

The effect of antiviral therapy for congenital *Cytomegalovirus* (CMV) on children hearing loss.

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Abstract

Introduction: Congenital Cytomegalovirus (CMV) is the most common viral pathogen encountered in newborns and the most prevalent congenital infection in human beings.

Objectives: To evaluate existing studies on the effect of antiviral treatment on long-term hearing loss in infants with congenital Cytomegalovirus infection and how it can aid in the prevention of such devastating outcomes.

Methods: Systematic review was performed by obtaining papers using a four-step procedure to ensure that all included studies meet the desired criterion. Additionally, PI was used to test the effect of antiviral treatment on hearing loss.

Results: The average PI among studies used was 0.4 indicating that the use of antiviral treatment improved hearing loss with an average of 40%. Also, Cochran's Q test was insignificant which indicates homogeneity between studies.

Conclusions: CMV infections are the most important cause of nongenetic hearing loss, neurodevelopmental delay, intellectual impairment, and multisystem organ failure in children. The reviewed studies showed that the antiviral treatment (ganciclovir) could be used as a treatment for patients including children and infants who are diagnosed with hearing loss due to CMV infection.

Keywords: Congenital *Cytomegalovirus*, CMV, Hearing loss, Antiviral therapy, Systematic review.

Accepted on 8th August, 2020

Introduction

Congenital *Cytomegalovirus* (CMV) is the most common viral pathogen encountered in newborns and the most prevalent congenital infection in human beings. It is a Herpes virus that has been documented to be linked to sensorineural hearing loss (SNHL) as it appears in 30 -65% of children infected [1,2]. In fact, it has been documented as the leading cause of nongenetic neurosensory hearing loss in developed countries [3]. The pathophysiology of the congenital CMV-related SNHL is not fully understood. There suggested direct cytopathic effects and a localized inflammatory response of the stria vascularis [4]. Also, local reactivation of the virus in this site may explain the late nature of hearing deterioration. CMV infection manifests no significant clinical findings at birth, as 90% of infants will be asymptomatic at that time [5-7]. Approximately 33% to 50% of SNHL due to congenital CMV infection is late-onset hearing loss. What makes SNHL in these patients quite challenging to diagnose is the fluctuating and progressive nature, for it can present as unilateral high-frequency losses or profound bilateral losses. Not only can the clinical features vary, but also the time of presentation. It has been documented that the majority of children develop late-onset loss during the preschool and early school years.

Although the disease often tends to leave an irreversible injury, antiviral therapy of newborns with CMV infection has been an option available to clinicians to reduce the impact of the

disease's sequels or even help to prevent the deterioration when started early on. The suggestion that antiviral therapy might be useful in newborns with congenital CMV infection first was raised in numerous reports in the late 1960s and early 1970s [8-11]. Additionally, in 1980, ganciclovir was first introduced for the treatment of congenital CMV infection and it has proved to be safe, effective, and well-tolerated [12-20]. There are many antiviral medications such as ganciclovir and its prodrug, valganciclovir, foscarnet, and cidofovir. However, controlled clinical studies suggested that ganciclovir therapy was able to limit the neurodevelopmental manifestations, including SNHL. Also, studies showed that antiviral agents could help limit the deterioration in hearing loss in children with congenital CMV infection; in fact, it has been reported in the literature to be linked to improvement in audiometric studies. The effect of treatment with antiviral therapy such as ganciclovir/valganciclovir may be related to a decrease in the CMV viral load [21-23]. Treatment of the reactivated virus may halt viral replication in the inner ear which would otherwise lead to irreversible damage. Based on such encouraging findings, ganciclovir/valganciclovir has been established as the treatment of infants with symptomatic congenital CMV infection [24,25]. Furthermore, several studies document the possibility of prevention of hearing deterioration with ganciclovir [26] and improvement of other neurological symptoms [27,28].

It was also showed that the ganciclovir/valganciclovir treatment beyond the neonatal period might be beneficial in preventing further deterioration of inner ear damage in children with late-onset hearing loss of congenital CMV infection. Congenital infection caused by human *Cytomegalovirus* (CMV) is a common occurrence, but its significance is underappreciated. It has conferred a substantial medical and economic burden on society. In recent years, an awareness of its impact in newborns, which includes sensorineural hearing loss (SNHL), has increased. Therefore, we believe it is essential to inform possible approaches to prevent complications.

