorter duration of CMV excretion (<4 years).
Numazaki ³²	2004	Prospective cohort	21 AcCMV	≥7 years	3	2/17 (11.8%) AcCMV cases developed late onset SNHL (age 2 and 4 years).
Boppana ¹⁴	2005	Prospective cohort	58 AcCMV 18 ScCMV	Mean 34.1 months	3	4/58 (6.9%) AcCMV cases developed SNHL. 8/18 (44.4%) ScCMV cases developed SNHL. CMV viral load in early infancy correlates with development of SNHL in AcCMV group only.

Barbi ³³	2006	Prospective cohort	14 AcCMV 2 ScCMV	2 years	3	1/14 (7%) AcCMV cases developed SNHL (regressed). 14/14 AcCMV cases had normal hearing by 2 years.
Lanari ²¹	2006	Prospective case-control	35 AcCMV 15 ScCMV 16 controls	Mean 18 months	3	1/35 (2.9%) AcCMV cases developed SNHL. 8/15 (53.3%) ScCMV cases developed SNHL. 0/16 controls developed SNHL. Neonatal CMV viral load and antigenemia correlates with development of sequelae.
Ancora ²²	2007	Prospective cohort	45 AcCMV	Mean 42.3 months	3	3/45 (6.7%) developed SNHL.
Iwasaki ³⁴	2007	Prospective cohort	16 AcCMV 2 ScCMV	Up to 4 years	3	4/16 (25%) SNHL in AcCMV cases. 2/4 (50%) delayed onset progressive SNHL. 1/4 (25%) fluctuating SNHL. 1/4 (25%) improved SNHL.
Dar ³⁵	2008	Prospective cohort	8 AcCMV	4 months	4	1/8 (12.5%) developed SNHL.

Engman ³⁶	2008	Prospective cohort	10 AcCMV	4 years	4	1/10 (10%) had SNHL on newborn screening. 0/9 developed late onset SNHL.
Foulon ²⁰	2008	Prospective cohort	57 AcCMV 3 ScCMV	Median 33 months	3	12/57 (21.1%) AcCMV cases developed SNHL compared to 1/3 (33.3%) ScCMV cases. 16% of AcCMV cases with SNHL had fluctuating course and 11% had a progressive course.
Lackner ³⁷	2009	Prospective case-control	8 AcCMV (10 AcCMV received GCV)	Mean 8.1 years	4	2/8 (25%) AcCMV cases without treatment developed SNHL (age 8 and 10 years). (0/10 AcCMV who received GCV developed SNHL).
Rosenthal ¹⁵	2009	Prospective cohort	420 AcCMV 160 ScCMV	Up to 8 years	2	For those asymptomatic at 6 months, 6.9% developed delayed SNHL by age 8 years, compared to 33.7% if symptomatic.

Ross ¹⁶	2009	Prospective cohort	36 AcCMV	3 years	3	2/36 with viral load <3500ge/mL and SNHL at <2 months = NPV of 94%. No association between viral load and hearing loss at 3 years.
Shan ³⁸	2009	Prospective case-control	52 AcCMV 21 controls	1 year	4	5/25 (20%) AcCMV cases had mildly abnormal thresholds compared to 0/21 controls on ABR, but difference not evident on OAE.
Yamamoto ³⁹	2011	Prospective cohort	75 AcCMV 11 ScCMV	≥12 months	3	4/75 (5.3%) AcCMV cases developed SNHL compared to 6/11 (54.5%) ScCMV cases.
Royackers ²³	2013	Prospective cohort	74 AcCMV 24 ScCMV	Mean 5.4 years	3	11/74 (15%) AcCMV cases had SNHL in newborn period: 7/11 (63.6%) stable; 2/11 (18.2%) resolved; 2/11(18.2%) progressed. 1/74 (1.4%) AcCMV cases developed late onset SNHL. 17/24 (71%) ScCMV cases developed SNHL.

Zavattoni⁴⁰	2014	Retrospective cohort	89 AcCMV 26 ScCMV	Up to 6 years	3	5/89 (5.6%) AcCMV cases developed SNHL compared to 6/26 (23.1%) ScCMV cases. No correlation between neonatal viremia or antigenemia and long-term sequelae.
Forner⁴¹	2015	Prospective cohort	33 AcCMV	6 years	3	8/33 (24.2%) AcCMV cases developed SNHL. Neonatal CMV viremia of $\geq 17,000$ copies/mL predictive of SNHL.
De Kegel²⁴	2016	Prospective case-control	38 AcCMV ^b	Up to 2 years	4	5/38 (13.2%) AcCMV cases developed SNHL.
Goderis²⁵	2016	Prospective cohort	256 AcCMV ^c	Up to 6 years	2	21/256 (8.2%) AcCMV developed SNHL. Mean age of delayed SNHL diagnosis 20 months (range 1-61 months).

