

Potentially predictive factors for hearing function improvement in pediatric cytomegalovirus infection therapy

Agung Triono, Elisabeth Siti Herini, Braghmandita Widya,
Dian Kesumapramudya Nurputra

Abstract

Background Symptomatic congenital cytomegalovirus (CMV) infection has an impact mainly on neurological sequelae, including sensorineural deafness. Because of the long-term impact, early treatment of CMV infection is mandatory. However, predictive factors for hearing function improvement in CMV infection therapy remain unexamined.

Objective To evaluate potential predictive factors for hearing improvement in pediatric CMV infection therapy.

Methods All medical record data of patients aged 0-6 years with CMV infection who completed a 6-week course of ganciclovir therapy or a combination of a 4-week course of ganciclovir and a 2-week course valganciclovir from January 2013 to December 2017 were collected. Age at onset of therapy, gender, gestational age, nutritional status, multi-organ involvement, and neurological symptoms were studied as potential predictive factors of hearing improvement in CMV therapy. The effectiveness of CMV infection therapy on improving hearing function was measured with the brainstem evoked response audiometry (BERA) test.

Results The BERA tests proportion in the right, left, and best ear showed significant improvement after therapy. All variables analyzed were not statistically significant as predictive factors for hearing improvement in CMV infection therapy.

Conclusion Ganciclovir/valganciclovir therapy in CMV infection patients accounted for the improvement of hearing impairment. However, none of the assessed factors were considered predictive for improving hearing function in CMV infection therapy. [Paediatr Indones. 2021;61:235-9 ; DOI: 10.14238/pi61.5.2021.235-9].

Keywords: CMV infection; hearing impairment; predictive factor; ganciclovir

Cytomegalovirus (CMV) infection is one of the most frequent causes of congenital infection and a significant health problem globally.¹ The incidence of CMV infection in the United States is 20.000-40.000 live births per year.^{2,3} Data on the prevalence of CMV infection in Indonesia was insufficient. However, as much as 90% of the general population was reported to be CMV seropositive.⁴ In the Pediatric Neurology Department, Dr. Sardjito General Hospital, Yogyakarta, there were 2-3 cases of CMV infection per month.⁵

The transmission of CMV infection can occur vertically (from mother to fetus) in three ways: in utero through trans-placental exposure to viremia of CMV in maternal circulation, intrapartum during labor when the fetus is exposed to cervical and vaginal secretions containing CMV, and post-natally through ingestion of breast milk containing CMV or blood transfusion contaminated with CMV.^{6,7} The percentage of viral transmission from mother to fetus is known to be about

From the Department of Child Health, Department of Child Health, Faculty of Medicine, Community Health and Nursing, Universitas Gadjah Mada-RSUP Dr. Sardjito, Yogyakarta, Indonesia.

Corresponding author: dr. Agung Triono, Sp.A(K). Department of Child Health, Universitas Gadjah Mada Medical School/Dr Sardjito Hospital. Jl. Kesehatan No.1 Sekip Yogyakarta 55284, Central Java, Indonesia. Telp +62-274-561616; Fax. +62-274-583745; Email: agungtrionodr@yahoo.com.

Submitted September 27, 2020. Accepted September 20, 2021.

30%, with 90% of fetuses remaining asymptomatic during the neonatal period.^{2,6} Approximately 60% of neonates with symptomatic CMV experience neurological sequelae, such as sensory neural hearing loss (SNHL), mental retardation, microcephaly, developmental disorders, seizures, and cerebral palsy.^{2,7} About 5-15% of infants with both subclinical and asymptomatic symptoms experience SNHL. Congenital CMV infection is the most common non-genetic cause for SNHL in children, with 6-25% of asymptomatic congenital CMV infections experiencing the slow onset of neurological sequelae.⁸

Detection of the CMV virus from urine and saliva samples of infants aged one to two weeks is the gold standard for the diagnosis of congenital CMV infection. However, the examination is only performed in symptomatic neonates. Therefore, early detection of asymptomatic congenital infection is very challenging.⁹ The sensitivity and specificity of the IgM serology test (ELISA) are 72.95% and 62.06%, respectively, but the examination can also be done by antigenemia test, which has sensitivity >90% and specificity >90%. The transmission of CMV infection can also occur horizontally (from one person to another) through close contact with contaminated body fluids.^{2,10,11}

Study on predictive factors for hearing function improvement of CMV infection therapy has been limited. We aimed to identify some of the risk factors to determine the best management of CMV infection in children.

