Published in final edited form as:

Otol Neurotol. 2018 August ; 39(7): 854–864. doi:10.1097/MAO.0000000000001861.

The Natural History and Rehabilitative Outcomes of Hearing Loss in Congenital Cytomegalovirus: A Systematic Review

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Abstract

Objective—The purpose of this study was to examine the literature regarding the natural history and rehabilitative outcomes of sensorineural hearing loss from congenital cytomegalovirus infections.

Data Sources and Study Eligibility Criteria—A systematic search was performed in PubMed, PsychINFO, CINAHL, and Web of Science to identify peer-reviewed research. Eligible studies were those containing original peer-reviewed research in English addressing either the natural history or rehabilitative outcomes of SNHL in cCMV.

Study appraisal and Synthesis Methods—Two investigators independently reviewed all articles and extracted data. Bias was assessed using the Cochrane Collaboration's tool and the Newcastle-Ottawa Assessment Scale.

Results—Thirty-six articles were reviewed. Universal screening identifies 0.2 – 1% of newborns with cCMV infection. SNHL ranged from 8–32% of infants and was more prevalent in symptomatic vs. asymptomatic cases. 9 – 68% of hearing loss occurs in a late or delayed fashion. In 7–71% of cases hearing loss is progressive. Cochlear implantation is a viable option for patients

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Disclosures:

The authors have no other financial relationships or conflicts of interest to disclose pertaining to the manuscript. The other authors have no other financial relationships or conflicts of interest to disclose pertaining to the manuscript.

with cCMV associated hearing loss and leads to improvements in hearing and language. There is limited literature comparing rehabilitation outcomes in cCMV and non-cCMV CI recipients.

Conclusion—Late onset and progressive hearing loss is seen in children who develop hearing loss from cCMV. Frequent audiologic follow-up is necessary considering the natural history of cCMV hearing loss. Universal screening should be pursued due to the number of asymptomatic children, at birth, who develop late onset/delayed hearing loss. Cochlear implantation is an effective means of improving speech and language in this population.

Keywords

Cytomegalovirus; Hearing Loss; Cochlear Implants; Hearing rehabilitation; Systematic Review

INTRODUCTION

While cytomegalovirus (CMV) is mostly innocuous to those who are immunocompetent, congenital CMV infections (cCMV) can lead to a very morbid disease with an incidence of 40,000 new cases annually in the US.¹ Due to the ubiquitous nature of the virus and the lack of agreement on how or whether it should be screened in pregnant mothers and newborns, these numbers are not expected to decline in the near future. When symptomatic, cCMV infection can result in growth retardation, prematurity, microcephaly, chorioretinitis, seizures and many other neurological abnormalities. Though 90% of those infected congenitally are asymptomatic, 7–21% of these children can develop sensorineural hearing loss (SNHL).² It is estimated that congenital CMV infection accounts for about 13–22% of all cases of neonatal hearing loss making it the leading nonhereditary cause of congenital hearing loss.³ Since the 1970s, we have known that the hearing loss can present bilaterally or unilaterally, be progressive or fluctuating in nature and range from mild to profound.¹ Importantly, it can also present late and be missed by neonatal hearing screening^{4,5}. It is vital that these children be identified and followed closely throughout childhood.

Given how important hearing is to the development of communication and behavior, it is expected that these affected children, like other children with hearing loss, would benefit from rehabilitative strategies. Many studies have established cochlear implantation (CI) as the strategy to restore hearing to those deafened with cCMV. A review by Shin et al. in 2011 examined the medical and surgical interventions (including cochlear implants) for hearing loss associated with cCMV. Since 2011, the literature has expanded regarding cochlear implantation in this population. The objective of this systematic review is to systematically review the literature on the natural history and rehabilitative outcomes of cCMV associated hearing loss in order to gain insight into screening, audiologic monitoring, and treatment strategies in this population.

METHODS

Search Strategy

This study was exempt from Institutional Review Board approval. The specific question addressed by this systematic review was: What is the onset, evolution, characteristics, necessary monitoring and rehabilitative outcomes in children with sensorineural hearing loss

