

Hearing impairment in children with congenital cytomegalovirus (CMV) infection based on distortion product otoacoustic emissions (DPOAE) and brain evoked response audiometry stimulus click (BERA Click) examinations

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Abstract. Congenital cytomegalovirus (congenital CMV) infection is a leading factor of non-genetic sensorineural hearing loss in children. Hearing loss caused by CMV infection does not have a pathognomonic configuration hence further research is needed. The development of knowledge on hearing loss caused by congenital CMV infection is progressing in many countries. Due to a lack of research in the context of Indonesia, this study assesses hearing impairment in children with congenital CMV infection in Indonesia, more specifically in the Cipto Mangunkusumo Hospital. Our objective was to profile hearing impairment in children 0-5 years of age with congenital CMV infection using Distortion Product Otoacoustic Emissions (DPOAE) and Brain Evoked Response Audiometry Stimulus Click (BERA Click) examinations. This cross-sectional study was conducted in the Cipto Mangunkusum Hospital from November, 2015 to May 2016 with 27 children 0-5 years of age with congenital CMV infection. Of individual ears studied, 58.0% exhibited sensorineural hearing loss. There was a significant relationship between developmental delay and incidence of sensorineural hearing loss. Subjects with a developmental delay were 6.57 times more likely (CI 95%; 1.88-22.87) to experience sensorineural hearing loss. Congenital CMV infection has an important role in causing sensorineural hearing loss in children.

1. Introduction

Congenital cytomegalovirus (congenital CMV) infection is a non-genetic disease that causes most cases of sensorineural hearing loss in babies and children. It is currently one of the main causes of deafness in children. CMV became a lead cause of non-genetic etiology hearing impairment in the United States [1,2]. Globally, congenital CMV infection occurs in 0.2-2.5% of neonatal babies. The prevalence of this infection in developed countries is 0.64-0.70%, while the prevalence in developing countries is 1-5% of every child born [3,4]. Cases of congenital CMV infection can be symptomatic (10-14% of all cases) or asymptomatic (86-90% of all cases).

Literature has stated that the prevalence of hearing loss caused by CMV infection is around 10-15%, with hearing loss starting at birth or within the few years after birth [2,5,6]. Around 20,000-40,000 babies suffer from congenital CMV in the United States every year, and around 5-10% of these cases are asymptomatic. Between 40% and 50% of asymptomatic cases is resulting in sensorineural hearing loss [7]. Gabrielli *et al.* [8], found that symptomatic congenital CMV infections in newborn



babies have a 30-65% likelihood of causing sensorineural hearing loss, but that asymptomatic infections causing hearing loss in only 7-15% of cases. Misono *et al.* [9], found in their case study that of 1.3% of children with congenital CMV infection, around 15% of these children experienced sensorineural hearing loss. Of those experiencing sensorineural hearing loss, around 40% experienced unilateral hearing loss and 60% experienced bilateral hearing loss [9]. Of these cases, 54% were progressive [9]. It is estimated that 8.9% of hearing loss cases in children in Washington DC are caused by congenital CMV infection. In this study, Furutate *et al.* [1], stated that sensorineural hearing loss occurred in 22-65% of children with symptomatic congenital CMV infection and in 6-23% of children with asymptomatic infection [1].

Numerous studies have recommended frequent audiology examinations by an ears, nose, and throat (ENT) specialist for children with congenital CMV infection. These children, who might have normal hearing at birth, run the risk of progressive hearing loss in the following months or years [10,11]. Hearing loss due to congenital CMV infection doesn't have a pathognomonic configuration. Therefore, studies on the relationship between congenital CMV infections and hearing impairment are still needed [12]. In this study, hearing impairment of children with congenital CMV infection was investigated in the context of Indonesia, more specifically, in Cipto Mangunkusum Hospital. This study is a descriptive study with a cross sectional design which aims to obtain an image of hearing impairment in children 0-5 years of age with congenital CMV based on Distortion Product Otoacoustic Emissions (DPOAE) and Brain Evoked Response Audiometry Stimulus Click (BERA Click) examinations [13].

