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Hearing Loss in Children with Congenital Cytomegalovirus Infection

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1. Introduction

Sensorineural hearing loss (SNHL) is a common birth defect. The genetic origins of SNHL can be identified in half of the prelingual cases; in the others, SNHL is caused by environmental or unidentified genetic factors. The most common environmental cause of SNHL is congenital cytomegalovirus (CMV) infection. CMV is also the most common cause of intrauterine and congenital viral infection, affecting 0.5% to 2.5% of all live neonates [1]. While 90% of CMV-infected children are asymptomatic at birth, 10% of those exhibit clinically apparent sequelae at birth, including SNHL, mental retardation, motor disability, and microcephaly [1-4]. Recent studies have revealed that children with asymptomatic congenital CMV infection are at risk of late-onset SNHL and/or deterioration of SNHL during early childhood. These developments may not appear until months or even years following birth. The frequency of SNHL associated with asymptomatic congenital CMV infection reportedly ranges from 13% to 24% [5-9]. Although asymptomatic CMV infection is associated with a lower incidence of SNHL than symptomatic CMV infection, SNHL caused by congenital CMV often remains undiagnosed because maternal screening for CMV infection is not routinely conducted and the detection of SNHL during newborn hearing screening (NHS) tests is difficult [7, 10].

Hearing loss is detected in approximately 50% of children with symptomatic congenital CMV infection. In 66% of these patients, hearing loss will deteriorate [3, 11]. Children with symptomatic congenital CMV infection are easily identified at birth. In children with symptomatic infection, intrauterine growth retardation and petechiae have been associated with the development of hearing loss [12]. SNHL is diagnosed in 7%–25% of children with asymptomatic congenital CMV infection. Rates of delayed-onset SNHL, progressive SNHL, and improvement of SNHL are reported to be 11%–18%, 23%–62%, and 23% – 47%, respectively [5-9].

Thus, the incidence of asymptomatic CMV infection and resulting SNHL may be higher, making it the leading cause of SNHL in children. Treatment of children with congenital CMV infection can prevent late-onset SNHL and/or deterioration of SNHL during early childhood. Cochlear implantation is also effective for the development of speech perception and auditory skills for deaf children with congenital CMV infection. Therefore, early identification of congenital CMV infection is very important.

2. Epidemiology of hearing-impaired children with congenital CMV infection

Of the 12,599 pregnant women included in a prospective study [13] conducted where from June 1996 to December 2003, maternal ages were as follows: <20 years, 1.6%; 20–24 years, 14.7%; 25–29 years, 41.4%; 30–34 years, 28.6%; 35–39 years, 7.9%; and >40 years, 0.8%. The annual seropositivity rate decreased over the 8-year study period, particularly during the last 4 years. The seropositivity rate of CMV immunoglobulin G (IgG) antibody was 75.3% in the sample as a whole. The seronegativity rate was 23.6%, and the percentage of cases borderline positive for IgG antibody was 1%. The seronegativity rate of CMV IgM antibody was 94.8% in the sample as a whole. The seropositivity rate was 2.2%, and 3% of cases were borderline positive for CMV IgM antibody. During the study period, in the cases positive for IgM antibody ($n = 146$), borderline positive for IgM antibody ($n = 73$), and borderline positive for IgG antibody ($n = 14$) and in cases with seroconversion of IgG antibody ($n = 3$), neonatal urine was analyzed for CMV DNA. Seroconversion of CMV IgG antibody occurred in 0.32% of the 929 cases negative for IgG antibody. Congenital CMV infection was identified in 18 infants by polymerase chain reaction (PCR) analysis of urine. Follow-up was conducted in these cases.