Methods

This case-control study collected data from medical records in Dr. Sardjito Hospital, Yogyakarta. The inclusion criteria were children with symptomatic CMV infection, aged 0-6 years, who had received ganciclovir with or without valganciclovir therapy as inpatients between January 2013 and December 2017. CMV infection was defined by detecting the CMV virus in body fluids or specimens (plasma, serum, blood, or urine) in children (positive IgM, positive antigenemia, or positive PCR). Ganciclovir and valganciclovir therapy were administered as follows: intravenous ganciclovir at 12mg/kg/day twice a day for six weeks, or ganciclovir therapy at the same dose for two weeks followed by oral valganciclovir for four

weeks. Incomplete medical record data were confirmed by phone, but if it remained incomplete, the patient was excluded.

Possible predictive factors of successful CMV infection therapy were age at therapy onset, gender, prematurity status, nutritional status, multi-organ involvement, and neurological symptoms. The dependent variable was an improvement in auditory function, as measured by the brain-stem evoked response audiometry (BERA) test. Hearing function was measured in all subject with BERA testing before and after therapy. It was classified as follows: 0 to 20 dB for normal hearing, 21 to 45 dB for mild hearing loss, 46 to 70 dB for moderate hearing loss, and 71 dB or higher for severe hearing loss.¹²

All measurement were taken and reviewed by the same independent audiologist. All audiometry reports were analyzed and classified based on hearing thresholds, yielding "total ear" classifications. The "best ear" was defined as the ear with the best function between the right and left ear. For example, if a participant had severe hearing loss in the right ear and moderate hearing loss in the left ear, the best-ear classification was moderate hearing loss.

This study was approved by The Medical and Health Ethics Committee of Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada. The purpose and methods of the study, expected effects, possibility of adverse events, and patient confidentiality were explained before parents provided written informed consent.

The data were entered into the *EpiData software* program. Statistical analyses were done with *SPSS program version 22.0 (IBM Corp., Chicago)*. Chi-square test was done to analyze for relationships between independent and dependent variables, with 95% confidence intervals and significance set at $P < 0.05$.

Results

The study involved 206 patients who were diagnosed with CMV infection and underwent treatment in Dr. Sardjito Hospital, Yogyakarta, from 2013 to 2017, only 37 patients had BERA testing both before and after therapy. Baseline characteristics are shown in **Table 1**. The mean age of subjects at diagnosis was 13.59 (SD 13.55) months, and at the onset of therapy was 15.18

(SD 14.04) months. Of the 37 subjects, 19 (51.4%) were male, and 18 (48.6%) were female. Twenty-one (56.8%) subjects received two weeks of ganciclovir therapy followed by valganciclovir therapy for four weeks, while 16 (43.2%) subjects received ganciclovir therapy for six weeks. All the patients were survived and none were admitted to intensive care unit.

The BERA test showed significant improvement in hearing function after 6 weeks antiviral treatment. There were persistent/improved hearing function in 29/37 patients in the right ear, 26/37 patients in the left ear, and 28/37 patients in the best ear (Table 2).

Most of the persistent/improved subjects group started therapy at > 6 months of age (80%). According to the gender, the group of persistent/improved subjects showed similar subjects. The number of male subjects were 17/30, while the female ones were 13/30. Most patients in this group were not premature (21/30; P=0.115) and 22/30 subjects had normal nutritional status, followed by severely wasted (6/30 subjects) and wasted (2/30 subjects) (P=0.841). Multiple organs involvement was found in this group, with different number of affected organ among the subjects. In this

group, 11/30 of the subject was found to have 3 organs involved and 10/30 with 2 organs involved (P=0.766). Only 8/30 subjects reported had neurological symptom in this group (P=0.919). However, none of the possible factors predictive of successful CMV infection therapy were statistically significant (Table 3).

Discussion

A comparison of BERA test results before and after administration of ganciclovir with and without valganciclovir therapy revealed significantly improved auditory function in CMV patients post-treatment (Table 2). Twenty-eight from 37 (76%) of our patients had significantly persistent or improved hearing function in the best ear. Similarly, some studies showed modest benefits that valganciclovir treatment for either six weeks or six months effectively improved hearing impairment and preserved the level of hearing in infants with congenital CMV infection, except in those with the severe form of hearing loss.^{9,13} While another study by found that there was an improvement in hearing function up to 55% in moderate or severe impairment.¹⁴