secondary to congenital cytomegalovirus infection? The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist was used to guide this systematic review⁶ (Figure 1). The research question is best addressed with two types of studies: those looking at the natural history of hearing loss in congenital cytomegalovirus infection and studies addressing outcomes of cochlear implantation in this population. A specific outcome measure was not required for inclusion in this review. The specific inclusion criteria included: 1) studies focusing on the natural history (onset, progression, fluctuation) of and monitoring of hearing in cCMV, 2) results of cochlear implantation in the cCMV population, 3) documentation of *congenital* CMV (as opposed to *post-natal* CMV) via appropriate testing (dried blood spot, cord blood, urine or saliva culture or polymerase chain reaction), 4) documentation of 2 separate audiograms separated by time (not to include Newborn Hearing screening (NBHS)). Exclusion criteria included: 1) Case reports or non-original research, 2) language other than English, 3) studies where greater than a minority of patients received antiviral treatments (i.e. ganciclovir). A search strategy was developed using The National Library of Medicine's medical subject heading (MeSH) browser in expanded concept view to identify MeSH indexed terms (<https://www.ncbi.nlm.nih.gov/mesh/advanced>). In an attempt to capture articles inclusive of the study objective, MeSH terms associated with hearing disorders and hearing loss were coupled with cytomegalovirus and cytomegalovirus infections. Once these terms were identified, an overarching search string was created. Figure 1 lists the terms utilized in the search string as well as the algorithm for inclusion/exclusion.

An initial overarching search was conducted in PubMed, utilizing the MeSH search string. [All Fields] was employed for assurance that all relevant articles including the search criteria were identified through the search so not to limit where the MeSH indexed terms were captured (as indexed, in title and in body of article). The original search was performed in July 2016. Next searches were conducted in CINAHL, PsycINFO, and Web of Science using the broad search terms "Cytomegalovirus" and "Hearing" (all fields).

Data Extraction

Article titles and abstracts were reviewed independently by 2 reviewers and were selected or removed based on the inclusion and exclusion criteria. In the event of disagreement over inclusion, the article was included for full text review to be more inclusive. A full-text review of all eligible articles was completed independently by the reviewers. After full-text review, disagreements regarding final inclusion were to be resolved by obtaining a majority consensus among the 2 reviewers and the senior author (MLB). Ultimately, there was no disagreement among the reviewers regarding the final list of articles included in the review.

Data was recorded separately and organized into tables 1–5. Symptomatic cCMV was typically defined as having 1 or more of the following findings at birth: hepatosplenomegaly, petechiae, purpura, jaundice or microcephaly, seizures, lethargy/hypotonia. Asymptomatic cCMV was defined as having no clinically apparent symptoms of CMV at birth. A delayed-onset hearing loss is defined as a normal hearing followed by hearing loss, documented on 2 separate evaluations. Progressive hearing loss was defined as a worsening of the auditory threshold with 10 decibel (dB) or more in successive hearing tests. Improvement of hearing

loss was defined when hearing thresholds improved with 10 dB or more. A fluctuating hearing loss was defined as an improvement of at least 10 dB after a prior worsening or a worsening after a prior improvement.

The level of evidence of each article was also assessed per the preferences of this journal. The risk of bias for quantitative research studies was determined using the Cochrane Collaboration's tool for assessing risk of bias⁷ (Table 6). This assesses selection, performance, detection, attrition, reporting and other forms of bias. Bias was assessed via the Newcastle-Ottawa Assessment Scale for cohort and level 3 and level 4 studies⁸ (Table 7). This evaluates the selection and comparability of the cohorts as well as the outcomes.

RESULTS

The initial search in PubMed yielded a total of 663 articles. Additional searches were conducted yielding 486 articles from CINAHL, 30 articles from PsycINFO, and 691 articles from Web of Science. The lists of articles were imported into reference managing software (EndNote® X7, Thomson Reuters™) and using the software and checking the list by hand a total of 543 duplicates were removed. 60 articles were excluded for publication in a non-english language. After title and abstract review, 1236 articles were excluded. A full-text and bibliography review of the remaining 91 articles was completed. 36 articles met all inclusion/exclusion criteria and were included. 25 articles focused on the natural history of hearing loss in cCMV, while 11 articles assessed outcomes of cochlear implantation in the cCMV population.^{2-4,9-41} Statistical measures were not uniform across all research articles selected for inclusion thus a meta-analysis was not conducted.

Natural History of hearing loss in cCMV

25 articles were selected which met inclusion and exclusion criteria after abstract and full article reviews and pertained to the natural history of hearing loss in cCMV. Table 1 summarizes the findings in these articles. There are 3 studies that look at the outcomes of children identified with cCMV where universal screening of all newborns was performed⁹⁻¹¹. In this sample of universally-screened infants, the percentage of children afflicted by cCMV varied from 0.2 – 1% and SNHL ranged from 8–22% in all children with cCMV. SNHL was higher in children with symptomatic cCMV versus those with asymptomatic cCMV, 33–54.5% compared to 5–21%.