The symptoms at birth and sequelae observed during the first 6 months of life in the 18 children with congenital CMV infection are shown in Table 1. Among these infants, 2 children (11.1%) were symptomatic and the remaining 16 (88.9%) were asymptomatic. In this study, newborn infants were considered symptomatic if central nervous system involvement such as microcephaly or ventricular dilatation was detected. SNHL was detected in 1 child (50%) with symptomatic infection and in 4 children (25%) with asymptomatic infection. Profound unilateral SNHL had developed in the child with symptomatic infection. In the 4 children with asymptomatic infection, the severity of SNHL varied from mild unilateral loss to profound bilateral loss. Of the 4 children, unilateral SNHL was identified in 3 (75%). Mild unilateral SNHL occurred in 2 children (66.7%), and profound unilateral loss occurred in 1 child (33.3%). Profound bilateral SNHL occurred in 1 child with asymptomatic infection. The unilateral hearing loss in case 1 was detected by a neonatal automatic auditory brainstem response (ABR) screener. SNHL in the other 3 children was detected by conventional ABR. Table 2 shows a summary of the findings from longitudinal audiological evaluations in the 5 children with asymptomatic congenital CMV infection. On subsequent audiological testing, delayed-onset SNHL was detected in 2 children who had passed the newborn hearing screening (NHS) test (1 bilateral and 1 unilateral). Two cases (40%) had progressive hearing loss and 2 (40%) had

improvement of hearing loss from the initial abnormal ABR (profound unilateral loss and profound bilateral loss, respectively).

| Symptoms | | Audiologic examinations |
|-----------|---|--|
| Case 1 | Not found | Automatic ABR: unilateral REFER ABR: unilateral moderate hearing loss |
| Case 2 | Not found | ABR: unilateral moderate hearing loss |
| Case 3 | Not found | ABR: unilateral profound hearing loss |
| Case 4 | Not found | ABR: bilateral severe hearing loss |
| Case 5 | Not found | Automatic ABR: bilateral PASS |
| Case 6-16 | Not found | ABR: normal |
| Case 17 | Microcephaly Ventricular dilatation | ABR: unilateral profound hearing loss |
| Case 18 | Microcephaly Ventricular dilatation Heart anomaly | ABR: normal |

ABR: auditory brainstem response. This table is cited from reference [11].

Table 1. Initial symptoms and audiologic results during the first 6 months of life in 18 children with congenital CMV infection.

| Initial hearing loss | | Results of follow-up audiologic examination | | | Outcome |
|----------------------|--|---|---------------------|------------------------------|-------------------------------|
| | | Age | Hearing loss | Characteristic | |
| Case 1 | Unilateral moderate (Unilateral REFER) | 36 mo | Bilateral profound | Delayed-onset Progressive | Cochlear implantation (39 mo) |
| Case 2 | Unilateral moderate | 53 mo | Unilateral moderate | Fluctuating | Normal speech development |
| Case 3 | Unilateral profound | 53 mo | Unilateral mild | Fluctuating Improvement | Normal speech development |
| Case 4 | Bilateral severe | 17 mo | Normal | Fluctuating Improvement | Normal speech development |
| Case 5 | Normal (Bilateral PASS) | 26 mo | Bilateral profound | Delayed-onset Progressive | Cochlear implantation (29 mo) |

SNHL: sensorineural hearing loss. This table is cited from reference [11].

Table 2. Results of longitudinal audiologic examinations in 5 children with SNHL caused by asymptomatic CMV infection.

In this prospective study, the rates of delayed-onset SNHL, progressive SNHL, and improvement of SNHL were 12%, 40%, and 40%, respectively. Although a low rate of fetal CMV infection was observed, the results of the present study regarding the rate of SNHL are in accordance with the findings of those previous studies. The prevalence of congenital CMV infection is affected by the socioeconomic and geographic differences, but it seems to be no differences on characteristics of hearing loss induced by congenital CMV infection.

Because they develop later, both delayed-onset and progressive hearing loss frequently remain undiagnosed during universal newborn hearing screening (NHS) test [7, 10]. The 1994 Joint Committee on Infant Hearing [14] pointed out that additional hearing evaluations after universal NHS are required to detect delayed-onset hearing loss. Combined neonatal screening for CMV infection and repeated auditory evaluation should be considered, particularly for children with asymptomatic congenital CMV infection. Counseling of pregnant women on prevention of CMV infection is also important.

2.1. Retrospective study of congenital CMV infection

Hearing loss in children with congenital CMV infection often presents at birth; however, in many instances, it may develop after months or even years. One report stated that children with normal hearing at 6 months of age develop hearing loss at a rate of approximately 1% per year; the cumulative risk of late-onset hearing loss is substantial (6.9%) in a population of infants with asymptomatic congenital CMV infection [15]. Speech is often delayed in children with bilateral hearing loss. For cases of severe bilateral SNHL, Ogawa et al. [16] reported that congenital CMV infection could be diagnosed through the detection of CMV DNA in the dried umbilical cord. In addition, genetic defects (particularly those related to *GJB2*) were identified in 15% and 30% of the children, respectively. However, the etiology of pediatric SNHL, including mild to moderate and unilateral SNHL, remains uncertain. In a study of congenital CMV infection retrospectively diagnosed by the detection of CMV DNA extracted from dried umbilical cord specimens, the prevalence of CMV in children with unilateral or bilateral SNHL was investigated. In many of these cases, SNHL developed several months or even years after birth.