2. Materials and Methods

The subjects of this study were all pedodontic patients with congenital CMV infection diagnosed by the Department of Pediatrics and confirmed by the supervisor of the Neurology Division of the Department of Pediatrics of the Cipto Mangunkusumo Hospital. This study was conducted at the Ear Nose Throat Department of the hospital and lasted for six months (November, 2015 through May, 2016). Primary data were collected via questionnaires and ENT clinical examinations. These data were supplemented with secondary data, obtained via medical records from January 2010 until November 2015. Examinations were preceded by filtration of mid-ear disturbances using tympanometry. All subjects filled the hearing criteria questionnaire and their parent or guardian provided informed consent. DPOAE and BERA click examinations were administered to the subjects. The results were recorded and processed using SPSS Statistics for Windows 20.0. Chi-square test was used for all categories except for gestation age, which required a Fisher's Exact test.

Children 0-5 years of age were chosen based on literature stating that children with congenital CMV infection experience hearing loss between the ages of 1 month and 70 months [14,15]. For medical record subjects, the questionnaires were filled out based on the medical records and status from the ENT Department of the hospital. Subjects that went through examinations were first asked for their anamnesis. They filled out the questionnaires before the ENT examinations, tympanometry, DPOAE and BERA Click examinations. All of the data needed for this study were included in the medical records of the hospital and also in the status of the ENT Department. Microcephaly, intracranial calcification and other intracranial anomalies were categorized as intracranial abnormalities.

3. Results and Discussion

3.1 Results

There number of children with congenital CMV infection aged 0-12 months was 17 (63.0%). This was the age group with the highest frequency of congenital CMV infection. There were seven subjects diagnosed before 6 months of age. There were only 6 (22.2%) children in the 12-36 months age group, and 4 (14.8%) children in the 36-60 months age group. The frequency of subjects with icterus was high in this study. Of subjects with icterus, 17 ears showed evidence of sensorineural hearing loss. The relationship between icterus and hearing loss was not significant ($p = 0.183$). Disturbance in fetus

growth in this study was recorded in two variables, which were birth weight (normal and low birth weight) and gestational age (normal and premature). In subjects with low birth weight, 6 ears showed evidence of sensorineural hearing loss. This relationship was not significant ($p > 0.05$). In premature subjects, 8 ears showed evidence of sensorineural hearing loss. This relationship was also not significant ($p > 0.05$). Icterus was seen in 16 subjects (59.3%) in this study.

Table 1. Subject distribution based on gender, age, symptoms, and determinant factors

Subject Characteristics	Frequency	%
Age		
0-12 months	17	60.0
12-36 months	6	24.0
36-60 months	4	16.0
Gender		
Male	16	59.3
Female	11	40.7
Symptoms		
Asymptomatic	1	3.7
Symptomatic	26	96.3
Icterus		
Yes	16	59.3
No	11	40.7
Fetal growth disturbances		
Yes	9	33.3
No	18	66.7
Gestational Age		
Normal	21	77.8
Premature	6	22.2
Weight at birth		
Normal	23	85.2
Less than normal	4	14.8
Intracranial abnormalities		
Yes	17	63.0
No	10	37.0
Head Circumference		
Normal	10	40.7
Microcephalic	16	55.6
Hydrocephalus	1	3.7
Delay in Growth and Development		
Yes	15	55.6
No	12	44.4
Other Disturbances		
Cholestasis	6	22.2
Eye anomalies	4	14.8
Other anomalies	16	22.2
None	1	3.7

Table 2. The results of DPOAE and BERA click examinations (n = 50 ears)

ENT Examination	Frequency	%
DPOAE Examination		
Pass	36	72.0
Refer	14	28.0
BERA Click Examination		
Normal	21	42.0
Sensorineural	29	58.0

Table 2 shows that 14 ears were referred in the DPOAE ear examination, and the number of sensorineural cases was 29 ears. According to the BERA Click examination, the number of ears that referred in the DPOAE examination should be 29 ears. This unsynchronized data is because some ears that passed the DPOAE examination only did so with an intensity of >20 dB in the BERA Click examination. Therefore, sensorineural hearing loss has been attributed using the BERA Click results.