There were also many prospective cohort studies as well as several retrospective studies looking at the natural history of hearing loss in cCMV^{4,12-26,28} (Table 2). Taking cCMV as a whole (including both symptomatic and asymptomatic cases), SNHL in cCMV ranged from 10.7% – 32.4%. In children with asymptomatic cCMV, SNHL ranged from 7 – 27%^{9,10,12,14,15,18,20,21,23,24}. In symptomatic cCMV, SNHL rates were higher; ranging from 40.7 – 100%, however most were between 40–60%^{9,10,12,14,15,18,20,25,26,29}.

Late or delayed hearing loss occurred in 9 – 68% of all children with cCMV who develop hearing loss^{4,10,12-18,20,22-26,28,32} (Table 3). In studies that focused only on asymptomatic cCMV, late/delayed hearing loss occurred in 11.1 – 18.2%^{23,24}. Children with symptomatic cCMV presented with late/delayed hearing loss as well, 9–29%^{25,26}. 13 studies documented

the age at which children developed late/delayed onset hearing loss which unfortunately varied considerably^{4,10,12–14,16,20–24,26,28}. Reporting methods for this varied as well, but it is apparent that hearing loss can occur quite late. The Dahle et al. study had a median age of late onset at 33 months but a range of 6 – 197 months for symptomatic children and 44 months with range 24 – 182 months for asymptomatic children²⁰. The Goderis et al. study published the mean age of late onset to be 18 months and found that 75% presented by 24 months and none presented after 61 months¹².

Progressive hearing loss was also documented by multiple studies^{4,10,12,14–17,19,20,22–27,29–32} (Table 4). Progression in hearing loss was present anywhere from 7 – 71% of the time. 6 studies looked at the age at which progression was noted in children with cCMV SNHL^{14,20,22–24,26}. This varied widely as well. Fowler et al found that the median time to progression was 18 months in children with asymptomatic cCMV²³. However, in the Dahle et. al study, the median age to first progression of HL was different in asymptomatic and symptomatic cCMV populations: 26 months symptomatic and 51 months asymptomatic²⁰. A fluctuating course was also noted in 22 – 100% in prospective studies^{4,10,14,17,20,22,23}.

Cochlear implant Outcomes

The literature search resulted in 11 articles, which met inclusion criteria and included 361 patients (98 diagnosed with congenital CMV (cCMV) hearing loss and 263 control non-CMV congenital hearing loss) (Table 5). Time following cochlear implantation intervention ranged from 6 – 60 months. Eight articles were non-randomized non-blinded clinical trials assessing outcomes following cochlear implantation and were a level 2C level of evidence^{2,3,33–35,38,39,41}. Three articles were retrospective chart reviews and were a level 4 level of evidence^{36,37,40}. Nine studies had controls^{2,3,33,34,37–41}.

Significant improvement in receptive and/or expressive outcomes was unanimously observed in all 11 studies following cochlear implantation in patients with cCMV (level 2C and level 4). A retrospective chart review conducted by Yamazaki et al. in 2012 revealed that cochlear implantation resulted in an improvement in the hearing threshold for patients with cCMV as measured by ABR. The study also demonstrated that the improvement was to the same degree as the non-CMV congenital hearing loss control cohort. A non-randomized non-blinded clinical trial conducted by Ciorba et al. in 2009 also demonstrated that patients with cCMV hearing loss had improved language development and speech perception 36 months following cochlear implantation compared to pre-implantation as assessed by the Geers and Moog scale and the Nottingham Speech Intelligibility Rating. Additional studies confirmed that cochlear implantation in patients with congenital CMV was associated with improved language outcomes^{2,35,36,38,39,41}. Laccourreye et al. conducted a non-randomized non-blinded clinical trial comparing speech perception, speech production, and speech intelligibility in 15 patients with cCMV hearing loss pre-implantation to 36 months post implantation. The study utilized the open and closed-list word recognition, speech production assessments, and the Nottingham Speech Intelligibility Rating. Following implantation, 74% of patients had improved speech perception as assessed by closed-list testing while 48% of patients had improved speech perception as assessed by open-list

testing. Approximately 80% had improved speech production and 60% improved speech intelligibility.

Although studies are consistent in that cochlear implantation results in an improvement in expressive and receptive outcomes, the degree of improvement varied between patients. Patients who had associated cognitive impairments (ex: intellectual disability, autism) in addition to cCMV had decreased improvement compared those patients with cCMV in isolation^{33,37,39}. In addition, Ciorba et al. also suggested that patients with asymptomatic cCMV had improved progress following implantation compared to patients with symptomatic cCMV.

