ORIGINAL ARTICLE

Hearing instability and abnormal auditory pathways in infants with congenital cytomegalovirus infection: An audiological and radiological single-centre prospective cohort analysis

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ABSTRACT

Introduction: This prospective cohort study aims to investigate the hearing dynamics and the changes in the central auditory pathways in infants with congenital cytomegalovirus (cCMV) infection.

Materials and Methods: cCMV-infected neonates aged ≤3 weeks old were recruited and underwent clinical and laboratory tests to detect viremia and symptomatic infection, hearing examinations at three and six months of age, and radiological imaging of brain auditory pathways using diffusion tensor imaging.

Results: From 26 eligible infants (52 ears), we detected symptomatic infection in nine (34.6%), viremia in 14 (14/25; 56.0%) and sensorineural hearing loss (SNHL) in 14 infants (53.8%). We observed 40 ears (76.9%) with unstable hearing thresholds, 17 (42.5%) of which fluctuated. Hearing fluctuation and progressivity were more common in symptomatic infection (66.7% vs. 14.7%, p<0.001; and 38.9% vs. 2.9%, p=0.002; respectively). A substantial proportion of ears had reduced fractional anisotropy (FA) in the medial geniculate body (59.1%), superior olivary nucleus (45.5%), trapezoid body (40.9%), auditory radiation (36.4%) and inferior colliculus (31.8%). Symptomatic infection was associated with an increased FA in the medial geniculate body (mean difference, MD: 0.12; 95% Confidence Intervals, 95%CI: 0.03, 0.22) and viremia in the inferior colliculus (MD: 0.09; 95%CI: 0.02, 0.16). An FA in the inferior colliculus of ≥0.404 had a sensitivity and specificity of 68.8% and 83.3% in predicting viremia (area under the curve 0.823; 95%CI: 0.633, 1.000, p=0.022).

Conclusion: SNHL along with its fluctuation and progression are common in cCMV-infected infants. cCMV infection may induce structural changes in the central auditory pathway.

KEYWORDS:
Auditory brainstem response, congenital cytomegalovirus, hearing instability, hearing loss, distortion product otoacoustic emission, diffusion tensor imaging

INTRODUCTION

Congenital cytomegalovirus (cCMV) infection is a pervasive concern in neonatal health due to its potential to induce a range of deleterious effects. The seroprevalence rate of cCMV infection ranges from 40-83% in developed countries to nearly 100% in developing countries.[1] In Indonesia, the seroprevalence rate is estimated to be as high as 87.8%.[2] Our centre, Dr. Cipto Mangunkusumo National General Hospital, a tertiary national referral hospital in Indonesia with an estimated 1000 hospital bed capacity,[3] reported a prevalence of 5.8% (24/411 neonates) in 2019.[4] These figures are quite detrimental especially considering the potential morbidity in the affected neonates including sensorineural hearing loss (SNHL), mental and developmental disabilities, and impaired vision.[1]

SNHL is the most common complication and may affect both symptomatic and asymptomatic neonates. The long-term sequelae of hearing loss in early life may cause debilitating effects in the growth and development of the affected neonates, especially in terms of language development.[1] This underscores the importance of early screening of hearing function in cCMV-infected infants to enable prompt treatment to prevent further complications. However, little is known about the dynamics and progressivity of hearing loss in infants infected with CMV. Foulon et al. stated that unstable hearing thresholds was observed in 29.4% cCMV-infected children, and fluctuations in 16.2%. The study also found that the hearing function of the affected children worsened in 27.3% and improved in 40.9%.[5] In addition, the current evidence focuses heavily on clinical manifestations of hearing loss in cCMV infection and there is limited evidence

This article was accepted: 20 May 2024
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on the association between cCMV infection and structural abnormalities related to key hearing structures.[6] Hence, this study aims to evaluate the hearing dynamics in infants with cCMV infection, and to explore whether cCMV infection induces structural changes in hearing, specifically the auditory nervous system.

MATERIALS AND METHODS

The study protocol has been approved by the Health Research Ethics Committee, Faculty of Medicine Universitas Indonesia and Cipto Mangunkusumo National General Hospital (ethical clearance no. 689/UN2.F1/ETIK/2017).