Table 3. The relationship of the determinant and sensorineural factors (n = 50 ears)

Determinant Factors	Sensorineural		P	OR	95% CI	
	Yes	No			Min	Max
Gender						
Male	15	14	0.291	1.87	0.58	5.98
Female	14	7				
Symptoms						
Symptomatic	29	20	0.420	2.45	1.75	3.43
Asymptomatic	0	1				
Fetal Growth Disturbances						
Yes	12	6	0.352	1.765	0.53	5.87
No	17	15				
Icterus						
Yes	17	14	0.335	0.71	0.22	2.28
No	12	7				
Delayed Growth and Development						
Yes	21	6	0.002	6.57	1.88	22.87
No	8	15				
Intracranial abnormalities						
Yes	19	12	0.547	1.43	0.45	4.23
No	10	9				
Weight at Birth						
Yes	6	2	0.441	2.48	0.45	13.73
No	23	19				
Gestational Age**						
Preterm	8	4	0.485	1.62	0.42	6.31
Aterm	21	17				
Head Circumference						
Abnormal	19	11	0.349	1.73	0.55	5.45
Normal	10	10				

Between November, 2015 and May, 2016, there were 27 children 0-5 years of age that presented with congenital CMV. Of these subjects, 50 individual ears were examined. The data of 11 subjects were taken from medical records, and the data from 16 subjects were collected through examinations. In our study, the Fisher's Exact Test showed that there was no significant difference in hearing loss between symptomatic and asymptomatic infection.

3.2 Discussion

This study is a descriptive study with a cross-sectional design that captures hearing impairment in children 0-5 years of age with congenital CMV. This study included 16 boys (59.3%) and 11 girls (40.7%). A previous study by Misono *et al.* [9] included 19 boys (54.3%) and 16 girls (45.7%). Previous study found a similar proportion of males and females, with 55 boys and 45 girls. Furthermore, boys might be more susceptible. A setback in this study was a difficulty in finding children 0-5 years of age with congenital CMV infection that fit the inclusion criteria. This is because CMV testing is not a routine examination for newborns. Sample size also has implications for the robustness of your results.

Previous studies on congenital CMV infection have focused on newborn babies who had urine or CMV blood examinations 2-3 weeks after birth. Therefore, this study is one of the few studies on congenital CMV in children. Congenital CMV infections are not always symptomatic. In this study, there were 25 subjects (96.3%) with symptomatic congenital CMV infection and only one subject (3.7%) with an asymptomatic infection. Previous studies have reported greater numbers of subjects with asymptomatic infections than symptomatic infections at birth. Vries *et al.* [16] reported that of 37,800 newborns with congenital CMV infection at birth, 12.7% of them were symptomatic and 87.3% were asymptomatic. A study by Boppana *et al.* [5] also reported a higher number of asymptomatic cases (85 subjects) than symptomatic cases (18 subjects).

The results of this study differed from previous studies, which may be due to the difference in population and subjects. CMV infection during pregnancy may affect the reticuloendothelial system and central nervous system [11]. Impacts on the reticuloendothelial system include icterus, hepatomegaly, splenomegaly, thrombocytopenia, and petechiae [11]. Impacts on the central nervous system include intracranial calcification, microcephaly, and sensorineural hearing loss [11]. Bale [17] reported that the manifestations usually found in patients with congenital CMV infections were icterus (70%) and thrombocytopenia (70%) followed by microcephaly, intracranial calcification, and hepatomegaly and splenomegaly, each at 50%.

Previous studies have found that 50% of periventricle calcifications are found in congenital CMV patients, making this a characteristic symptom of the infection [17-19]. In this study, intracranial abnormalities were present in 17 subjects (63%), with microcephaly present in 15 subjects (55.5%). The presence of periventricle calcification, on the other hand, was only seen in 2 subjects. However, this may be because not all subjects went through full examinations (such as ultrasonography, computed tomography, or magnetic resonance) of the head/cranium. Other disturbances seen in congenital CMV infections that were analyzed in this study include cholestasis and chorioretinitis. In this study, there were 6 subjects (22.2%) who experienced cholestasis and enlargement of the heart. Chorioretinitis is expected in 10% of patients with congenital CMV infection. In this study, chorioretinitis was seen in 4 subjects (14.8%), which is consistent with previous studies.