In total, 134 patients (70 males and 64 females) with bilateral ($n = 46$; 34.3%) or unilateral ($n = 88$; 65.7%) SNHL were evaluated. These cases were referred to the Department of Otolaryngology, Shinshu University School of Medicine from May 2008 to September 2009 (Table 3) [17]. The age of these children ranged from 1 month to 138 months (mean age: 37.7 ± 36.2 months). In children with bilateral SNHL, both genetic testing for deafness and CMV DNA analysis were performed. For children with unilateral SNHL, CMV DNA analysis and genetic testing for gene mutations of *GJB2*, *Mitochondrial1555* were performed. Objective audiometric evaluation was performed for each patient using ABR and auditory steady-state evoked response systems (MASTER 580-NAVPRO; NIHON KOHDEN Co., Ltd, Tokyo, Japan). Behavioral audiological tests and/or pure-tone audiometry were also performed. Hearing levels were classified into 2 categories on the basis of the severity of hearing loss in the worse ear as severe (>70 dB) to profound (>90 dB) and mild (20–40 dB) to moderate (41–70 dB). Follow-up hearing assessments were performed at intervals of 6–12 months. Progressive hearing loss

was defined as a decrease in hearing of ≥ 10 dB at 1 or more frequencies. Fluctuating hearing loss was defined as a decrease in hearing of >10 dB followed by an improvement of >10 dB at 1 or more frequencies. To analyze congenital CMV infection, CMV DNA quantitative PCR (qPCR) analysis was performed. Prior to qPCR analysis, total DNA, including genomic DNA and CMV DNA, was extracted from preserved dried umbilical cords. The results of this study revealed that in 9.0% (12/134) of children, SNHL could be attributed to congenital CMV infection. CMV DNA from preserved umbilical cords was detected in 8.7% (4/46) of children with bilateral SNHL and 9.1% (8/88) of those with unilateral SNHL. Congenital CMV infection caused bilateral severe-to-profound SNHL, bilateral mild-to-moderate SNHL, unilateral severe-to-profound SNHL, and unilateral mild-to-moderate SNHL in 14.3% (4/28), 0% (0/18), 9.6% (7/73), and 6.7% (1/15) of hearing-impaired children, respectively. This study also revealed that both congenital and late-onset SNHL could be caused by congenital CMV infection.

| Hearing loss | Gender | Hearing level | Severe-profound HL | | Mild-moderate HL | |
|-------------------------|--------------|----------------------------|--------------------|--------------------|------------------|--------------------|
| | (n) | (dB) | n | Diagnostic age | n | Diagnostic age |
| Total (N=134) | M: 70, F: 64 | | 101 (75.4%) | 34.4 \pm 34.7 mo | 33 (24.6%) | 48.8 \pm 38.7 mo |
| Bilateral HL (N=46) | M: 31, F: 15 | 71.8 dB [R] 71.7 dB [L] | 28 (20.9%) | 16.6 \pm 19.9 mo | 18 (13.4%) | 11.1 \pm 39.1 mo |
| Unilateral HL (N=88) | M: 39, F: 49 | 89.5 dB (W) 13.6 dB (B) | 72 (54.5%) | 41.2 \pm 36.6 mo | 15 (11.2%) | 40.3 \pm 36.8 mo |

HL: hearing loss. Diagnostic age: age diagnosed as hearing loss.

M: male, F: female. R: right, L: left. B: better ear, W: worse ear. This table is cited from reference [16].

Table 3. Summary of characteristics of children with bilateral or unilateral hearing loss.

Table 4 shows the clinical characteristics of 12 children in whom CMV DNA was identified. Of these 12 children, bilateral SNHL was detected in 4 and unilateral SNHL in 8. All 4 children with bilateral SNHL had late-onset profound SNHL. Hearing fluctuation and PASS at the NHS test were confirmed in 3 children (75%). Of the 8 children with unilateral SNHL, detectable defects were confirmed in 2 children. Hearing fluctuation was detected in only 1 child (12.5%). No inner ear anomaly was found in any of the 8 children with unilateral SNHL.