Study Design and Participants

This was a prospective cohort study conducted at the paediatric outpatient clinic at the Dr. Cipto Mangunkusumo National General Hospital, a tertiary national referral hospital in Jakarta, Indonesia. Neonates up to three weeks of age were consecutively screened for congenital CMV infection between January 2018 and August 2020, and patients confirmed with either serological tests or polymerase chain reaction (PCR) were included in this study. The newborns were excluded if they had: (1) a family history of congenital deafness, (2) craniomaxillofacial abnormalities including ear canal atresia or stenosis, (3) congenital syndromes affecting the patient's hearing function, (4) a 5-minute APGAR score of ≤3, (5) a history of sepsis or mechanical ventilation for >5 days, or (6) a history of maternal consumption of ototoxic drugs during pregnancy. The parents or guardians of the neonates provided written informed consent for the children's participation in this study.

Study Procedure and Outcomes

Eligible infants were further examined clinically by a paediatric neurologist and a neurotologist during the initial visit. Clinical and anthropometrical data including age, sex, clinical manifestations, birth weight, head circumference, developmental milestones and gestational age were collected. In addition, ancillary tests such as bilirubin index and CMV viremia (with PCR or serological tests) were also conducted. Symptomatic cCMV were diagnosed when the patient manifested symptoms such as chorioretinitis and/or neurological defects (e.g., microcephaly, hypotonia, poor suckling reflex, seizures, periventricular calcification, ventriculomegaly or ventricle cysts).

The children were followed up at 3 and 6 months of age for hearing function and central auditory neuroanatomy evaluation. Otoscopic examination and tympanometry was performed before each hearing function examination. At the age of 3 months, the patients underwent audiological examinations with distortion product otoacoustic emissions (DPOAE) and auditory brainstem response (ABR) tests, and radiological imaging with diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI) technique that allows the visualisation of nerve tissue integrity. The subjects were sedated by an anaesthesiologist during the MRI-DTI examination. The MRI-DTI results was analysed by two radiologists using Functool 9.4.04b software. DPOAE was performed using Bio-logic® AuDX® PRO (Natus Medical Inc.; WI, USA) and a REFER result was determined when the signal-to-noise ratio (SNR), the resultant between DPOAE amplitude with noise floor, was <6 in ≥4 frequency.[7] Meanwhile, ABR click (Natus Medical Inc.; WI, USA) was performed to evaluate the function of nerve tracts connecting the vestibulocochlear nuclei and the brainstem. An ABR result was deemed abnormal when V waves occurred at a hearing threshold of >30 dBnHL or no V waves detected, and normal if V waves were noted at <30 dBnHL.[8] Bone conduction ABR was performed if the ABR results >30 dBnHL to exclude the conductive factors.

From the MRI-DTI (GE Optima; GE Operations Indonesia, Jakarta, Indonesia), we collected fractional anisotropy (FA) values from five key auditory pathways: trapezoid body (TB, reference value 0.39±0.02), superior olivary nucleus (SON, 0.38±0.01), inferior colliculus (IC, 0.46±0.02), medial geniculate body (MGB, 0.36±0.01) and auditory radiation (AR, 0.38±0.03). Three months after the first follow-up (at the age of six months), we re-evaluated the patients' hearing function with DPOAE and ABR. According to the ABR click tests, we classified the patients' hearing to be fluctuating there were ±10 dB changes in hearing threshold compared to the first evaluation, and progressive when the hearing threshold increased by ≥10 dB during the second follow-up.[5]

Statistical Analysis

Descriptive data were tabulated and presented in frequencies and proportions for dichotomous variables, and in mean±standard deviation (SD). We analysed the association between the independent variables with hearing function at 3 months old (as tested using ABR) and the hearing thresholds changing at 3 months and 6 months of age with cCMV status (symptomatic or asymptomatic) using Pearson's chi-square or Fisher's exact tests. In addition, we also assessed the association between subject characteristics and DTI findings (FA of the five tested brain regions) using Student's t-tests. Differences between groups were expressed as mean differences (MD) and 95% confidence intervals (CI). When the FA of a brain region was found to be correlated with viremia, we calculated the sensitivity, specificity, and area under the curve (AUC), and plotted the receiving operating characteristic (ROC) curve. All analyses were performed using SPSS (Statistical Package for the Social Sciences) 24.0 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of Study Population

A total of 254 infants aged ≤3 weeks old were screened for CMV infection, of which 26 (10.2%, 52 ears) returned positive and underwent audiological examination at three months old. Of those, 15 patients (57.7%) refused to complete MRI-DTI examination, and six patients (23.1%) lost to follow-up at the six months visit. The study flow diagram is illustrated in Figure 1.