The pathogenesis of hearing loss in CMV infection is not widely known, but there are studies that hypothesize that the CMV virus can damage the endolymphatic structure and stria vascularis causing degeneration of the neural structure. Antivirals are thought to reduce the endolymphatic CMV load which may regenerate the endolymphatic potential.¹⁵ Twenty-one out of 37 subjects received 2 weeks of ganciclovir therapy followed by valganciclovir therapy for 4 weeks, while 16/37 subjects received ganciclovir therapy for six weeks. A study in 2008 showed that 16 mg/kg/dose of valganciclovir twice daily gave the same systemic exposure and plasma concentrations as intravenous ganciclovir in the disease.⁵ Consistent with study in

Table 1. Subjects' characteristics

Characteristics	N=37
Mean age at diagnosis (SD), months	13.59 (13.55)
Mean age at therapy onset (SD), months	15.18 (14.04)
Gender, n	
Male	19
Female	18
Therapy, n	
Ganciclovir	16
Ganciclovir + valganciclovir	21
ICU treatment, n	
Yes	0
No	37
Outcomes, n	
Survived	37
Died	0

Table 2. Proportions of hearing improvement after therapy

	Assessments	Frequency	Proportion	95% CI	P value
BERA AD	Persistent/improved	29	0.78	0.65 to 0.92	< 0.001
	Worsen	8	0.22	0.08 to 0.35	
BERA AS	Persistent/improved	26	0.70	0.56 to 0.85	0.02
	Worsen	11	0.30	0.15 to 0.44	
Best ear	Persistent/improved	28	0.76	0.62 to 0.90	0.003
	Worsen	9	0.24	0.10 to 0.38	

Notes: BERA = brain evoked response audiometry, AD=auricula dextra, AS=auricula sinistra

Table 3. Analysis of possible predictive factors for successful CMV infection therapy based on auditory evaluation

Subjects' characteristics	Persistent/improved (n=30)	Worsen (n=7)	P value
Age at therapy onset, n			0.701
<1 month	1	0	
1-6 months	5	2	
>6 months	24	5	
Gender, n			0.181
Male	17	2	
Female	13	5	
Prematurity, n			0.115
Yes	8	0	
No	21	7	
Nutritional status, n			0.841
Above -2 (normal)	22	4	
Between -2 and -3 (wasted)	2	1	
Under -3 (severely wasted)	6	1	
Multi-organ involvement, n			0.766
1 organ	3	0	
2 organs	10	3	
3 organs	11	2	
>3 organs	6	2	
Neurological symptoms, n			0.919
Yes	8	2	
No	22	5	

CMV-infected murine populations, it showed that treatment with ganciclovir would decrease viral load, ameliorate CMV-induced hearing loss, and attenuate outer hair loss.¹ Besides improvement in hearing function, valganciclovir has been effectively improved neurological outcomes too. In this study, viral load was decreased but not eliminated.¹⁶

Studies on predictive factors for successful ganciclovir therapy have been limited. One study showed that age at enrollment/starting therapy was a significant predictive factor for successful CMV infection therapy (P=0.08).¹⁰ Other studies showed that symptomatic congenital CMV infection who achieve complete viral suppression (defined as ≤ 2.5 logs) by day 14 of valganciclovir therapy and maintain it until the next four months are statistically more likely to have improved hearing function in the first two years of life.¹⁷ However, our analysis of all potentially predictive factors did not show any statistical significance for any of these factors (Table 3). Interestingly, the earlier age of initial therapy was not predictive factor for hearing function improvement in CMV infection therapy.

The lack of predictive factors may have been due to several limitations, such as the small sample size or the limited number of predictor factors analyzed. Only 37 of 206 patients diagnosed with

CMV infection underwent BERA tests before and after administration of ganciclovir and valganciclovir. Only a few cases of CMV infection who receive therapy because ganciclovir and or valganciclovir therapy for congenital CMV infection have not been approved by government health insurance worldwide, including Indonesia.¹⁸ Nonetheless, a recommendation from the *International Congenital Cytomegalovirus Conference* showed that valganciclovir twice daily for six months to treat moderate to severe symptomatic CMV infection is beneficial.¹⁹

Moreover, not all of these patients underwent the examination at 6 and 12 months after therapy. However, many previous studies measured the outcomes at those time intervals. On the other hand, this result was expected because most of the symptomatic CMV patients' outcomes were severe due to multiorgan involvement. Another limitation was the absence of a control group for comparison. While all patients had been diagnosed with CMV, the diagnosis did not distinguish between symptomatic vs. asymptomatic, congenital vs. acquired CMV, or maternal presence vs. absence of CMV, although those criteria were almost always used in previous CMV related studies.

Conflict of Interest

None declared.