Retrospective diagnosis of congenital CMV infection is important to improve our understanding of the etiology of pediatric SNHL. In previous reports (Table 5), the frequency of congenital CMV infection in children with bilateral SNHL has varied from 3% to 36% because of variations in parameters (number of subjects, severity of SNHL) and methods [CMV IgM testing, DNA urinalysis, DNA from dried blood spots (DBS) in Guthrie cards] [19-24]. In 2 Japanese studies based on the retrospective diagnostic method of analysis of preserved dried umbilical cords, congenital CMV infection was detected in 10%–12% of children with bilateral SNHL [25, 26];

however, these studies included few subjects (10–26 cases). In children with unilateral SNHL, CMV DNA from preserved umbilical cords was detected in 9.1% (8/88). The frequency of congenital CMV infection was similar in children with unilateral and bilateral SNHL. It has been speculated that approximately 10% of SNHL in children is caused by congenital CMV infection. Few reports have examined the frequency of congenital CMV infection using retrospective diagnostic methods in children with unilateral SNHL. However, using the CMV DNA detection method, 25% (1/4) [16] and 19% (8/42) [19] of children with unilateral SNHL were diagnosed with congenital CMV infection.

| Case no. | Sex | Diagnostic age | Bilateral/ Unilateral | Severity | Average HL (R/L: dB) | Onset | NHS |
|----------|-----|----------------|--------------------------|----------|-------------------------|-------------|-----------|
| 1 | F | 60 mo | Bilateral | Profound | 87.5/108.8 | Late | Pass |
| 2 | F | 52 mo | Bilateral | Profound | 87.5/110.0 | Late | Pass |
| 3 | M | 50 mo | Bilateral | Profound | 100.0/100.0 | Late | Pass |
| 4 | M | 62 mo | Bilateral | Profound | 110.0/46.3 | Likely late | – |
| 5 | M | 6 mo | Unilateral | Profound | 32.5/103.8 | Congenital | Refer (L) |
| 6 | M | 65 mo | Unilateral | Profound | 107.5/17.5 | Unknown | – |
| 7 | M | 50 mo | Unilateral | Profound | 6.3/100.0 | Unknown | – |
| 8 | F | 98 mo | Unilateral | Profound | 110.0/15.0 | Unknown | – |
| 9 | F | 55 mo | Unilateral | Profound | 15.0/92.5 | Late | Pass |
| 10 | F | 2 mo | Unilateral | Profound | 90.0/18.3 | Congenital | Refer (R) |
| 11 | M | 80 mo | Unilateral | Severe | 13.3/70.0 | Unknown | – |
| 12 | F | 44 mo | Unilateral | Moderate | 15.0/58.3 | Late | Pass |

F: female, M: male. Mo: month. HL: hearing loss. R: right, L: left. NHS: newborn hearing screening. Diagnostic age: age diagnosed as hearing loss. This table is cited from reference [16].

Table 4. Clinical data of CMV DNA-positive children

2.2. Genetic hearing loss and congenital CMV infection

Genetic testing for deafness has become valuable for precise diagnosis of hearing loss. The most frequently implicated gene in nonsyndromic hearing loss is *GJB2*, the most prevalent gene responsible for congenital hearing loss worldwide. *GJB2*, *SLC26A4*, *CDH23*, and mitochondrial 12s ribosomal RNA (rRNA) are the other major genes that cause hearing loss in Japan. One study stated that genetic mutations were responsible for deafness in 40%–45% of children with congenital hearing loss [27]. In our study [17], 10 gene mutations associated with deafness (*GJB2*, n = 7; *SLC26A4*, n = 3) were identified in 21.7% (10/46) of children with bilateral SNHL. In children with bilateral severe-to-profound SNHL, gene mutations causing deafness