Of 26 infants, 53.8% (14 infants) were boys, 65.4% (17) had asymptomatic cCMV infection, and 44.2% (23) had developed hearing loss at the age of three months. The proportion of children with microcephaly and global developmental delay were significantly higher in those with symptomatic cCMV infection (33.0% vs. 0.0% and 88.9% vs.

Table I: Characteristics of the study participants, stratified by congenital CMV infection status and hearing function at 3 months old.

Subject characteristics	cCMV infection; n(%)				Hearing function at 3 months old; n(%)			
	Total (n=26)	Symptomatic (n=9; 34.6)	Asymptomatic (n=17; 65.4)	P-value	Total (n=52)	Abnormal (n=23; 44.2)	Normal (n=29; 55.8)	p-value
Sex			0.683[b]				0.366	
Boys	14 (53.8)	4 (44.4)	10 (58.8)		28 (53.8)	14 (60.9)	14 (48.3)	
Girls	12 (46.2)	5 (55.6)	7 (41.2)		24 (46.2)	9 (39.1)	15 (51.7)	
cCMV infection								<0.001
Symptomatic					18 (34.6)	16 (69.6)	2 (6.9)	
Asymptomatic					34 (65.4)	7 (30.4)	27 (93.1)	
CMV viremia[a]	14 (56.0)	3 (37.5)	11 (64.7)	0.389[b]	22 (44.0)	12 (42.9)	10 (45.5)	0.854
Hyperbilirubinemia (>10 mg/dL)	12 (46.2)	1 (12.5)	11 (64.7)	0.014[b]	24 (46.2)	7 (30.4)	17 (58.6)	0.043
Low birth weight (<2500 g)	13 (50.0)	3 (33.3)	10 (58.8)	0.080	26 (50.0)	12 (52.2)	14 (48.3)	0.780
Microcephaly	6 (23.1)	6 (33.3)	0 (0.0)	<0.001[b]	25 (48.1)	11 (47.8)	3 (10.3)	<0.001
Global developmental delay	16 (61.5)	8 (88.9)	8 (47.1)	<0.001	24 (46.2)	17 (73.9)	7 (24.1)	<0.001
Preterm birth	11 (42.3)	2 (22.2)	9 (52.9)	0.030	22 (42.3)	7 (30.4)	15 (51.7)	0.120
Hearing function at 3 months old				0.001[b]				
Abnormal	14 (53.8)	9 (100)	5 (29.4)					
Normal	12 (46.2)	0 (0.0)	12 (70.6)					

Unless otherwise stated, data are presented in frequencies and proportions, and p-values were derived from chi-square tests. [a]One data was missing from analysis. [b]p-value derived from Fisher's exact tests. [c]CMV, congenital cytomegalovirus infection

Table II: Changes in hearing thresholds between successive auditory brainstem response examinations at three and six months of age among the ears with fluctuating hearing.

cCMV infection	Improvement	Worsening	p-value
Symptomatic	6 ears	5 ears	0.588
Asymptomatic	4 ears	1 ear	

p-value derived from Fisher's exact tests. cCMV, congenital cytomegalovirus infection

47.1%; both p<0.001), while the proportion of infants with hyperbilirubinemia and preterm birth were higher in those with asymptomatic cCMV infection (12.5% vs. 64.7%, p=0.014; and 22.2% vs. 52.9%, p=0.030, respectively). Interestingly, all patients with symptomatic cCMV infection had hearing disorders (9/9 infants, 100%), while only 29.4% (5/17) of infants with asymptomatic cCMV infection had hearing loss (p=0.001). From the 14 patients with hearing loss, we detected 23 ears with increased hearing thresholds (44.2%). The proportion of ears with hearing loss was higher in those with microcephaly (47.8% vs. 10.3%), with global developmental delay (73.9% vs 24.1%), and with symptomatic cCMV infection (69.6% vs. 6.9%) (all p<0.001), while the proportion of ears with hearing loss was lower in those with hyperbilirubinemia (30.4% vs. 58.6%, p=0.043; Table I).