The SNHL remains a catastrophic complication of the disease. Nonetheless, data on the use of antiviral agents for the prevention of SNHL in children with congenital CMV remain relatively insufficient, because of the lack of prospective data. It is still vague to some clinicians whether it will provide long-term benefit for congenital or perinatal acquired CMV infection and its sequel such as SNHL which we intend to focus on in our paper.

So far, many studies have found that patients with congenital CMV benefit from antiviral treatment. They reported a delay and limitation go the worsening of their hearing loss and the data available served as observational evidence of the benefits of antiviral treatment in these children [29]. We collected and evaluated existing data on the effect of antiviral therapy on long term hearing loss on infants with congenital *Cytomegalovirus* infection and how it can aid in the prevention of such devastating outcomes.

Literature Review

We obtained papers for this review using a four-step procedure. First, we performed a search of the peer-reviewed literature using PubMed and identified potential studies for inclusion using the following keywords: "antiviral therapy" and "CMV" and "hearing loss". Second, we analyzed abstracts for all studies identified and excluded papers that did not satisfy selection criteria. Third, we analyzed the full-text version of all remaining studies and excluded those that did not meet selection criteria. Finally, we started reviewing the results. The PRISMA flow diagram showed in Figure 1 below shows the procedure followed to identify studies used in this research.

Selection criteria

We collected 52 published papers. We excluded case reports, systematic reviews, and other researches that didn't use antiviral therapy for their patients. We reviewed fifteen original research papers from 2003-2018. Table 1 shows the analyzed data of the papers.

Data extraction

The data were extracted from eligible studies by the investigators found through the PubMed database.

Statistical methods

The percent of improvement (PI) expresses the effect-size in each study. PI represents the number of improved cases relative to the sample size. PI was used to test the effect of antiviral treatment on hearing loss. If PI=0, then there is no effect which means there is no improvement. If PI=1, then all cases improved. In general, the larger the PI value, the greater the effect.

Heterogeneity

In order to test the homogeneity between studies included in the meta-analysis, Cochran's Q is used. The Cochran's Q is computed by summing the squared deviations of each study's estimate from the overall meta-analytic estimate using the following formula:

$$I_2 = 100\% \times (Q - df) / Q,$$

where $df = k - 1$ and k is the number of studies included in the analysis. I_2 lies between 0% and 100%, where a value of 0% indicates no heterogeneity and larger values show increasing heterogeneity.

Results

The 15 research papers from 2003-2018 summarized in Table 1 include 3 prospective studies, 3 randomized control trials, 8 retrospective studies, and 1 review article. We categorized the results after the antiviral therapy to improved, didn't improve, no change as shown in Figure 2.

In article number (1) only 6 patients were observed, 1 had an improvement after the therapy and 5 had no change. Whereas in article (2), a total of 96 neonates 47 VGCV for 6 months 2 had an improvement, 36 had worsening hearing loss, and 5 had no change versus 49 VGCV for 6 weeks (placebo) where 3 had an improvement, 37 had worsening hearing loss, and 3 had no change. In article (3) 25 received the treatment 20 had an improvement, 5 had no change after one year follow up. In another study 29 out of 42 ears had an improvement, 13 ears had no change. In study number (5), 2 had an improvement, 3 had worsening, and 3 had no change. In the other study that was done in 2012, 7 out of 26 ears had an improvement, 18 had worsening hearing loss and 9 ears had no change. In article number (7), 8 patients received the treatment 3 had an improvement, 2 had worsening hearing loss and 3 had no change in the hearing. Whereas in study number (8), all of the 10 patients who received the treatments had no change in the hearing loss. In study number (9), 4 out of 24 had an improvement in the hearing loss, 5 had deteriorated and 17 had no change. 9 patients in study (10) received the treatment 2 had an improvement and the rest had no change in the hearing loss.