There are discrepancies between studies regarding whether patients with cCMV have comparable outcomes to patients who have non-CMV associated congenital hearing loss post implantation. Yoshida et al. compared language perception and production between four individuals with cCMV and 17 individuals with non-CMV associated congenital hearing loss following cochlear implantation. Individuals with cCMV had delayed language perception and language production at 12 months compared to the control cohort as assessed by the Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS) and the Enjoji Scale. Twelve months post implantation, however, there was no statistical difference between individuals in the cCMV cohort compared to control. Ciorba et al., however, described that language development in 8 individuals with cCMV was delayed compared to a control cohort of 8 individuals with congenital hearing loss at 36 months post implantation. Ciorba et al. attributed to delay in development to cognitive impairments that were present in addition to the cCMV infection. Malik et al. conducted a retrospective chart review and compared 14 patients with cCMV to 45 patients with non-CMV associated congenital hearing loss utilizing the Modified Categories of Auditory Performance and the Manchester Spoken Language Development Scale. The study reported that patients with cCMV hearing loss had decreased improvement in language following implantation compared to control. Similar to the study conducted by Ciorba and colleagues, Malik and colleagues suggested the discrepancy was a result of additional cognitive impairments. Other studies, however, report that there was no difference in improved hearing and language between individuals with cCMV and a control cohort^{2,34,38,39}. Iwasaki et al. compared 7 individuals with cCMV to 5 control patients with non-CMV congenital hearing loss at 36 months and demonstrated there was no difference in speech and perception as measured by IT-MAIS. In addition, Philips et al. reported in 2010 that the improvement in speech perception and speech improvement in 8 individuals with cCMV as assessed by Categories of Auditory Performance (CAP) and the Speech Intelligibility Rating (SIR) was not statistically different compared to 8 controls with congenital hearing loss due to Connexin-26 mutation.

DISCUSSION

Hanshaw et al. published in The New England Journal of Medicine in 1976 regarding school failure and deafness after “silent” cCMV infection⁴². Since that time there has been an explosion of research on this topic, as evidenced by the number of studies included in this systematic review. Since the 1970s, research has shown that the natural history of cCMV is

quite variable and unpredictable. Symptomatic children are more easily diagnosed considering the well-described constellation of findings including growth retardation, hepatosplenomegaly, petechiae, jaundice and microcephaly. Hearing loss, however, may be the only finding in asymptomatic cases⁴³. This hearing loss ranges from moderate to profound, unilateral or bilateral, and may present in a delayed fashion, and follow an erratic, progressive and/or fluctuating course.

One of the most striking features of research regarding pediatric CMV-related hearing loss is the great variation in reporting of the prevalence of hearing loss in this population. This was highlighted in a systematic review/meta-analysis conducted by Goderis et al which assessed the prevalence and character of hearing loss associated cCMV⁴⁴. This meta-analysis was limited by very high heterogeneity in samples and study methodology. This great variation in reporting of incidence of hearing loss is related to the nature of CMV-related hearing loss (delayed onset, fluctuating, and often progressive), missed or delayed diagnosis (often the case with unilateral hearing loss), and the high percentage of CMV-affected infants who are otherwise asymptomatic. This study highlights the need for monitoring for CMV-related hearing loss for an extended period of time. Certainly, the incidence of CMV may differ among different populations, but it appears that a critical factor in the variation of prevalence of CMV-related hearing loss is the duration of follow-up. The studies with a shorter follow-up period after birth (less than 3 years) may have a lower prevalence of SNHL than those studies which assessed for hearing loss over 5 years. Our review is unique in that we assessed for the age at which children presented with delayed hearing loss and the age at which their known hearing loss progressed. Even through many studies mention this fact, few have characterized it well. Previous recommendations have been to screen children with known cCMV through 6 years of life^{4,44-47} however, in our review, delayed onset and progression of hearing loss can occur as late as the mid-teens²⁰. This aspect should be further investigated and audiological screening may need to be carried out longer, likely into adulthood.

Infant hearing loss screening is not sufficient to identify hearing loss in CMV-affected infants and universal screening for CMV could increase the identification of CMV-related hearing loss in a timely manner. Potentially most concerning is the lack of universal screening for cCMV and the fact that these asymptomatic children may suffer from a diagnostic delay in identifying their hearing loss. Universal screening for cCMV has been performed at the University Hospital in Birmingham since 1967 for research purposes, but this practice far from universal⁴⁸. It has been estimated that several thousand children could benefit each year from newborn CMV screening, early detection and interventions^{49,50}. A potential cost savings to the health system as a whole has been described⁵¹. This screening does not need to be invasive: a saliva real-time polymerase chain reaction test has been shown to be a feasible and effective means of universal neonatal CMV screening⁵². Early detection is important considering there is now level 1b evidence to support medical treatment with systemic antivirals to protect hearing in children with symptomatic cCMV⁵³. A systematic review by Shin et al reviewed the literature regarding systemic antivirals and found a preponderance of data to support antiviral therapy⁵⁴. Specific drug (IV ganciclovir vs. oral valganciclovir) and duration remains controversial. Some authors feel the side effect profile (anemia, neutropenia, thrombocytopenia, hepatic dysfunction) is too great to

advocate use in asymptomatic children with normal hearing who may never acquire hearing loss.