Hearing Dynamics at 3 and 6 Months Old

We observed 40 ears (76.9%) with unstable hearing thresholds based on successive ABR examinations at three and six months of age. Among the 40 ears, 23 (57.5%) had persistent SNHL and 17 (42.5%) fluctuated – ten of which (52.9%) had improved hearing and seven (47.1%) worsened. Hearing fluctuation was more common in symptomatic cCMV infection (vs asymptomatic: 66.7% vs 14.7%, p<0.001). Particularly, the rate of progressive hearing loss was higher in children with symptomatic cCMV infection compared to asymptomatic cCMV-infected children (38.9% vs. 2.9%, Fisher's p=0.002), while the rate of improvement was similar between cCMV infection type (27.8% vs. 11.8%, Fisher's p=0.247).

Changes in hearing thresholds ranged from 10-40 dBnHL on the same side of ears. Among three ears with improved hearing, one had an improvement in hearing threshold by 40 dBnHL while the other two improved by only 10 dBnHL. We observed three and four ears at three- and six-months follow-up visits with PASS result based on DPOAE tests but had a hearing threshold of ≥40 based on ABR examinations (data not shown). Details on the hearing dynamics among the ears with fluctuating hearing thresholds are summarized in Table II.

Structural Changes in Auditory System

MRI-DTI examination was done on 22 cCMV-infected neonate ears. Compared to the reference values, we found that the FA of the medial geniculate body was reduced in 13 ears (59.1%), superior olivary nucleus in 10 ears (45.5%), trapezoid body in 9 ears (40.9%), auditory radiation in eight ears (36.4%), inferior colliculus in seven ears (31.8%; data not shown). We found that CMV viremia was associated with a higher FA in the inferior colliculus (man difference, MD: 0.09; 95% Confidence Intervals, 95%CI: 0.02, 0.16), while hearing loss was associated with a lower FA in the same brain region (MD: -0.07; 95%CI: -0.14, -0.01). Additionally, in the medial geniculate body, we found that the FA was higher in children with symptomatic cCMV infection (MD: 0.12; 95%CI: 0.03, 0.22), microcephaly (MD: 0.14; 95%CI: 0.05, 0.23) and global developmental delay (MD: 0.12; 95%CI: 0.0003, 0.23), and was lower in children with hyperbilirubinemia (MD: -0.14; 95%CI: -0.04, -0.24), low birth weight (MD: -0.10; 95%CI: -0.21, -0.0001), and premature birth (MD: -0.14; 95%CI: -0.24, -0.04) (Table III). We further plotted a ROC curve to explore

Table III: Association between subject characteristics and fractional anisotropy of the selected five brain regions of auditory pathway using magnetic resonance imaging with diffusion tensor imaging (MRI-DTI) examination (n = 22 ears).