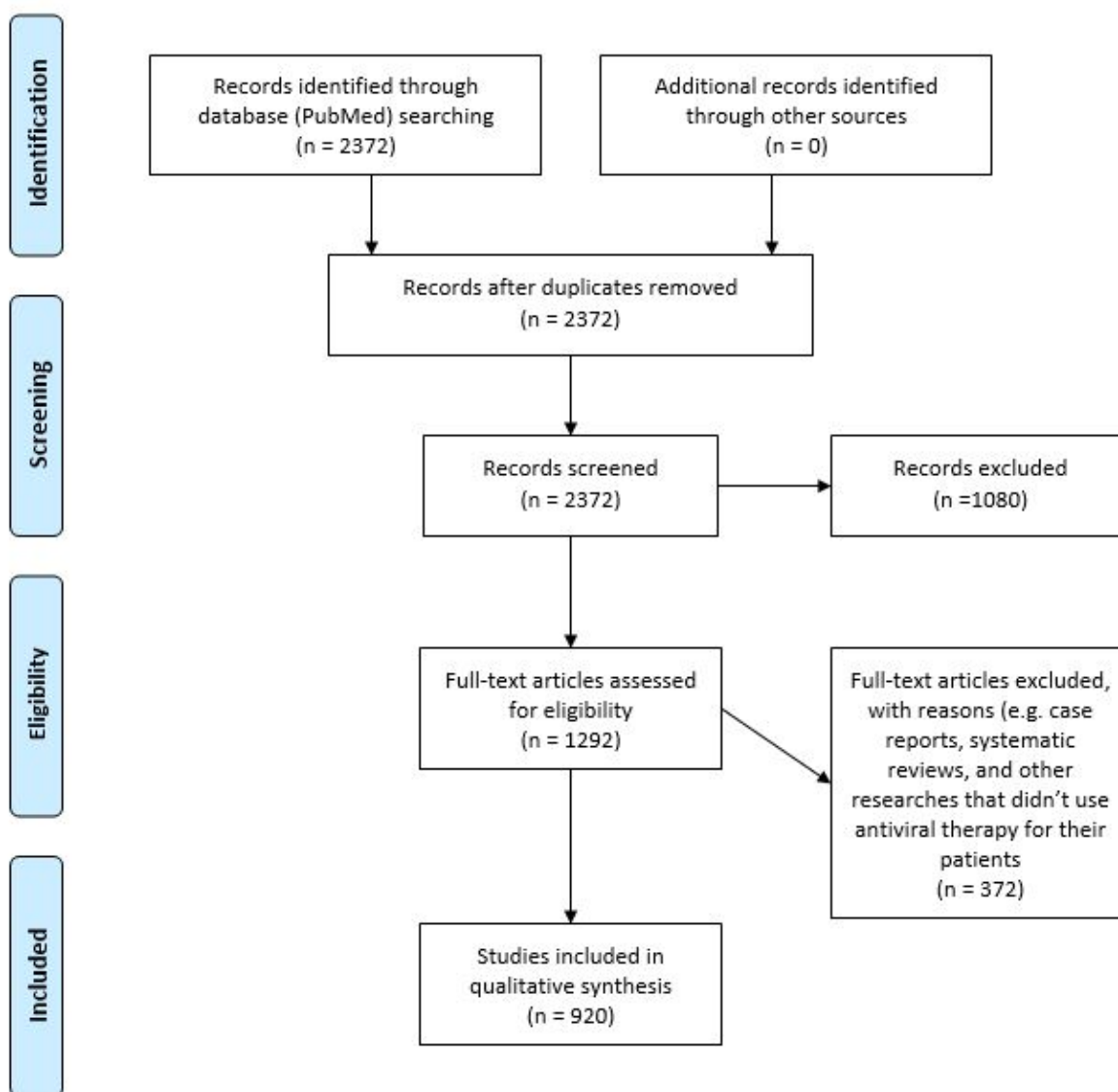


Figure 1. PRISMA Flow diagram.

Table 1. Summary of characteristics of the studies included in the meta-analysis.

Study	Author	Year	Type	Patients	Results	Limitations
Viral load in children with congenital Cytomegalovirus infection identified on newborn hearing screening	Jun-ichi Kawada	2015	Prospective enroll	9 patients congenital CMV infection was identified in 6 (4.7%) by PCR using urine or saliva specimens.	Hearing improvement was in 1 of the 6 patients. 5 of 6 had no changes in 6 weeks vs. 6 months of oral VGCV treatment the trial showed that 6 months of treatment resulted in better outcome	Neurologic involvement or late-onset SNHL are missed. Because more than 80% of children with congenital CMV infection are estimated to be asymptomatic
Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease	D.W. Kimberlin	2015	Randomized controlled trial	A total of 96 neonates 47 VGCV for 6 months vs 49 VGCV for 6 weeks (placebo)	The results in 6 months and 6 weeks: Improved 2 and 3. Got worse 36 and 37 No change 5 and 3	Data did not apply to infants with asymptomatic congenital CMV infection
Effect of ganciclovir therapy on hearing in symptomatic congenital Cytomegalovirus disease involving the central nervous system	David W. Kimberlin	2003	Randomized, Controlled trail	100 patients were enrolled randomly assigned to receive ganciclovir treatment or no treatment	(84%) of ganciclovir recipients had improved hearing or maintained normal hearing vs (59%) of control patients (0%) had worsening in hearing vs (41%) of control patients.	Loss to follow-up. Hard for families to continue the infants' stay in the hospital for 6 weeks or to have frequent follow-up visits