CMV infection of pregnant women may impair the growth of the fetus, causing premature birth or low birth weight [18,20]. One study found that premature birth was present in 34% of 106 patients with symptomatic congenital CMV infection. Boppana *et al.* [21], reported that a third of subjects with symptomatic congenital CMV infections were premature or had a low birth weight [21]. Congenital CMV infection may also result in cognitive and motor deficiencies that can cause a delay in growth and development [13,22]. In our study, deficiency in growth and development were seen in 6 subjects (22.2%), and there were 4 subjects (14.8%) with low birth weight. An additional 15 subjects (55.6%) experienced deficiency in growth and development. Rivera *et al.* [13] stated that the clinical manifestation seen in patients with congenital CMV infection may be the predicting factor of sensorineural hearing loss. Therefore, the relationship between these factors and hearing loss needs to be studied further [13].

Assessment of hearing function cannot be done by one examination. The examinations recommended by the Joint Committee on Infant Hearing (JCIH) in 2007 were assessment of the function of the cochlea with otoacoustic emissions (OAE) and an assessment of auditory pathway with a BERA Click examination. Examination of the cochlea in this study was conducted using DPOAE

and the assessment of the auditory pathway was conducted using BERA Click. Foulon *et al.* studied the hearing threshold in patients with congenital CMV infection. The examination was conducted using BERA Click at intensities 20 dB, 40 dB, 60 dB, 80 dB, and if needed, 100-110 dB. The results showed that 16 children (23.5%) experienced sensorineural hearing loss. In the age group 0-12 months, there were 13 ears out of 31 ears (41.9%) with sensorineural hearing loss, 8 ears out of 11 (72.7%) in the 12-36 months age group, and 8 ears out of 8 (100%) in the 36-60 months age group [15].

Out of 27 ears with sensorineural hearing loss, 15 ears (51.72%) experienced heavy deficiency, where the V waves were detected at 80 dB or were no longer detected until 80 dB. Instances of heavy sensorineural hearing loss found in this study was higher compared to levels reported by Grosse *et al.* [23], who found that out of the 14% of children with congenital CMV infection experiencing sensorineural hearing impairment, 3-5% suffered from heavy hearing loss [23]. In this study, 12 children (48.1%) experienced bilateral hearing loss and 5 children (14.8%) experienced unilateral hearing loss. Barbi *et al.* [24], found that sensorineural hearing loss due to congenital CMV infection occurred in 9 out of 87 babies (10%) diagnosed two months after birth [24]. These findings were supported by Dahle *et al.* [14] who found that 50% of babies with congenital CMV infection experienced sensorineural hearing loss in the neonatal period.

This study found that sensorineural deficiency experienced by 29 subjects (59.2%) having symptomatic and asymptomatic infection did not result in hearing loss. This result is similar to previous studies that reported the number of subjects with hearing loss as greater in subjects with symptomatic CMV infection than in subjects with asymptomatic CMV infection. A study by Smiechura *et al.* [3] found that 17% of subjects with symptomatic congenital CMV infection experienced sensorineural hearing loss [3]. Dahle *et al.* [14] found that 7.4% of children with asymptomatic congenital CMV infection experienced hearing loss while 40.7% of children with symptomatic infections experienced hearing loss. Foulon *et al.* [25], also found a higher percentage of hearing loss in children with symptomatic infections (33%) than with asymptomatic infections (21%). The OR score was 2.45 with 95% CI 1.75-3.43, meaning that even if it was significantly different, the presence of symptoms in children with congenital CMV infection poses a 2.45 times greater risk of hearing loss than the asymptomatic infection.

This study tried to define the relationship between intracranial abnormality and hearing loss. This study was supported by an additional autopsy study of the brain and ear by Gabrielli *et al.* [8], which aimed to obtain an understanding of the etiology of sensorineural hearing loss in congenital CMV infection by assessment of the anatomy of the brain and ear. This study found that 30% of fetuses with intracranial abnormalities had brain damage and positive CMV in their inner ear. The results of our study showed that 17 subjects had intracranial abnormalities; there were 16 subjects who were microcephalic and 1 subject who was hydrocephalus. Of these, 2 subjects showed calcification in multiple periventricle areas, which is a characteristic of congenital CMV infection shown in computed tomography [17].