Subject characteristics	TB	SON	IC	MGB	AR
cCMV infection	p=0.327	p=0.942	p=0.286	p=0.016	p=0.960
Symptomatic (n=12, 54.6%)	0.33±0.05	0.36±0.09	0.41±0.08	0.43±0.11	0.31±0.10
Asymptomatic (n=10, 45.4%)	0.36±0.09	0.37±0.11	0.44±0.09	0.31±0.11	0.31±0.08
Δ	-0.03 (-0.09, 0.03)	-0.003 (-0.09, 0.09)	-0.04 (-0.11, 0.03)	0.12 (0.03, 0.22)	0.002 (-0.08, 0.08)
CMV viremia	p=0.614	p=0.252	p=0.017	p=0.106	p=0.771
Yes (n=16, 72.7%)	0.35±0.07	0.38±0.10	0.45±0.02	0.35±0.12	0.31±0.08
No (n=6, 27.3%)	0.33±0.07	0.32±0.10	0.36±0.02	0.45±0.11	0.32±0.10
Δ	0.02 (-0.06, 0.09)	0.05 (-0.04, 0.15)	0.09 (0.02, 0.16)	-0.10 (-0.22, 0.02)	0.01 (-0.10, 0.08)
ABR at 3 months	p=0.109	p=0.173	p=0.035	p=0.453	p=0.694
SNHL (n=13, 59.1%)	0.32±0.06	0.34±0.08	0.39±0.02	0.39±0.13	0.30±0.10
Normal (n=9, 40.9%)	0.37±0.08	0.39±0.11	0.47±0.03	0.35±0.11	0.32±0.06
Δ	-0.05 (-0.11, 0.01)	-0.06 (-0.14, 0.03)	-0.07 (-0.14, -0.01)	0.04 (-0.07, 0.16)	-0.02 (-0.09, 0.06)
Hyperbilirubinaemia (>10 mg/dL)	p=0.524	p=0.709	p =0.052	p=0.006	p =0.954
Yes (n=8, 36.4%)	0.36±0.10	0.37±0.12	0.47±0.03	0.28±0.11	0.31±0.08
No (n=14, 63.6%)	0.34±0.05	0.36±0.09	0.40±0.02	0.43±0.10	0.31±0.09
Δ	0.02 (-0.05, 0.09)	0.02 (-0.07, 0.11)	0.07 (-0.001, 0.14)	-0.14 (-0.24, -0.04)	-0.002 (-0.08, 0.08)
Low birth weight (<2500 g)	p=0.015	p=0.098	p=0.655	p=0.050	p=0.813
BBLR (n=10, 45.5%)	0.31±0.07	0.33±0.12	0.41±0.10	0.32±0.11	0.31±0.07
Normal (n=12, 54.6%)	0.38±0.06	0.40±0.07	0.43±0.07	0.42±0.10	0.31±0.10
Δ	-0.07 (-0.02, -0.13)	-0.07 (-0.15, 0.01)	-0.02 (-0.09, 0.06)	-0.10 (-0.21, -0.0001)	0.01 (-0.07, 0.09)
Microcephaly	p=0.197	p=0.932	p=0.441	p=0.005	p=0.359
Yes (n=10, 45.5%)	0.33±0.05	0.36±0.10	0.41±0.08	0.45±0.11	0.33±0.10
No (n=12, 54.6%)	0.36±0.08	0.37±0.10	0.44±0.08	0.31±0.10	0.29±0.08
Δ	-0.04 (-0.10, 0.02)	-0.004 (-0.09, 0.08)	0.03 (-0.10, 0.05)	0.14 (0.05, 0.23)	0.04 (-0.04, 0.11)
Global developmental delay	p=0.723	p=0.698	p=0.552	p=0.050	p=0.618
Yes (n=16, 72.7%)	0.34±0.07	0.36±0.10	0.42±0.08	0.41±0.12	0.31±0.08
No (n=6, 27.3%)	0.34±0.08	0.38±0.10	0.44±0.09	0.29±0.09	0.29±0.10
Δ	0.01 (-0.06, 0.09)	-0.02 (-0.12, 0.08)	0.02 (-0.11, 0.06)	0.12 (0.0003, 0.23)	0.02 (-0.07, 0.11)
Premature birth	p=0.267	p=0.804	p=0.351	p=0.010	p=0.915
Yes (n=8, 36.4%)	0.32±0.07	0.36±0.11	0.45±0.09	0.29±0.12	0.31±0.08
No (n=14, 63.6%)	0.36±0.07	0.37±0.09	0.41±0.08	0.42±0.10	0.31±0.10
Δ	-0.04 (-0.10, 0.03)	-0.01 (-0.10, 0.08)	0.04 (-0.04, 0.11)	-0.14 (-0.24, -0.04)	-0.004 (-0.09, 0.08)

Unless otherwise stated, data are expressed in mean±standard deviation or mean difference (95% confidence interval), and p-values were derived from Student's t-tests. TB: trapezoid body; SON: superior olivary nucleus; IC: inferior colliculus; MGB: medial geniculate body; AR: auditory radiation.