Cochlear implantation in patients with congenital hearing loss due to cCMV results in improved receptive and expressive outcomes compared to pre-implantation^{2,3,35,36,38,39,41}. There appears to be variability, however, in the degree of improvement following implantation. cCMV is associated with a spectrum of symptoms, and some of the variation can be attributed to severity of disease^{33,34}. For example, patients with asymptomatic cCMV had improved progress compared with patients with symptomatic cCMV³⁴. In addition, patients with associated congenital cognitive delays had delayed improvement compared with patients without additional cognitive delays independent of cCMV diagnosis^{33,37,39}.

Although it is clear that cochlear implantation is beneficial for patients with cCMV associated hearing loss, there are inconsistencies between studies as to whether patients with cCMV have similar outcomes following implantation as patients with non-CMV associated congenital hearing loss. While some studies reported that there were no differences in outcomes between the two groups^{2,34,38,39}, others reported that patients with non-cCMV associated congenital hearing loss had improved outcomes compared to patients with cCMV associated hearing loss^{33,37,41}. The discrepancy in results may be accounted for by the variability in presentation severity of cCMV and whether there are associated cognitive delays. Data appears to be mixed on this regard with some studies finding no difference in objective intelligence measures^{55–58}, while in another intelligence quotient was lower in children with asymptomatic cCMV compared with controls⁵⁹. Despite the fact that patients with cCMV associated hearing loss may not have the same outcomes as patients with non-CMV associated congenital hearing loss following cochlear implantation, implantation remains a viable option for patients with cCMV associated hearing loss and can lead to improvements in hearing and language.

CONCLUSION

The natural history of hearing loss associated with cCMV is fraught with issues. Hearing loss can be moderate to profound, unilateral or bilateral, and may present in a delayed fashion, and follow an erratic, progressive and/or fluctuating course. The age at which delayed onset and progression of hearing loss occurs may be later than previously appreciated. Audiologic monitoring for an extended period is necessary. Universal screening should be further investigated and ideally implemented. Rehabilitation of deafness using cochlear implantation is a valid approach to improve hearing and speech in this population. Further study should evaluate outcomes after rehabilitation between CMV and non-CMV related hearing loss.

Acknowledgments

This work was supported by the National Institute of Deafness and Other Communication Disorders (1K23DC014074)(MLB). MLB is a consultant for MED-EL and Oticon Medical and receives research funding from Advanced Bionics.