| Reference | Year | Subjects | CMV positive rate | | | Diagnostic methods | Country |
|------------------------|------|-------------------------------|-------------------|---------------|--------------|--------------------|------------|
| | | | Total | Bilateral | Unilateral | | |
| Barbi et al. [19] | 2003 | > 40 dBHL | 9/79 (11.4%) | 1/37 (2.7%) | 8/42 (19%) | DBS, qPCR | Italy |
| Ogawa et al. [16] | 2007 | > 20dB, nonsyndromic SNHL | 10/67 (10.5%) | 9/63 (14.3%) | 1/4 (25%) | US, PCR | Japan |
| Samileh et al. [21] | 2008 | > 40 dBHL | 33/95 (34.7%) | NR/75 | NR/20 | Cerologic test | Iran |
| Stehel et al. [22] | 2008 | NHS refer | 16/256 (6%) | 16/256 (6%) | NR | DNA from urine | USA |
| Walter et al. [43] | 2008 | unexplained SNHL | 8/35 (22.9%) | NR | NR | DSS, qPCR | UK |
| Mizuno et al. [44] | 2008 | only bilateral | 3/45 (6.7%) | 3/45 (6.7%) | 0 | UC, qPCR | Japan |
| Jakubikova et al. [20] | 2009 | > 60 dBHL, NHS refer | 4/71 (5.6%) | 4/55 (7.3%) | 0/16 (0%) | Cerologic test | Slovak Re. |
| Boudewyns et al. [45] | 2009 | NHS refer, > 20 dB | 4/55 (7.3%) | NR | NR | DBS, qPCR | Belgium |
| Choi et al. [18] | 2009 | NHS refer | 13/479 (2.7%) | 13/479 (2.7%) | NR | DBS, qPCR | USA |
| Tagawa et al. [26] | 2009 | > 70 dB, deaf school children | 3/26 (11.5%) | 3/26 (11.5%) | 0 (0%) | UC, qPCR | Japan |
| Kimani et al. [46] | 2010 | NHS refer | 11/109 (10.1%) | 8/92 (8.8%) | 3/17 (17.6%) | DBS, qPCR | USA |
| Adachi et al. [47] | 2010 | NHS refer, >35dB, bilateral | 13/77 (17%) | 13/77 (17%) | 0 | US, qPCR | Japan |

NR: not reported. NHS: newborn hearing screening. DBS: dried blood spot. UC: umbilical cord. qPCR: quantitative PCR. HL: hearing level. SNHL: sensorineural hearing loss. Re.: republic. This table is cited from reference [16].

Table 5. List of previous reports on children with congenital CMV nfection.

and CMV DNA positivity were detected in 32.1% (9/28) and 14.3% (4/28) of patients, respectively [17]. The diagnostic rate has been concluded to be 46.4% (13/28). If analysis of CMV DNA from preserved dried umbilical cords could be combined with genetic testing for deafness, approximately 50% of cases of bilateral severe-to-profound hearing loss in children could be detected.

Congenital CMV infection is also often diagnosed by detecting CMV DNA in urine within the first 2 weeks of life and serological testing for CMV-specific IgM antibody from mother and child [28]. In recent years, the detection of CMV DNA by retrospective methods has been more valuable not only in diagnosing congenital CMV infection during later stages of life but also in identifying children at highest risk of late-onset and progressive SNHL. Some reports have stated that DBS stored on Guthrie cards has been used for the retrospective diagnosis of congenital CMV infections [18, 29]. Similarly, preserved umbilical cords have been recently used in Japan [25, 26, 30]. The sensitivity varies widely depending on the DNA extraction method in the DBS case. Some investigators have reported sensitivities of 71%–100% and specificities of 99%–100% [19, 29]. In this study, the qPCR method and preserved umbilical cords were used because they were useful for more accurate detection of CMV DNA.

3. Diagnosis of congenital CMV infection

3.1. Detection methods

The gold standard for diagnosis of congenital CMV infection is isolation of the virus from urine or saliva in the first 2 weeks of life. However, asymptomatic congenital CMV infection in children who develop SNHL after the first 2 weeks following birth cannot be diagnosed on the basis of viral isolation from urine or saliva. Detection of CMV DNA in infant blood or the umbilical cord using PCR assays is a more feasible method for identifying children with late-onset SNHL. The method involves analysis of blood stored as DBS on Guthrie cards. In Japanese culture, the dried umbilical cord is generally stored at home as a memento of the birth. These specimens are suitable for retrospective diagnosis of congenital CMV infection. The sensitivity varied widely depending on the DNA extraction method from DBS on Guthrie cards. Some investigators reported sensitivities of 71-100% and specificities of 99-100% [19, 29]. The qPCR method and dried umbilical cord could be useful for more precise detection of CMV DNA.

