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Late-onset Hearing Loss From Congenital Cytomegalovirus Infection After Newborn Period in a Highly Immune Population in China

Chengbin Wang, PhD[#*], Xiaolin Liu, MD[#†,‡], Shiwen Wang, MD, PhD[#§], Wenqiang Zhang, MD, PhD[†,‡], Haiyan Wang, MS[†,‡], Wei Ma, MD[¶], Xiangxin Meng, MD[‖], Xingqu Xu, MD[*,*], Zhan Li, MD[†,†], Qiang Shuxia Pan, MD[‡‡,§§], Ping Wang, MD[¶¶], Qian Lin, MD[‖‖], Xiaofang Wang, MD, PhD[§], Minal Amin, MS[*], Sheila Dollard, PhD[*], Aiqiang Xu, MD, PhD[†,‡], Winnie Chung, AuD[*]

[*]Centers for Disease Control and Prevention, Atlanta, Georgia [†]Academy of Preventive Medicine, Shandong University [‡]Shandong Provincial Center for Disease Control and Prevention, Jinan, Shandong [§]Chinese Center for Disease Control and Prevention, Beijing [¶]School of Public Health, Shandong University, Jinan [‖]Pingyin County Center for Disease Control and Prevention, Pingyin [**]Yinan County Center for Disease Control and Prevention, Yinan [††]Jinan Municipal Center for Disease Control and Prevention, Jinan [‡‡]Linyi Municipal Center for Disease Control and Prevention, Linyi [§§]Pingyin County Maternal and Children Healthcare and Family Planning Service Center, Pingyin [¶¶]Yinan County Maternal and Children Healthcare Center, Yinan [‖‖]Jinan Municipal Maternal and Children Healthcare Center, Jinan, Shandong, China.

[#] These authors contributed equally to this work.

Abstract

After following 141 children with likely asymptomatic congenital cytomegalovirus infection in a highly immune population in China, four children (2.8%) were found to have late-onset hearing loss. No maternal or childhood factors, except higher saliva cytomegalovirus viral load at birth (P = 0.03), were associated with increased risk of developing a hearing loss.

Keywords

congenital cytomegalovirus infection; hearing loss; viral load

Congenital cytomegalovirus (cCMV) infection is well documented as the leading viral cause of permanent hearing loss and developmental disabilities in developed countries,[1]

Address for correspondence: Winnie Chung, AuD, Chief of Audiology & Speech Pathology, Veterans Health Care System of the Ozarks, 180 E. Sunbridge Dr, Fayetteville, AR 72703. Winnie.Chung@va.gov or Aiqiang Xu, MD, PhD, Shandong Provincial Center for Disease Control and Prevention, 16992 Jingshi Road, Jinan, Shandong 250014, China. aqxuepi@163.com.
Chengbin Wang, PhD, is currently at Merck & Co., Inc., Rogers, AR.

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where CMV seroprevalence is moderate and cCMV infection is attributable to primary and nonprimary maternal infection.[2,3] However, hearing loss from cCMV infection in highly immune populations has not been well examined.[4] We followed a group of children likely with asymptomatic cCMV infection in Shandong province, China, where the maternal CMV seroprevalence was above 95%,[5] to examine the prevalence of the hearing loss and associated risk factors.

METHODS

Screening for cCMV infection was carried out in newborns within 1 week after birth in three hospitals from 2011 to 2015 in Pingyin and Yinan Counties of Shandong province, China. The procedures related to parental consent, maternal and newborn data collection, saliva specimen collection, storage and polymerase chain reaction (PCR) testing (100% sensitivity and 99.9% specificity) had been described in a previous report.[5] cCMV infection was defined as ≥5 copies of CMV DNA per PCR reaction on saliva specimens collected within 7 days after birth. Likewise, the $\log_{10}$ transformation on saliva viral loads, definition and categorization of maternal and newborn factors such as maternal age, microcephaly and intrauterine growth retardation (IUGR) were also described in the previous report.[5]

Classifying children into asymptomatic or symptomatic ideally should include brain imaging to detect cCMV-related brain abnormalities and ophthalmic assessment to detect cCMV-related eye abnormalities. However, both were not performed. Therefore, we can only infer the children enrolled in this study as likely asymptomatic based on the absence of microcephaly, petechiae and seizure.

Newborns who were tested positive for CMV were contacted for consent and enrollment in late-onset hearing loss follow-up study from January 2014 through January 2017 in Pingyin County and February 2016 through February 2018 in Yinan County. All newborns in both counties received their initial automated auditory brainstem response (ABR) hearing screen within 1 week after birth. The hearing screen was conducted using the AccuScreen but was later switched to MAICO MB11 in February 2016. Infants who failed the initial newborn hearing screen were rescreened at 42 days after birth. infants who failed the rescreen were referred for an audiologic evaluation at tertiary hospitals.