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Figure 1.
PRISMA Sheet

Table 1

Natural History of cCMV associated hearing loss

Study	Country of Origin	Study Type	Level of evidence	Population	Sample Size	SNHL in cCMV	SNHL in asymptomatic cCMV	SNHL in symptomatic cCMV	Late/Delayed onset HL in cCMV w/HL	Age of Late Onset	Progressive HL in cCMV with HL	Age at Progression	Fluctuating HL in cCMV w/HL	Follow-up
Yamamoto et al., 2011	Brazil	prospective cohort study	1b	all newborns	121/12195 (1%) screened had cCMV	10/85 (11.8%)	4/75 (5.3%)	6/11 (54.5%)	-	-	-	-	-	median age last hearing eval 56 months (36–84 months)
Foulon et al., 2008 J Pediatr	Belgium	prospective cohort study	1b	all newborns	74/14,021 (0.5%) screened	13/60 (22%)	12/57 (21%)	1/3 (33%)	3/13 (23%)	mean 34 months (8, 15, 79 months)	5/13 (38%)	-	7/13 (54%)	-
Engman et al., 2008	Sweden	prospective cohort study	1b	all newborns	12/6060 (0.2%) screened	1/12 (8.3%)	-	-	0/1 (0%)	-	-	-	-	9/12 seen at 2 and 4 years
Goderis et al., 2016	Belgium	prospective cohort study	1b	cCMV	379	98/379 (26%)	21/256 (8%)	77/123 (63%)	33/98 (33.7%)	mean 18 months, 50% by 14 mo, 75% by 24 months, none detected after 61 months	EARS with HL (not patients); 37/144 (25.7%)	-	-	mean age last f/u: scCMV 27.5mo+/- 19.5, acCMV 30.3mo+/-22.7
Pati et al., 2013	USA	prospective cohort study	1b	cCMV	131	26/131 (20%)	-	-	2/5 (40%)	12.4 and 16.4 mo	-	-	-	-
Foulon et al., 2012	Belgium	prospective cohort study	1b	cCMV	68	22/68 (32.4%)	16/59 (27%)	6/9 (67%)	2/22 (9%)	12–15 months, 6 years	6/22 (27%)	4 pts between 31–47 mo; 2 pts between 79–118 mo	11/22 (50%)	minimum of 18 mo f/u
Iwasaki et al., 2007	Japan	prospective cohort study	1b	cCMV	18	5/18 (28%)	4/16 (25%)	1/2 (50%)	2/5 (40%)	-	2/5 (40%)	-	-	thru 4 years of age
Ross et al., 2007	USA	prospective cohort study	1b	cCMV	149	19/149 (12.8%)	-	-	13/19 (68%)	median 15 mo (3–60 mo)	1/13 (7.7%)	-	-	-
Ross et al., 2006	USA	prospective cohort study	1b	cCMV	300	32/300 (10.7%)	-	-	14/32 (43.8%)	-	14/32 (43.8%)	-	13/32 (40.6%)	mean f/u: non-primary maternal infection 53mo +/-44, primary maternal infection 64+/-49 mo
Boppiana et al., 2005	USA	prospective cohort study	1b	cCMV	76	12/76 (16%)	4/58 (7%)	8/18 (44%)	8/12 had “delayed onset HL, progressive HL or both	-	-	-	-	34.1 months +/- 17.9 months
Noyola et al., 2000	USA	prospective cohort study	1b	cCMV	70	21/70 (30%)	-	-	-	-	15/21 (71%)	-	-	thru at least 6 years of age
Dahle et al., 2000	USA	prospective cohort study	1b	cCMV	860	133/860 (15.5%)	48/651 (7.4%)	85/209 (40.7%)	41 /133 (30.8%)	median age symptomatic 33 mo (6–197) and asymptomatic 44mo (24–182)	72/133 (54.1%)	median age first progression: symptomatic 26mo (2–209), asymptomatic 51mo (3–186)	51/133 (38.3%)	median 5 years (1mo – 19 years)
Fowler et al., 1999	USA	prospective cohort study	1b	cCMV	388	60/388 (15.4%)	-	-	10.2% of total	5.2% at birth; increased to 15.4% by 72 months	48%	-	35%	mean age last f/u: 55mo +/- 45
Fornier et al., 2015	Italy	prospective cohort study	1b	asymptomatic cCMV after maternal primary infection	33	-	8/33 (24%)	-	8/8 (100%)	mean 13.9 mo; median 9 mo (range 3–36 mo)	-	-	-	thru 6 years of age