3.2. Serological method

Diagnosis of symptomatic CMV infection is easier in children who display cognitive or neuromuscular abnormalities than in asymptomatic children with CMV infection. Without neonatal viral screening, the prevalence of SNHL caused by asymptomatic CMV infection remains undetermined. To diagnose primary CMV infection, a serological method has been used [31]. Pregnant women who test positive for CMV IgG seroconversion or CMV IgM antibody may transmit the virus to the fetus. Production of IgM antibody persists for 6–9 months [28]; therefore, a CMV IgM-positive result alone does not accurately predict the risk of fetal infection.

3.3. Detection of CMV DNA from umbilical cord

For the detection of congenital CMV infection, CMV DNA qPCR analysis was performed. Prior to qPCR analysis, total DNA, including genomic DNA and CMV DNA, was extracted from preserved dried umbilical cords. The procedure is as follows. Each 5-mm tissue section was incubated in a lysis buffer containing proteinase K and incubated overnight at 56°C. Total DNA was extracted using the DNeasy® Blood & Tissue Kit (Qiagen GmbH, Hilden, Germany), according to the manufacturer's instructions. The total amount of DNA was measured using the Qubit® Fluorometer with Quant-iT™ dsDNA BR Assay Kit (Life technologies-Invitrogen, Carlsbad, CA, USA). Total DNA (10 pg) was analyzed using the Step One Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) and TaqMan® Universal Master Mix II (Applied Biosystems). The qPCR primers and TaqMan® probe used for CMV DNA qPCR analysis were as follows: US14-1F: 5'-ACGTCCACGTTAGGATGAGG-3', US14-1R: 5'-GTATGTGGCGCTTCTCTCGT-3', and US14-1 TaqMan probe: 5'-FAM- AACCTGTGCACCACAGCGCC -TAMRA-3'. To quantify the input DNA amount in each sample, qPCR of each genomic region was also per-

formed using the following primers and TaqMan® probe: GJB2-2F: 5'-ACGTCCACGT-TAGGATGAGG-3', GJB2-2: 5'-GTATGTGGCGCTTCTCTCGT-3', and GJB2-2 TaqMan probe: 5'-FAM- AACCTGTGCACCACAGCGCC -TAMRA-3'. The initial preheating steps were performed for 2 min at 50°C and 10 min at 95°C. Following this, qPCR was performed for 43 cycles of 15 s at 95°C and 60 s at 60°C. After qPCR analysis, relative CMV concentrations in each sample were evaluated as ΔC_t (delta cycle threshold), which was calculated by determining the threshold cycle of CMV qPCR minus that of *GJB2* qPCR. The invader assay described by Abe [32] was used for genetic testing for deafness.

4. Treatment for hearing loss induced by congenital CMV infection

4.1. Cochlear implantation in children deafened by symptomatic CMV infection

Cochlear implantation for the correction of congenital deafness is an effective way to ensure the development of speech recognition. Cochlear implantation in children deafened by symptomatic CMV infection has been reported [33, 34]. The prognosis of children with symptomatic CMV infection is worse than that of those with asymptomatic CMV infection with regard to cognitive and neurological development. It has been suggested that cochlear implantation should be contraindicated for infants with symptomatic CMV infection and deafness because they are less likely to develop spoken language [35]. In contrast, other reports [33, 34] have suggested that cochlear implantation may improve quality of life, even if progress is slower or lesser than that expected in congenitally deaf children not infected with CMV. Pyman et al. [35] suggested that the prognosis in terms of linguistic outcome after cochlear implantation is poorer for CMV-infected deaf children than for other congenitally deaf children because of coexisting central disorders. Wide variation in speech perception and intelligibility after cochlear implantation has also been reported in children deafened by symptomatic CMV infection [33]. In that report, poor development in these areas was observed in 50% of children with symptomatic CMV infection, whereas development similar to that in congenitally deaf children not infected with CMV was evident in 31% of children and development better than that in noninfected congenitally deaf children was evident in 19% of children. In addition, a recent study has shown that deafness caused by symptomatic congenital CMV infection associated with motor and cognitive delays is not a contraindication for cochlear implantation. Early diagnosis of hearing loss and subsequent cochlear implantation is important for successful speech perception [34].