					(21%) had worsening of hearing vs (68%) of control patients	
Treatment of Late-Onset Hearing Loss in Infants With Congenital Cytomegalovirus Infection	Jacob Amir	2013	Retrospective	21 infants	In 35 of 42 ears (83%) Hearing thresholds improved in 29 ears (69%). No change in 13 ears (31%)	Lack of an untreated control group, small number of patients, and short-term follow-up. No available means of differentiating hearing threshold fluctuation from permanent hearing loss.
Long-term audiological follow-up of children with congenital Cytomegalovirus	L. Royackers	2013	prospective study	98 In the Seventy children 28 had unilateral or bilateral hearing loss.	Eight children in the group with hearing loss received ganciclovir. In the treated group, 37.5% of the children had stable hearing loss, and 37.5% had progressive and/or fluctuating hearing loss.	Short audiological follow-up
Treatment of symptomatic congenital Cytomegalovirus infection beyond the neonatal period	Teresa del Rosal	2012	Retrospective case series	13 No control	By ears, 18 ears showed hearing loss, 9 remained stable, 7 had improved and none had worsened.	The lack of a control group. The small sample size. Age at the beginning and duration of antiviral therapy varied among patients. Valganciclovir has been administered considering the neonatal dosage, due to the lack of pharmacokinetic data in infants.
Hearing status in children with congenital Cytomegalovirus: Up-to-6-years audiological follow-up	Royackers Liesbeth	2010	Prospective study	70	As for the treated group, 37.5% of the children had stable hearing loss, one child had progressive and one child had fluctuating hearing loss. Improvement occurred in 37.5% of the children. the untreated symptomatic children, hearing loss were stable in 50%, progression occurred in 37.5%. But In the asymptomatic children hearing loss was stable (72.7%).	We did not take into account viral load
Effect on hearing of ganciclovir therapy for asymptomatic congenital Cytomegalovirus infection: four to 10 year follow up	Lackner A	2009	clinical trial	23 5 lost in the follow up	Sensorineural hearing loss occurred in two (11.1 per cent). Neither child had been treated with ganciclovir. In the treated group (nine children), 0% showed sensorineural	
Antiviral therapy of congenital Cytomegalovirus infection. Study 53 is included in this article	Schleiss MR	2005	Review article		Infants with congenital CMV infection, could be considered as candidates for antiviral therapy, and neurodevelopmental and hearing screening follow-up	
Treatment of children with congenital Cytomegalovirus infection with ganciclovir	Michaels MG	2003	Retrospective cohort	9 all treated with ganciclovir.	Hearing loss before therapy in five of nine. No progression of hearing loss; improvement occurred in two.	Retrospective the lack of a randomized control group and variations in total duration of intravenous and oral therapy.
Long-term hearing outcomes of children with symptomatic congenital CMV treated with valganciclovir	Hilary McCrary	2018	Retrospective	16 patients.	9 of them were started on therapy before one month of age. While 7 patients were started therapy after one month of age. (87.5%) were found to have clinically significant worsening in hearing	The limitations for this study, the patients need continue close monitoring.
Valganciclovir Is Beneficial in Children with Congenital Cytomegalovirus and Isolated Hearing Loss	Yehonatan Pasternak	2005-2017	Retrospective study	329 infants 128 with SNHL at birth 114 with >1yr f/u 69 with isolated SNHL Study group: 59 started Tx < 12wks 10 started Tx > 12wks	29 infants 128 with SNHL at birth 114 with >1yr f/u 69 with isolated SNHL Study group: 59 started Tx < 12wks 10 started Tx > 12wks	It is retrospective methodology and absence of control group