Funding acknowledgement

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

References

- Haller TJ, Price MS, Lindsay SR, Hillas E, Seipp M, Firpo MA, Park AH. Effects of ganciclovir treatment in murine model of cytomegalovirus-induced hearing loss. *The Laryngoscope*. 2009; 00:1-6. DOI: 10.1002/lary.28134
- Ross SA, Novak Z, Pati S, Boppana SB. Overview of the diagnosis of cytomegalovirus infection. *Infect Disord Drug Targets*. 2011;11:466-74. DOI: 10.2174/187152611797636703.
- Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol*. 2006;35:226-31. DOI: 10.1016/j.jcv.2005.09.016.
- Hadinegoro SRS, Moedjito U, Hapsari MMD, Alam A. Buku ajar infeksi dan pediatri tropis. Jakarta: Badan Penerbit IDAI; 2008. p. 122-7, 43-54, 276-91, 458-65.
- Triono A, Herini ES, Indraswari BW, Nurputra DK, Wardhani S. Luaran terapi ganciclovir dan atau valganciclovir pada pasien infeksi cytomegalovirus di Instalasi Kesehatan Anak RSUP Dr Sardjito. *Sari Pediatri*. 2020; 22:1-6. DOI: 10.14238/sp22.1.2020.1-6.
- Kimberlin DW, Acosta EP, Sanchez P, Sood S, Agrawa; V, Homans J, et al. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. *J Infect Dis*. 2008;197:836-45. DOI: 10.1086/528376.
- Kim CS. Congenital and perinatal cytomegalovirus infection. *Korean J Pediatr*. 2010;53:14-20. DOI: 10.3345/kjp.2010.53.1.14.
- Picone O, Simon I, Benachil A, Brunelle F, Sonigo P. Comparison between ultrasound and magnetic resonance imaging in assesment of fetal cytomegalovirus infection. *Prenat Diagn*. 2008;28:753-8. DOI: 10.1002/pd.2037.
- Boppana SB, Pass RF, Britt WJ, Stagno S, Alford CA. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. *Pediatr Infect Dis J*. 1992;11:93-9. DOI: 10.1097/00006454-199202000-00007.
- Harrison GJD, Morven SE, Leonard EW, Carrie A. Uptodate. 2018. [cited YEAR MONTH DATE]. Available from: <https://www.uptodate.com/contents/congenital-cytomegalovirus-infection-clinical-features-and-diagnosis?>
- Bathia J, Shah BV, Mehta AP, Deshmukh M, Sirsat RA, Rodriguez C. Comparing serology, antigenemia assay and polymerase chain reaction for the diagnosis of cytomegalovirus infection in renal transplant patient. *J Assoc Phys India*. 2004;52:297-300. PMID: 15636331.
- Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Bogor R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med*. 2015;372:933-43. DOI: 10.1056/NEJMoa1404599.
- Kimberlin DW, Lin CY, Sanchez PJ, Demmler GJ, Dankner W, Shelton M, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr*. 2003;143:16-25. DOI: 10.1016/S0022-3476(03)00192-6.
- Ohyama S, Morioka I, Fukushima S, Yamana K, Nishida K, Iwatani S, et al. Efficacy of valganciclovir treatment depends on the severity of hearing dysfunction in symptomatic infants with congenital cytomegalovirus. *Int J Mol Sci*. 2019;20:1388. DOI: 10.3390/ijms20061388.
- Teissier N, Delezoide AL, Mas AE, Khung-Savatovsky S, Bessières B, Nardelli J, et al. Inner ear lesions in congenital cytomegalovirus infection of human fetuses. *Acta Neuropathol*. 2011;122:763-74. DOI: 10.1007/s00401-011-0895-y.
- Acosta E, Bowlin T, Brooks J, Chiang L, Hussein I, Kimberlin D, et al. Advances in the development of therapeutic cytomegalovirus infections. *The Journal Of Infectious Diseases*. 2020;221(Suppl 1). DOI: 10.1093/infdis/jiz493.
- Marsico C, Aban I, Kuo H, James SH, Sanchez PJ, Ahmed A, et al. Blood viral load in symptomatic congenital cytomegalovirus infection. *J Infect Dis*. 2019; 219:1398-1406. DOI: 10.1093/infdis/jiy695.
- Morioka I, Kakei Y, Omori T, Nozu K, Fujioka K, Yoshikawa T, et al. Efficacy and safety of valganciclovir in patients with symptomatic congenital cytomegalovirus disease. *Medicine*. 2020; 99:17. DOI: 10.1097/MD.00000000000019765.
- Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis*. 2017;17:e177-88. DOI: 10.1016/S1473-3099(17)30143-3.