4.2. Cochlear implantation in children deafened by asymptomatic CMV infection

The effectiveness of cochlear implantation in children deafened as a result of symptomatic congenital CMV infection has been evaluated by various groups, but there are only limited outcome data for deaf children with asymptomatic CMV infection. Children with asymptomatic congenital CMV infection have a better prognosis than symptomatic children, but it is difficult to evaluate the SNHL because children with asymptomatic congenital CMV infection

are at risk of development of delayed onset SNHL and progressive SNHL. As a result, they are also at risk of late-onset learning difficulties and/or progressive learning difficulties.

A prospective study was conducted on deaf children with asymptomatic CMV infection to assess the development of speech perception and auditory skills. This study examined 2 deaf infants before and after cochlear implantation using the Infant/Toddler Meaningful Auditory Integration Scale (IT-MAIS) [36]. Vocalization behavior in case 1 was observed 6 months after implementation and showed slow improvement but finally overtook after 36 months. After 3 months of cochlear implant use, the 2 children responded to speech and environmental sounds in everyday situations and interpreted sounds in a meaningful way. They continued to improve at 36 months postoperatively. IT-MAIS scores in these 2 children were similar to the mean scores in the 5 congenitally deaf children without CMV infection. No difference was observed in the effect of early cochlear implantation for deafness induced by CMV infection between the groups of children. Another group reported that significant improvement in auditory and language skills could be achieved in cochlear implanted children with asymptomatic CMV infection, but they did not achieve the same levels of outcome as congenitally deaf children without CMV infection [37]. They found a wide variation in the outcome of cochlear implantation in these children and speculated that the variation is related to the degree of cognitive impairment. There are only a few studies available on outcomes of cochlear implanted children with asymptomatic CMV infection. Therefore, more studies will be needed to evaluate the effectiveness of cochlear implantation in these children.

4.3. Treatment for hearing-impaired children with congenital CMV infection

To prevent late-onset and/or deterioration of SNHL, treatment with intravenous ganciclovir (GCV) and/or oral valganciclovir (VGCV) has been recommended in children with symptomatic congenital CMV disease involving the central nervous system [38–41]. In previous reports, treatment with intravenous GCV was initiated within the first 10–14 days of life for 2–6 weeks, and GCV doses ranged from 5 to 12 mg/kg twice daily. One report revealed that in 5 of 9 children with congenital CMV infection and SNHL, treatment with intravenous GCV induced improvement of SNHL in 2 children and prevented deterioration of SNHL in 5 children [38]. Another report revealed that in 4 of 6 children with congenital CMV infection and SNHL, treatment with intravenous GCV induced improvement of SNHL in 2 children and no deterioration of SNHL in 4 children during the 21-month observation period [39]. Improvement of SNHL or maintenance of normal hearing was reported in 84% of children treated with intravenous GCV and 59% of untreated children. Deterioration of SNHL was reported in 21% of treated children and 68% of untreated children [40]. According to these reports, good results have been observed in the group of children treated with GCV. Treatment with intravenous GCV and oral VGCV can prevent the development of SNHL during an 18-month administration period [41]. Treatment with intravenous GCV has been investigated in hearing-impaired children with asymptomatic congenital CMV infection. No SNHL was found for 4–11 years in 12 children with asymptomatic congenital CMV infection treated with intravenous GCV, but SNHL developed in 2 of 11 untreated children [42]. Unfortunately there is no evidence for the efficacy of longer treatment with oral VGCV.

5. Conclusion

Congenital CMV infection is a major cause of bilateral and unilateral SNHL in children. In total, 9.0% of SNHL cases of unknown causes (bilateral SNHL: 8.7%, unilateral SNHL: 9.1%) are attributed to congenital CMV infection. Screening tests such as the detection of CMV DNA from preserved dried umbilical cords and genetic testing are important for the detection of SNHL in children. Using this combined methodology, detection of the cause of SNHL is possible in approximately 50% of children with hearing loss.

Cochlear implantation is effective to ensure the development of speech perception and auditory skills in deaf children with asymptomatic congenital CMV infection. No significant difference in growth of meaningful auditory integration was observed between the overall pediatric cochlear implant population not infected with CMV and that with asymptomatic CMV infection. Implementation of CMV screening models is important to prevent late-onset SNHL and deterioration of hearing loss.

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