Hearing outcome of infants with congenital Cytomegalovirus and hearing impairment.	Efraim Bilavsky	2005 and 2013	Retrospective study	77 ears No control	50 ears improved. 5 got worse and 22 didn't change	Small number of infants, lack of control group
Treatment of symptomatic congenital Cytomegalovirus infection with intravenous ganciclovir followed by long-term oral valganciclovir	Jacob Amir & Dana G. Wolf & Itzhak Levy	2010	observational-retrospective cohort	46 ears	26% improved 2% got worse and 72% didn't change.	Retrospective design lack of a control group, small sample size, relatively short duration of follow-up, and no standardized developmental assessment.
Symptomatic congenital Cytomegalovirus deafness: the impact of a six-week course of antiviral treatment on hearing improvement.	Fulvia Mazzaferri	2017	Retrospective analysis	13 patients were identified	All the 5 treated ones had hearing improvement after 2 years, the impairment enhanced in none of the 4 untreated children.	Small sample size of our cohort and single-centre experience

Surprisingly in study number (11), 87.5% of the patients who received the treatments had worsening in the hearing. In another study were 80 affected ears at baseline, (68.8%) improved and (2.5%) deteriorated, both from moderate-to-severe hearing loss. In another, out of the 77 ears which received treatment, 50 ears improved, 5 worsened, and 22 did not change. In another study, out of 46 ears 26% improved, 2% worsened and 72% did not change. In the last study, all the 5 treated ones achieved significant hearing improvement after 2 years, whereas the impairment enhanced in none of the 4 untreated children. A summary of the results of the meta-analysis for the included studies are shown in Table 2 shown below.

Table 2. PI among studies used in the meta-analysis.

No.	Study	Year	PI	Relative risk	Effect type	Heterogeneity test
1	Jun-ichi Kawada	2015	0.166	1.16	Positive	Q=0.096 p-value=1 I2=0%
2	David W. Kimberlin	2015	0.058	1.05	Positive	
3	David W. Kimberlin	2003	0.8	1.42	Positive	
4	Jacob Amir	2013	0.69	1.69	Positive	
5	L. Royackers	2013	0.25	1.25	Positive	
6	Teresa del Rosal	2012	0.53	1.53	Positive	
7	Royackers Liesbeth	2010	0.388	1.38	Positive	
8	Lackner A	2009	0.375	1.37	Positive	
9	Schleiss MR	2005	0	1	No effect	
10	Michaels MG	2003	0.17	1.17	Positive	
11	Hilary McCrary	2018	0	1	No effect	
12	Yehonatan Pasternak	2017	0.688	1.68	Positive	
13	Efraim Bilavsky	2013	0.649	1.64	Positive	

14	Jacob Amir & Dana G. Wolf & Itzhak Levy	2010	0.26	1.26	Positive
15	Fulvia Mazzaferri	2017	1	2	Positive
Total Mean=0.4 Mean=1.37 Confidence Interval (0.33,0.47) (1.29-1.44)					

The average PI among studies used in the meta-analysis was 0.4 or 40%, which means that that use of antiviral treatment improved hearing loss with an average percent of 40%. Two studies resulted in no effect while 13 studies resulted in positive effect. The Cochran's Q test was insignificant which indicates homogeneity between studies. Also, I₂ index was 0% indicating that there is no observed heterogeneity between studies shows that in most studies included, the percent of improvement was moderate or less than average and five studies only showed high percent of improvement.

Discussion

Ganciclovir is known to be one of the most common treatments of hearing loss due to CMV. The results showed high percentages of positive effect of ganciclovir in improving hearing loss in children and infants, especially in the long term. 85% of treated children showed improvement or maintained original hearing loss when using ganciclovir for 6 months while only 17% of the treated children showed improvement or maintained original hearing loss when using ganciclovir for 6 week. Also, the results from the 6-month treatment trial showed a significant improvement in audiologic and neurodevelopmental outcomes. Therefore, patients with severe SNHL require a long-term ganciclovir treatment. The long term, 6-month treatment trial, decreased the worsening of hearing loss from 68% to 21% [20-22]. Ganciclovir can also be used as a treatment of late-onset hearing loss in infants with congenital Cytomegalovirus infection. 69% of infants using oral valganciclovir showed improvement in hearing loss due to CMV while 31% of these infants showed no change in hearing