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Study	Country of Origin	Study Type	Level of evidence	Population	Sample Size	SNHL in cCMV	SNHL in asymptomatic cCMV	SNHL in symptomatic cCMV	Late/Delayed onset HL in cCMV w/HL	Age of Late Onset	Progressive HL in cCMV with HL	Age at Progression	Fluctuating HL in cCMV w/HL	Follow-up
Foulon et al., 2008 Pediatrics	Belgium	prospective cohort study	1b	cCMV after maternal primary infection	28	5/28 (18%)	-	-	1/5 (20%)	8 mo	2/5 (40%)	(during the first year of life)	5/5 (100%)	median 34.2 mo (4–122mo)
Fowler et al., 1997	USA	prospective cohort study	1b	asymptomatic cCMV	307	-	22/307 (7.2%)	-	4/22 (18.2%)	median age 27 months (range 25–62)	11/22 (50%)	median age first progression: 18mo (range 2–70 mo)	5/22 (22.7%)	median age last hearing eval for pbs with HL 63 months (12–143 months); without HL 43mo (2–184)
Williamson et al., 1992	USA	prospective cohort study	1b	asymptomatic cCMV	59	-	9/59 (15.3%)	-	1/9 (11.1%)	13 mo	5/8 (62.5%)	median age first progression: 12mo (range 7–36 mo), mean age 18.2 mo	-	-
Dreher et al., 2014	USA	prospective cohort study	1b	symptomatic cCMV	178	-	-	80/178 (44.9%)	23/80 (29%)	-	43/80 (54%)	-	-	4.6 yrs +/-3.77 yrs
Williamson et al., 1982	USA	prospective cohort study	1b	symptomatic cCMV	17	-	-	11/17 (65%)	1/11 (9%)	3 years	3/11 (27%)	9 years	-	last f/u age 5.5 yrs (range 1–10 yrs)
Korver et al., 2009	The Netherlands	prospective cohort study	1b	hearing loss	179	14 cCMV patients (7.8%)	-	-	-	-	6/14 (42.8%)	-	-	-
Korver et al., 2009	The Netherlands	prospective cohort study	1b	hearing loss	179	14 patients identified with cCMV (7.8%)	-	-	-	-	6/14 (42.8%)	-	-	-
Rosenthal et al., 2009	USA	retrospective case review	2b	cCMV	465	115/465 (24.7%)	-	-	38/115 (33%)	range 6 mo – 95 months	-	-	-	normal hearing mean fu 63.3+/-47.4 mo; HL at birth 76.6 +/-40.9; Delayed HL 102.7+/-51.1
Madden et al., 2005	USA	retrospective case review	2b	symptomatic cCMV	21	-	-	21/21 (100%)	-	-	8/21 (38%)	-	2/21 (10%)	97 months (8–158)
Park et al., 2014	USA	retrospective case review	2b	hearing loss	83	25 HL patients identified with cCMV (30%)	-	-	-	-	10/25 (40%)	-	-	mean fu 305 days
Misono et al., 2011	USA	retrospective case control	2b	hearing loss	222	22 HL patients identified with cCMV (9.9%)	-	-	-	-	16/35 (45.7%)	-	0%	-
Furukata et al., 2011	Japan	retrospective case review	2b	hearing loss	134	12 HL patients identified with cCMV (9%)	-	-	5/12 (42%)	-	4/12 (33%)	-	25% (3/12)	-

Table 2

Hearing Loss in cCMV

# studies identified	Population	% with Hearing Loss
17	cCMV	10.7–32.4%
10	Asymptomatic cCMV	7–27%
10	Symptomatic cCMV	40.7–100%

Table 3

Delayed Hearing Loss in cCMV

# studies	Population	% Delayed Hearing Loss	Median Age at onset, months (range) ⁶
17	cCMV	9–68%	
2	Asymptomatic cCMV	11–18%	44 mo (24 – 182mo)
2	Symptomatic cCMV	9–29%	33 mo (6–197 mo)

Table 4

Progressive Hearing Loss in cCMV

# studies	Population	% Progressive Hearing Loss	Median Age Progression, month (range) ⁶
19	cCMV	7–71%	
2	Asymptomatic cCMV	50–62.5%	12–51 mo (2–186 mo)
3	Symptomatic cCMV	27–54%	26 mo (2–209 mo)

Table 5

Rehabilitative Outcomes in CMV

Study	Study Type	Level of Evidence	Subjects	Measurement	Follow up Post CI	Results
Ciorba et al., 2009	Non-randomized, non-blinded clinical trial	2C	22 (14 cCMV; 8 Connexin-26 mutation control)	Behavioral audiometry; ABR; ECoG; Geers and Moog scale; Nottingham Speech Intelligibility Rating	6 months, 12 months, 36 months	Improved language development and speech perception in both groups. Delayed speech perception compared to language development in cCMV group.
Iwasaki et al., 2009	Non-randomized, non-blinded clinical trial	2C	7 (2 cCMV; 5 non-cCMV congenital deaf control)	ABR; Behavioral audiometry; IT-MAIS	36 months	Improved hearing and speech perception in both groups with no difference between groups.
Lacourreye et al. (2015)	Non-randomized, non-blinded clinical trial	2C	15 (15 cCMV)	Word recognition open-list; Word recognition closed list; Speech production; Nottingham Speech Intelligibility Rating	36 months	Improved speech perception (74% closed-list and 48% open-list testing), improved speech production (80%), and improved speech intelligibility (60%).
Lee et al. 2005	Retrospective chart review	4	13 (13 cCMV)	ABR; WIPI; PBK-word; PBK-phoneme; NuChips; GASP-word; GASP-sentences; LNT-word; LNT-phoneme; MLNT-phoneme; HINT-quiet; Speech Perception Categories; Speech Perception Scores; Peabody Picture Vocabulary Test; Reynell Language Development Scales; Clinical Evaluation of Language Fundamentals-Preschool; Clinical Evaluation of Language Fundamentals 3	Every 3 months for 1 year, every 6 months after 1 year (up to 48 months)	Improved speech perception (73% closed-set word recognition and 64% open-set word recognition);
Malik et al., 2011	Retrospective chart review	4	59 (14 cCMV; 45 non-cCMV congenital deaf control)	Bench scores; Kowal scores; Bamford scores; M-CAP; MSLDS	6–48 months	Decreased improvement in speech perception and speech intelligibility cCMV cohort compared to control
Matsui et al., (2012)	Non-randomized, non-blinded clinical trial	2C	12 (5 cCMV; 7 Connexin-26 mutation control)	Audiology; IT-MAIS; MUSS; S-S method	12–48 months	Improvement in hearing, speech production, and speech intelligibility in both groups. Delay in improvement independent of cCMV diagnosis and was associated with coexisting disabilities in both groups.