Table 2. Characteristics and findings of eligible studies included in the systematic review for neurodevelopmental outcomes.

First Author	Year	Study design	Participants	Length of follow-up	Quality of evidence (level)	Findings
Reynolds²⁶	1974	Prospective case-control	18 AcCMV 18 controls	38 months	4	No difference in mean IQ.
Ahlfors²⁸	1983	Prospective cohort	28 AcCMV 13 ScCMV	Up to 7 years	3	1/28 (3.6%) AcCMV cases with neurodevelopmental impairment compared to 4/13 (30.7%) ScCMV cases.
Kumar²⁹	1984	Prospective case-control	17 AcCMV 21 controls	Mean 7.6 years	3	No difference in psychometric testing.
Conboy⁴²	1986	Prospective case-control	18 AcCMV 18 controls	6.5-12.5 years	4	No difference in overall achievement or incidence of learning disabilities.

Pearl ⁴⁶	1986	Prospective case-control	35 AcCMV 6 ScCMV 73 controls	Up to 2 years	4	Similar performance between AcCMV and control groups. ScCMV group performed significantly worse than AcCMV and control groups.
Williamson ³⁰	1990	Prospective case-control	28 AcCMV 13 controls	Up to 1 year	4	No difference in developmental indices or neurologic status.
Sohn ⁴⁵	1992	Prospective cohort	6 AcCMV	1 year	4	No neurological abnormalities.
Barbi ³¹	1998	Prospective cohort	12 AcCMV 3 ScCMV	Up to 2 years	4	0/12 AcCMV cases with sequelae compared to 2/3 (66.7%) ScCMV cases with psychomotor deficit.
Kashden ⁴³	1998	Cross-sectional	204 AcCMV ^a 177 controls	Mean 4 years (AcCMV) Mean 6 years (controls)	3	Intelligence testing: no difference between 109 AcCMV cases and 139 controls. Developmental profile: no difference between 159 AcCMV cases and 130 controls.

Casteels¹⁹	1999	Prospective cohort	13 AcCMV	1 year	4	0/12 AcCMV cases developed neurodevelopmental impairment.
Noyola¹⁸	2000	Prospective cohort	58 AcCMV 12 ScCMV	≥6 years	3	No correlation between duration of CMV excretion and intellectual/developmental outcomes.
Temple⁴⁴	2000	Cross-sectional	109 AcCMV 173 controls	≥4 years of age	3	AcCMV group (age 4-6 years) performed worse in full-scale IQ and some motor tasks compared to control group. No differences in age group >6 years.
Numazaki³²	2004	Retrospective cohort	21 AcCMV	≥7 years	4	18/21 (85.7%) average IQ. 3/21 (14.3%) mild IQ impairment. 1/21 (4.8%) growth retardation.
Lanari²¹	2006	Prospective case-control	35 AcCMV 15 ScCMV 16 controls	Mean 18 months	4	1/35 (2.9%) AcCMV cases with neurodevelopmental impairment compared to 10/15 (66.7%) ScCMV cases and 0/16 controls. Correlation between neonatal CMV viral load and

						antigenemia and development of sequelae.
Ancora ²²	2007	Prospective cohort	45 AcCMV	Mean 42.3 months	3	All had normal DQ and no motor delay.
Zhang ⁴⁷	2007	Prospective case-control	49 AcCMV 50 control	6 years	4	Global DQ lower in AcCMV group (mainly impaired language development, but audiology not reported). Similar rates of mental retardation (DQ/IQ < 70).
Shan ³⁸	2009	Prospective case-control	52 AcCMV 21 controls	1 year	4	No differences in development.
Zavattoni ⁴⁰	2014	Prospective cohort	89 AcCMV 26 ScCMV	Up to 6 years	3	5/89 (5.6%) AcCMV cases with neurocognitive impairment compared to 11/26 (42.3%) ScCMV cases. No correlation between neonatal viremia or antigenemia and long-term sequelae.

Forner ⁴¹	2015	Prospective cohort	33 AcCMV	6 years	3	3/33 (9.1%) developed neurodevelopmental impairment. Neonatal CMV viremia of $\geq 12,000$ copies/mL predictive of sequelae (neurodevelopmental or SNHL).
De Kegel ²⁴	2016	Prospective case-control	17 AcCMV 28 controls	2 years	4	No significant difference in psychomotor performance.

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