[20]. After 1 year of using ganciclovir, children with congenital hearing loss showed 25% to 30% improvement in the hearing threshold. That improvement took place during or shortly after treatment. Thus, there is enough evidence to prove that ganciclovir has the propensity to increase the likelihood of improvement in hearing and reduces the likelihood of deterioration in hearing. In a 4 to 10 years follow-up, none of the children treated with ganciclovir has sensorineural hearing loss whereas 11% of the children in the untreated control group showed sensorineural hearing loss. Studies also showed that there is no significant difference hearing outcome between oral and intravenous treatment. Sometimes the use of ganciclovir in treating hearing loss has no significant effect on patients. In a study conducted by Amir et al. [20] 72% of the infants treated by a long-term oral ganciclovir for congenital *Cytomegalovirus* infection showed no change in the symptoms. Worsening of hearing usually has a low occurrence percentage (between 2%-16%). However, recently one study showed significant negative effect of using ganciclovir in treating hearing loss, where 87.5% of the treated children were found to have clinically significant worsening in hearing after the treatment. Ganciclovir can also have other side effects in the long run, such as central venous catheter/site infection, catheter malfunction and moderate neutropenia. These possible side effects are dose-related and can be easily managed by dose reduction. Despite all the negative side effects of the use of ganciclovir, this systematic review determined that the use of antiviral treatment improved hearing loss by 40% on average. Synthesis of the studies on results for children with congenital CMV show no observed heterogeneity between studies (Figure 3) [25-30].

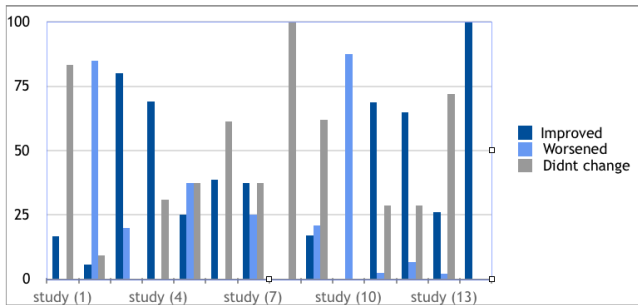


Figure 2. Percent of improved, worsened and no change cases in the studies included in the meta-analysis.

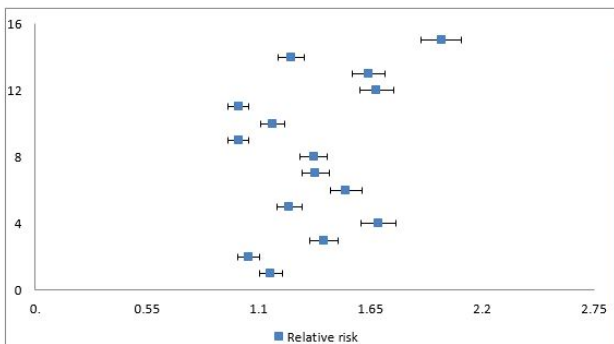


Figure 3. Forest plot diagram for results of the meta-analysis.

As is the case in most research, all the reviewed studies had limitations. One of the common limitations is the loss of follow-up due to the number of required follow-ups that make it hard for family to continue in studies. Also, the lack of untreated control group and small sample size in multiple studies caused difficulties comparing groups to obtain an accurate effect of ganciclovir. Sometimes the retrospective nature of the design can add to the limitations of the study. Missing data and information related to the patients, such as other neurologic involvement, late-onset SNHL, pharmacokinetic data, is another common limitation in similar studies. Other times, the studies do not consider important aspects, such as accounting for the viral load. Another limitation of the review process includes enclosing to few search motors, searching only in English language. There is still a need for better screening tool for congenital CMV infection. Thus, other studies are needed to obtain screening tools that are cost effective and simple to use by the general population [30].

Conclusion

CMV infections are the most important cause of nongenetic hearing loss, neurodevelopmental delay, intellectual impairment, and multisystem organ failure in children. It is a global health threat affecting approximately 0.3–1.7% of all newborns. The reviewed studies and experiments showed more positive effects than negative effects for using antiviral treatments for hearing loss in children and infants with CMV infections. Hence, after reviewing 15 well-performed studies and obtaining an overage of 40% improvement in hearing loss using antiviral treatment (ganciclovir), ganciclovir could be used as a treatment for patients including children and infants who are diagnosed with hearing loss due to CMV infection.

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