Study	Study Type	Level of Evidence	Subjects	Measurement	Follow up Post CI	Results
Philips et al., 2010	Non-randomized, non-blinded clinical trial	2C	16 (8 cCMV; 8 control Connexin-26 mutation)	CAP; SIR	2 – 49 months	No difference in speech perception and speech production improvement between groups
Philips et al. 2014	Non-randomized, non-blinded clinical trial	2C	24 (12 cCMV; 12 Connexin-26 mutation control)	CAP; SIR	Mean cCMV: 3 year 11 month; Control: 4 year 6 month	No difference between groups in speech intelligibility and speech production
Ramirez Inscio and Nikolopoulos, 2004	Non-randomized, non-blinded clinical trial	2C	147 (16 cCMV; 131 non-CMV congenital deaf control)	SIR; Iowa Matrix Closed Set Sentence	1 – 5 years	No difference in language perception and language intelligibility in cCMV cohort compared to control
Yamazaki et al., 2012	Retrospective chart review	4	25 (11 cCMV; 14 non CMV congenital deaf control)	Hearing threshold; Closed-set word discrimination; Open-set word discrimination; K-test	11 – 36 months	No difference in improved hearing threshold in cCMV cohort compared to control. Decreased improved language development in cCMV cohort compared to control.
Yoshida et al. 2009	Non-randomized, non-blinded clinical trial	2C	21 (4 cCMV; 17 non-CMV control)	ABR; -MAIS; Enjoji Scale	Mean: 39 months	Decreased improved language perception and language production at 12 months in cCMV compared to control; no difference in improvement in language perception and language production after 12 months

Abbreviations: CAP – Categories of Auditory Performance; cCMV – congenital cytomegalovirus; ECoG – Electrocochleography; Enjoji Scale – Enjoji Scale of Infant Analytical Development; IT-MAIS – Infant-Toddler Meaningful Auditory Integration Scale; K-Test – Kyoto Scale of Psychological Development; M-CAP – Modified Categories of Auditory Perception; MSLDS – Manchester Spoken Language Development Scale; MUSS – Meaningful Use of Speech Scale; S-S Method – Test for Japanese Language Retardation Based on Sign-Analytical Development Significant Relations; SIR – Speech Intelligibility Rating

Table 6

Cochrane Tool: Level 1 and Level 2 Bias Assessment

	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other
Study	Random Sequence Generation	Allocation of Concealment	Blinding of Participants	Outcome Assessment	Incomplete Outcome Data Addressed	Selective Reporting	Other
Ciorba et al., 2009	No	No	No	Yes	Yes	No	None
Iwasaki et al. 2009	No	No	No	Yes	Yes	No	None
Laccourreya et al., 2016	No	No	No	Yes	Yes	No	None
Matsui et al., 2012	No	No	No	Yes	Yes	No	None
Philips et al., 2010	No	No	No	Yes	Yes	No	None
Philips et al., 2014	No	No	No	Yes	Yes	No	None
Ramirez Inscoc and Nikolopoulos, 2004	No	No	No	Yes	Yes	No	None
Yoshida et al., 2009	No	No	No	Yes	Yes	No	None

Table 7
Newcastle-Ottawa Assessment Scale: Level 3 and 4 Cohort Study Assessment

Study	Selection (Maximum 4 asterisks)	Comparability (Maximum 2 Asterisks)	Outcome (Maximum 3 Asterisks)
Lee et al., 2005	**	*	***
Malik et al., 2011	**	*	***
Yamanazi et al., 2012	*****	*	***
Yamamoto et al., 2011	*****	**	**
Foulon et al., 2008 J Pediatr	*****	**	***
Engman et al., 2008	*****		***
Goderis et al., 2016	***	**	**
Pati et al., 2013	***	**	*
Foulon et al., 2012	***	**	**
Iwasaki et al., 2007	***	*	***
Ross et al., 2007	***	*	**
Ross et al., 2006	*****	**	***
Boppana et al., 2005	*****	**	***