The comprehensive audiologic evaluation included the tympanometry test to assess the integrity of the middle ear, and distortion product or transient otoacoustic emission test to assess the integrity of the cochlear outer hair cell. For children less than 3 years of age, hearing acuity was rescreened by the ABR test using click and or tone pip stimuli. Hearing loss was present if the ABR threshold was greater than 20 dBnHLwith a broad-band click stimuli, or greater than 40 dBnHL at 500 Hz or 30 dBnHL at 1000, 2000 or 4000 Hz with frequency specific tone pip stimuli. When patients were ≥3 years, hearing was assessed using pure tone conditioned-play behavioral audiometry for frequencies from 250 to 8000 Hz. Hearing loss was present if the behavioral threshold was greater than 20 dBnHL in any frequency. Hearing data were transmitted to the Centers for Disease Control and Prevention (CDC) in the United States for independent verification and confirmation of the hearing diagnosis by a board certified and licensed CDC audiologist (W.C.). Late-onset

sensorineural hearing loss was defined as a hearing loss diagnosed after 1 year of age, with normal tympanogram without other middle ear disease at time of the evaluation, and the test result fitting the criteria mentioned above for the different assessment methods.[6]

Information on other newborn conditions or risk factors associated with hearing loss were also collected during annual follow-up visits, such as family history of childhood hearing loss, craniofacial abnormality, head surgery or trauma, ear surgery, seizure, chemotherapy and other childhood infections. These newborn conditions and risk factors, along with the maternal and newborn characteristics at birth and viral loads were assessed for their association with hearing loss by Mantel–Haenszel chi-square test or Fisher exact test for categorical variables or Mann–Whitney U test for continuous variables. The statistical significance was defined as $P < 0.05$. The China CDC Ethics Committee on Human Subjects reviewed and approved the study protocol.

RESULTS

A total of 155 (0.8%) children were identified with cCMV infection from 18,796 infants screened, and 141 were enrolled. Fourteen children were not enrolled because of loss of contact, parental refusal or the family moved out of the study region. There was no significant difference in maternal and newborn characteristics at birth between the children who were and were not followed up, except that there were proportionally more males who did not return for follow-up ($P = 0.03$) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E175).

Among 141 children enrolled for annual follow-up, a total of 302 annual visits were conducted with an average of 2 visits per child (range 1–4 visits). Four children (2.8%) were identified with sensorineural hearing loss (2 bilateral and 2 unilateral) at 1–4 years of age. All 4 children passed their initial hearing screening after birth and none experienced conductive hearing loss. Two children were found to have late-onset hearing loss during the last follow-up visit at the ages of 4.0 and 4.3 years. The third child was found to have hearing loss at 1.4 years but was later found to have normal hearing at the last visit, at 3.2 years of age. The fourth child was the only one who was found to have hearing loss at 1.2 and at 2.2 years of age. The degree of hearing loss ranged from mild to moderate, and none has severe hearing loss.

Children with late-onset hearing loss had higher median CMV salivary viral loads at birth than children without hearing loss (median: 5.3 vs. 3.5 $\log_{10}$ copies/mL, $P = 0.03$). Other variables on maternal and children factors did not differ significantly among children with or without late-onset hearing loss (Table 1).

DISCUSSION

We found the prevalence of late-onset hearing loss was 2.8% among children with likely asymptomatic cCMV infection in the highly immune population of China.[5] Higher CMV viral load at birth was found to be associated with increased risk of developing late-onset hearing loss. Also the prevalence of hearing loss in this study was lower than other populations with moderate and high maternal seroprevalence reported in other studies.[1, 4]

Although IUGR and preterm birth were previously reported to be associated with hearing loss, we did not find either factor to be associated with hearing loss in this study. Several reasons might explain the lower hearing loss prevalence and the lack of association between IUGR and preterm birth with hearing loss in this study. First, the characteristics of children with cCMV infection at birth in this study were different from children in other studies. For example, in the Brazilian study, the prevalence of preterm birth was higher (29.4%) among the cohort of children with cCMV[7] than the 2.8% found in this study. Also the prevalence of IUGR rate found in the Brazilian study 28.9% was also higher than the 3.5% found in this study.[7] The lower prevalence of preterm birth and IUGR suggested that the cCMV infection in this study could be less severe than the one found in the Brazilian study, even though maternal seroprevalence was high in both countries (>95%).[4,5] Because both the preterm birth and IUGR rates were low in this cohort of children with cCMV infection, the lower prevalence of hearing loss was to be expected. Furthermore, the small number of children with IUGR (n = 5) and preterm birth (n = 4) in this study resulted in insufficient power to properly detect the association of IUGR and preterm birth on hearing loss. In a systematic review of 14 longitudinal studies, Goderis et al[1] noted the heterogeneity in late-onset hearing loss definition in the studies rendering comparison across studies challenging. The duration of follow-up was also critical in estimating the rate of late onset hearing loss. Scott et al[8] proposed a follow-up through adolescence might be necessary to reliably estimate the late-onset hearing loss rate. In light of other authors' and our findings,[1,8] an additional study with a reference group of children without cCMV infection in the same population will be helpful in estimating the relative risk of cCMV infection on hearing loss.