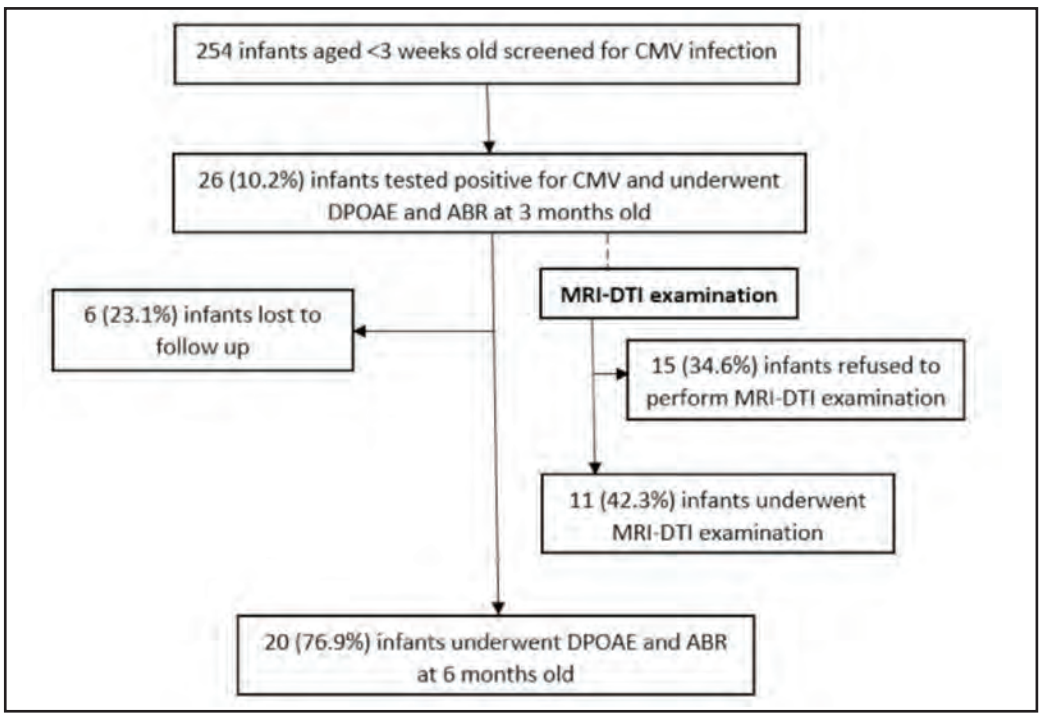

Fig. 1: Study flow diagram. ABR: auditory brainstem response; CMV: cytomegalovirus; DPOAE: distortion product otoacoustic emission; MRI-DTI: magnetic resonance imaging with diffusion tensor imaging.

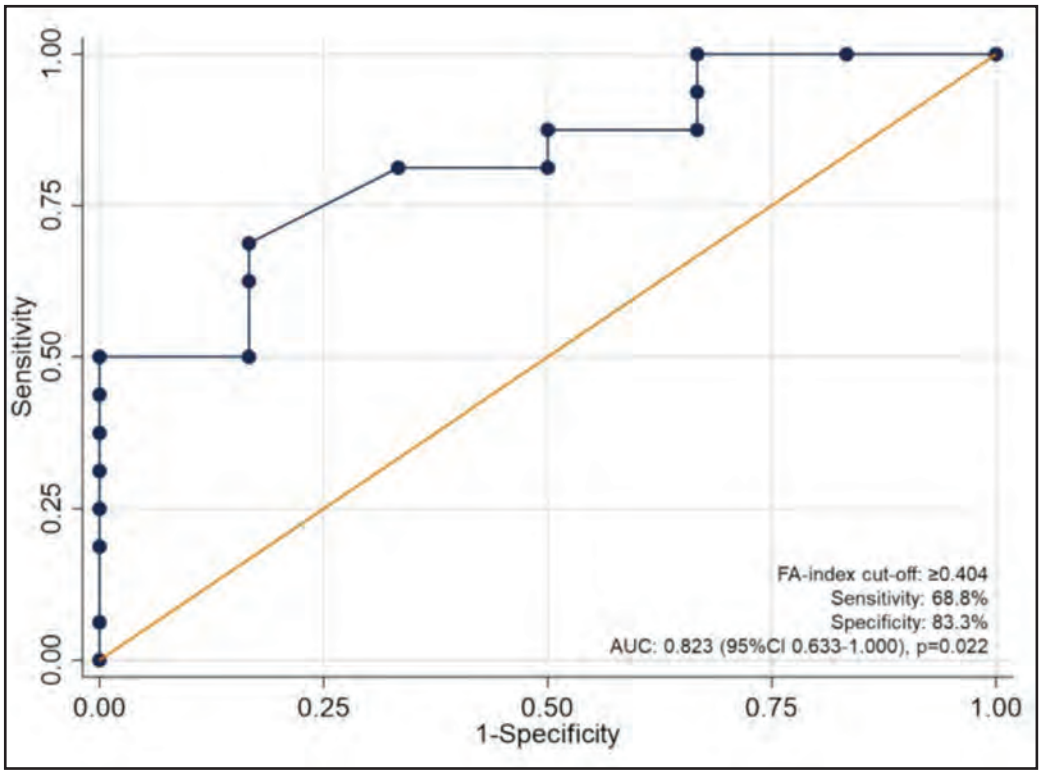

Fig. 2: Receiver operating characteristics curve for fractional anisotropy cutoff to predict viremia in inferior colliculus. AUC: area under the curve; FA: fractional anisotropy.