This study also showed that out of the 17 subject's intracranial abnormalities, most subjects experienced hearing loss. There were 19 ears that experienced sensorineural hearing loss, 12 ears that were without deficiency, and 3 ears that were excluded. The fact that 12 ears did not have hearing loss in spite of intracranial abnormalities is in accordance with literature. Sensorineural hearing loss has not been found to be influenced by head circumference [26,27]. The correlation of intracranial abnormality and hearing deficiency was not significant in this study ($p > 0.05$). However, more patients with intracranial abnormalities in this study showed hearing disturbances compared to those not experiencing hearing deficiency. Therefore, early examination and routine evaluation and control are needed.

Children with sensorineural disturbances are likely to have a low birth weight and be born premature. According to Rivera *et al.* [13], the clinical manifestations of symptomatic CMV that most accurately predict sensorineural hearing deficiencies are low birth weight and premature birth [13]. This study also searched for the relationship between growth deficiencies and hearing deficiencies in

subjects with congenital CMV infection. In subjects with growth deficiencies, 21 ears experienced sensorineural hearing loss. Our results agree with Rivera *et al.* [13]. Subjects with growth deficiencies were 6.57 times more likely to experience sensorineural hearing deficiencies. This may be because CMV infection causes failure in growth and development of the neural system, including the auditory nerves. A consequence of CMV infection is cognitive and motor deficiency, which can cause growth and development deficiencies.

4. Conclusion

An assessment of hearing function disorders in children 0-5 years of age with congenital CMV infection was conducted via DPOAE and BERA Click examinations. Of individual ears, 58.0% experienced sensorineural hearing loss. Heavy sensorineural hearing loss was found in 51.72% of all ears that experienced sensorineural hearing loss. Children with congenital CMV infection and growth deficiencies are 6.5 times more likely to have sensorineural hearing loss than children with congenital CMV infection who do not have growth deficiencies. Based on these results, early evaluation of hearing loss in children with growth deficiencies and congenital CMV infection, especially symptomatic, is recommended. Routine monitoring should be provided so that the treatment can be given as soon as signs of hearing loss are evident.

References

- [1] Furutate S, Iwasaki S, Nishio S-Y, Moteki H and Usami S-I 2011 Clinical profile of hearing loss in children with congenital cytomegalovirus (CMV) infection: CMV DNA diagnosis using preserved umbilical cord. *Acta. Oto-Laryngologica*. **131** 976-82.
- [2] Korver A M H, de Vries J J C, Konings S, de Jong J W, Dekker F W, Vossen A C T M, *et al.* 2009 DECIBEL study: Congenital cytomegalovirus infection in young children with permanent bilateral hearing impairment in the Netherlands. *J. Clin. Virol.* **46S** S27-S31.
- [3] Smiechura M, Struzycka M and Konopka W 2014 Congenital and acquired cytomegalovirus infection and hearing evaluation in children. *Otol. Laryngol. Polska*. **68** 303-7.
- [4] Harrison G J. N.d. Cytomegalovirus. *Viral Infections*. p. 1968-91e10.
- [5] Boppana S B, Fowler K B, Pass R F, Rivera L B, Lakeman F D and Britt W J. 2005 Congenital cytomegalovirus infection: Association between virus burden in infancy and hearing loss. *J. Pediatr.* **146** 817-23.
- [6] Rosenthal L S, Fowler K B, Boppana S B, Britt W J, Pass R F, Schmid D S, *et al.* 2009 Cytomegalovirus shedding and delayed sensorineural hearing loss: results from longitudinal follow-up of children with congenital infection. *Pediatr. Infect. Dis. J.* **28** 515-20.
- [7] Ross SA, Novak Z, Fowler K B, Arora N, Britt W J and Boppana S B 2009 Cytomegalovirus blood viral load and hearing loss in young children with congenital infection. *Pediatr. Infect. Dis. J.* **28** 588-92.
- [8] Gabrielli L, Bonasoni M P, Santini D, Piccirilli G, Chierghin A, Guerra B, *et al.* 2013 Human fetal inner ear involvement in congenital cytomegalovirus infection. *Acta. Neuro. Comms.* **1** 1-9.
- [9] Misono S, Sie K C Y, Weiss N S, Huang M-l, Boeckh M, Norton S J, *et al.* 2011 Congenital cytomegalovirus infection in pediatric hearing loss. *Arch. Otolaryngol. Head. Neck. Surg.* **137** 47-53.
- [10] Kadambari S, Williams E J, Luck S, Griffiths P D and Sharland M 2011 Evidence based management guidelines for detection and treatment of congenital CMV. *J. Ear. Hum. Dev.* **87** 723-8.
- [11] Swanson E C and Schleiss M R 2013 Congenital cytomegalovirus infection: New prospects for prevention and therapy: for pediatric clinics of North America: Advances in evaluation, diagnosis and treatment of pediatric infectious disease. *Pediatr. Clin. North. Am.* **60** 1-17.