Previous studies have suggested that viral loads might be more predictive of hearing loss in children with asymptomatic than symptomatic cCMV infection.[9] In the present study, we found higher viral load at birth was associated with increased prevalence of hearing loss among children with cCMV infection in China. This is consistent with previous findings that investigated the association between viral load and hearing loss in the United States.[10] At present, this study lacks sufficient power for us to investigate the predictive value of viral loads for hearing loss because the number of children with hearing loss was too small.

In summary, we reported a 2.8% prevalence of late-onset hearing loss after 4 years of follow-up since birth among a cohort of children with likely asymptomatic cCMV infection in a highly immune population in China. Additional studies with longer follow-up period and with a reference group of children without cCMV infection could be helpful in assessing whether there is an increased risk of developing late-onset hearing loss in children with cCMV infection in China. This will be important for informing the development of evidence-based public health policy related to the prevention of and screening for cCMV infection in China and other countries with high levels of immunity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

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Table 1.

The Maternal and Newborn Characteristics and Hearing Loss Status of Children with Congenital CMV Infection in Two Counties of Shandong Province, China

	Hearing Loss		
	Yes, n (%)	**No, n (%)**	***P***
Overall	4 (2.8)	137 (97.2)	
Maternal age			0.85
16–25 years	2 (3.0)	65 (97.0)	
26–35 years	2 (3.1)	62 (96.9)	
>35 years	0 (0)	10 (100)	
Study site			0.33
Pingyin county	3 (4.7)	61 (95.3)	
Yinan county	1 (1.3)	76 (98.7)	
Calendar year at birth			0.56
2011	0 (0)	14 (100)	
2012	1 (7.7)	12 (92.3)	
2013	1 (5)	19 (95)	
2014	2 (3.5)	55 (96.5)	
2015	0 (0)	37 (100)	
Preterm birth (<37 weeks)			1.00
Yes	0 (0)	4 (100)	
No	4 (2.9)	133 (97.1)	
Sex			1.00
Male	2 (2.9)	67 (97.1)	
Female	2 (2.8)	70 (97.2)	
Intrauterine growth restriction			1.00
Yes	0 (0)	5 (100)	
No	4 (2.9)	132 (97.1)	
Singleton			1.00
Yes	4 (3)	129 (97)	
No	0 (0)	8 (100)	

	Hearing Loss		
	Yes, n (%)	No, n (%)	*P*
Salivary viral load $\log_{10}$ copies/mL: median (IQR)	5.30 (4.80, 6.00)	3.52 (1.05, 4.96)	0.03
Body weight at birth in kilograms: median (IQR)	3.38 (2.84, 4.29)	3.30 (3.0, 3.68)	0.72
Family history of childhood hearing loss			1.00
Yes	0 (0)	0 (0)	
No	4 (2.8)	137 (97.2)	
Ever had craniofacial abnormality			1.00
Yes	0 (0)	1 (100)	
No	4 (2.8)	137 (97.2)	
Ever had head surgery during follow-up			1.00
Yes	0 (0)	1 (100)	
No	4 (2.9)	136 (97.1)	
Ever had seizure during follow-up			1.00
Yes	0 (0)	2 (100)	
No	4 (2.9)	135 (97.1)	
Ever had meningitis/encephalitis during follow-up			1.00
Yes	0 (0)	0 (0)	
No	4 (2.8)	137 (97.2)	
Ever had measles during follow-up			1.00
Yes	0 (0)	0 (0)	
No	4 (2.8)	137 (97.2)	
Ever had severe hand-foot-mouth disease during follow-up			1.00
Yes	0 (0)	3 (100)	
No	4 (2.9)	134 (97.1)	
Ever had otitis media during follow-up			1.00
Yes	0 (0)	3 (100)	
No	4 (2.9)	134 (97.1)	
Ever had ear surgery during follow-up			1.00
Yes	0 (0)	0 (0)	
No	4 (2.8)	137 (97.2)	
Ever had chemotherapy during follow-up			1.00

	Hearing Loss		*P*
	Yes, n (%)	**No, n (%)**	
Yes	0 (0)	0 (0)	
No	4 (2.8)	137 (97.2)	