the discriminating performance of FA in predicting CMV viremia in the inferior colliculus region in cCMV-infected children. FA with a cut-off of ≥0.404 had a sensitivity of 68.8% and a specificity of 83.3% in predicting viremia in inferior colliculus (area under the curve, AUC: 0.823;95%CI: 0.633, 1.000, p=0.022; Figure 2).

DISCUSSION

Hearing loss in early life may induce debilitating cascading events leading to poor speech and language communication skills, cognitive and mental retardation, and low academic performance.[9] This is particularly aggravating as about 60% of cases of prelingual hearing loss in children are preventable, including CMV infection.[10] In this study, we found that the prevalence of cCMV infection in neonates was 10.2%, twice higher than a previous report in our centre which found a prevalence of 5.8% in 2016-2017.[4] This alarming prevalence surge suggests that the burden of CMV infection, particularly in neonates and infants, should not be overlooked. While it is widely known that cCMV infection may cause SNHL, there is limited evidence on the hearing dynamics in cCMV-infected children and the effects of CMV infection on structural changes in the central auditory pathways.

CMV is known to be capable of invading multiple auditory organs especially the inner and the middle ears. There are two main pathways in which cCMV infection may cause SNHL in neonates: (1) immune responses and (2) cell degeneration and injuries. In the early stage of the disease, the virus particles can invade the inner ear through blood, cochlea's aqueduct from the subarachnoid cavity or through the round window. The presence of CMV viral antigens induces immune response through the activation of inflammatory responses and release of interleukins, the interaction between the M157 on the virus surface and the LY49 cell surface receptor on NK cells, and the disruption of blood-labyrinth barrier integrity. The activated immune responses, coupled with the virus' pathogenicity, causes microcirculation disorders, hyperplasia of the organs of Corti, and apoptosis of the spiral ganglion neurons cells, thus disrupting the endolymphatic potentials and thereby causing hearing loss.[11]

In this study, we found that three out of four cCMV-infected children had unstable hearing thresholds, 57.5% of which had persistent progressive SNHL, and 42.5% of which had fluctuating hearing loss. This number is higher than those reported by Foulon et al. where only about 29.4% and 16.2% of children with cCMV infection had unstable hearing thresholds and fluctuating hearing loss, respectively. In other previous studies, the progression of hearing thresholds has been already reported varied between 43% and 62% of the congenitally infected children. The higher number of unstable hearing thresholds from ccMV infected children in our study can be caused of smaller study population and we assessed the hearing threshold disturbances based on each ear of study population.

In addition, we also found that children with cCMV infection were more likely to have progressive SNHL, while improvements were similar between children with symptomatic and asymptomatic cCMV infection. This is also in contrary to the study by Foulon et al. who found that symptomatic cCMV infection were less likely to have an

improved hearing.[5] In other study by Goderis et al found the risk developing SNHL in those symptomatic children is much higher (30-65%) than in asymptomatic children (5 to 20%).[12] Nonetheless, our study confirms previous findings suggesting that fluctuating hearing thresholds are more common in symptomatic than asymptomatic cCMV infections.[5,13] While numerous previous studies have noted the common occurrence of fluctuating hearing thresholds in cCMV-infected children,[5,11,14] its pathogenesis remains unknown. However, Fowler et al. stated that fluctuating hearing loss not explained by concurrent middle ear infections is a unique characteristic of CMV-related hearing loss.[14]