- [12] Goderis J, Leenheer E D, Smets K, Hoecke H V, Keymeulen A and Dhooge I 2014 Hearing loss and congenital CMV infection: A systematic review. *Pediatrics. Official. J. Am. Ac. Ped.* **134** 972-82.
- [13] Rivera L B, Boppana S B, Fowler K B, Britt W J, Stagno S and Pass RF 2002 Predictors of hearing loss in children with symptomatic congenital cytomegalovirus infection. *Am. Ac. Ped.* **110** 762-7.
- [14] Dahle A J, Fowler K B, Wright J D, Britt W J and Pass R F. 2000 Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. *J. Am. Acad. Audiol.* **11** 283-90.
- [15] Foulon I, Naessens A, Faron G, Foulon W, Jansen A C and Gordts F 2012 Thresholds in children with congenital CMV infection: A prospective study. *Int. J. Pediatric. ORL.* **76** 712-7.
- [16] De Vries J J, Vossen A C, Kroes A C and van den Zeijst B A 2011 Implementing neonatal screening for congenital cytomegalovirus: addressing the deafness of policy makers. *Rev. Med. Virol.* **21** 54-61.
- [17] Bale J F 2012 Cytomegalovirus infection. *Semin. Pediatr. Neurol.* **19** 101-6.
- [18] Kim C S 2009 Congenital and perinatal cytomegalovirus infection. *Korean. J. Ped.* **53** 14-20.
- [19] Cheeran M C J, Lokensgard J R and Schleiss M R 2009 Neuropathogenesis of congenital cytomegalovirus infection: disease mechanism and prospects for intervention. *Clin. Microbiol. Rev.* **22** 99-126.
- [20] Revello M G and Gerna G 2002 Diagnosis and management of human cytomegalovirus infection in the mother, fetus and newborn infant. *Clin. Microbiol. Rev.* **15** 688-715.
- [21] Boppana S B, Ross S A and Fowler K B. 2013 Congenital cytomegalovirus infection: clinical outcome. *Clin. Infect. Dis.* **57** 178-81.
- [22] Pugel E P and Cekinovic D 2011 Patogenesis of congenital cytomegalovirus infection of the central nervous system. *Period. Biol.* **113** 51-60.
- [23] Grosse S D, Ross D S and Dollard S C 2008 Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: A quantitative assessment. *J. Clin. Virol.* **41** 1-6.
- [24] Barbi M, Binda S, Caroppo S, Amrosetti U, Corbetta C and Sergi P 2003 A wider role for congenital cytomegalovirus infection in sensorineural hearing loss. *Pediatr. Infect. Dis. J.* **22** 39-42.
- [25] Foulon I, Naessens A, Foulon W, Casteels A and Gordts F 2008 A 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus. *J. Pediatr.* **152** 84-8.
- [26] Hood L J 1998 Clinical applications of the ABR in neurological testing. Clinical applications of the auditory brainstem response. (San Diego, London : Singular publishing group, Inc.) p. 67-91.
- [27] Hall JW. 2006 *ABR Pediatric Clinical Applications and Populations*. (Boston: New Handbook of Auditory Evoked Responses) p. 313-65.