Further analysis revealed that cCMV infection resulted in a lower FA in central auditory pathways including the medial geniculate body, superior olivary nucleus, trapezoid body, auditory radiation, and inferior colliculus. In normal hearing process, sound stimuli received by the inner ear are converted to electrical stimuli and are relayed from the auditory nerve to the auditory cortex via several neuroanatomy structures including cochlear nucleus, trapezoid body, superior olivary nuclei, lateral lemniscus, inferior colliculus, medial geniculate body and auditory radiation.[15-17] All these structures especially the superior olivary nuclei and inferior colliculus are responsible of localising sound,[17] while inferior colliculus additionally generates startle responses and vestibulo-ocular reflexes.[18] The reduction of FA in these regions in cCMV-infected infants imply that cCMV infection, in addition to causing disarray in the peripheral hearing process, may also cause disintegration of central auditory tracts – as a lower FA has been thought to represent a lower neural density.[19] The presence of CMV in certain anatomical structures, including the central nervous system, may be explained by several theories. First, UL148 protein, a viral endoplasmic reticulum-resident glycoprotein influencing the viral tropism by regulating the gH/gL complexes composition on progeny virions, may enable the virus to infect certain cells, tissues and hosts, including the human central auditory pathways. Second, CMV infection may manipulate host metabolism by increasing the flow of carbons from glucose and glutamine to fatty acid metabolism, thus subsequently increasing the elongation of fatty acids to generate very long chain fatty acid tails which are essential for viral envelope formation. Third, CMV may modulate viral latency by insulating active epidermal growth factor receptor (EGFR) and regulate UL135 and UL138 proteins which antagonistically regulate viral replication thus allowing the infected cells to react to extracellular signals. Lastly, CMV-specific CD8+ T cells may accumulate over time thus extending the latency of the virus. All in all, these theories suggest that CMV infection may not only be localized in the blood and peripheral hearing organs, but also the central auditory pathways.[20]

Interestingly, we found that viremic and symptomatic cCMV infection resulted in a higher FA in the inferior colliculus and medial geniculate body, respectively. While specific reasons for these remain unknown, these may be explained by potential paradoxical atrophy or degradation of other nerve fibers,[21] or compensatory neuroplasticity following cCMV infection.[19] Previous research has found that, albeit with limited evidence, symptomatic and viremic cCMV infections may yield higher virulence and thus cause a more severe disease spectrum.[22] Hence, in these cases, the body may initiate compensatory neuroplasticity to preserve hearing function in the affected children.[23]

Altogether, our findings indicate that cCMV infection may dynamically induce structural and functional alterations in the central and peripheral hearing organs. This underscores the importance of intensive and consecutive clinical, audiological and radiological examinations in children infected with CMV to monitor their hearing function, thus ensuring their optimal growth and development. Advanced hearing examinations with DPOAE and ABR tests, as well as MRI-DTI examinations, may be performed as ancillary tests in cCMV-infected infants, especially in those with viremic and symptomatic infection. In addition, the potential morbidity risks of CMV infection, especially on their hearing and development, warrants routine screening of CMV infection in all pregnant women. While this is the case in several developed countries including the United States, Europe, Israel and Australia,[24] CMV screening is still suboptimal in most developing countries including Indonesia. In fact, CMV infection, as part of the TORCH panel, is only offered optionally to pregnant women and has yet to be included in the universal screening program.[25] Considering the scale of the potential loss of disability-adjusted life years and quality of life following CMV infection,[1] and the high rate of asymptomatic CMV infection in pregnant women,[26] we recommend CMV screening to be routinely performed in pregnant women in Indonesia.

The present study is limited by the small number of infants included in the analysis and the absence of healthy control. In addition, the relatively short follow-up period also suggests that we were unable to draw conclusions on the long-term trends of hearing dynamics in cCMV-infected children, and thus were unable to make recommendations on the timing of hearing examinations in the affected children. Nonetheless, to our knowledge, this is the first study reporting the association between symptomatic and viremic cCMV infection and structural brain changes in the inferior colliculus and medial geniculate body. Further larger studies with a longer follow-up period, and mechanistic studies exploring the molecular changes in the affected brain regions are required to confirm our findings.

CONCLUSION

We found a striking prevalence of sensorineural hearing loss (SNHL) among congenital cytomegalovirus (cCMV) -infected children in our cohort, in which fluctuation and progression of hearing loss are frequently encountered. Symptomatic cCMV infection is associated with an increased fractional anisotropy (FA) in the medial geniculate body, while viremic cCMV infection in the inferior colliculus. An FA of ≥0.404 has a high specificity in predicting viremia in cCMV-infected infants. Further studies with a larger sample size and a longer follow-up period, and explanatory studies investigating the molecular changes in the inferior colliculus and medial geniculate body following cCMV infection are warranted to substantiate our findings.

ACKNOWLEDGEMENTS
None

FUNDING
This project received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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