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Longitudinal Investigation of Hearing Disorders in Children with Congenital Cytomegalovirus

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Abstract

This investigation consisted of a longitudinal study of the effects of congenital cytomegalovirus (CMV) infection on hearing sensitivity in 860 children with documented asymptomatic or symptomatic congenital CMV infection. Of the 651 children with asymptomatic CMV infection, 48 (7.4%) developed sensorineural hearing loss (SNHL), compared to 85 (40.7%) of the children with symptomatic CMV infection. Children in both groups experienced latent effects consisting of delayed onset of loss, threshold fluctuations, and/or progressive loss of hearing. It can be concluded that congenital CMV infection is a leading cause of SNHL in children. The late onset and progression of loss necessitates continued monitoring of hearing sensitivity in this population.

Key Words: Congenital cytomegalovirus infection, delayed-onset hearing loss, fluctuating hearing loss, progressive hearing loss, sensorineural hearing loss

Abbreviations: ABR = auditory brainstem response, CMV = cytomegalovirus, OAEs = otoacoustic emissions, SNHL = sensorineural hearing loss

Viral infections are known to invade the structures of the inner ear, causing sensorineural hearing loss (SNHL), and viruses are especially damaging to hearing when the infection occurs prenatally (Bergstrom, 1977). Cytomegalovirus (CMV) is the most frequently occurring congenital viral infection in humans. An estimated 40,000 newborns are infected annually (Demmler, 1991). Congenital CMV infection has been identified as one of the leading causes of SNHL in children (Hanshaw, 1982; Harris et al, 1984), accounting for at least one-third of sensorineural impairments in young children (Hicks et al, 1993). It is estimated that more than 6000 children are born annually who develop permanent hearing impairment as a result of congenital CMV infection (McCollister et al, 1996). The symptomatic form of CMV infection results in a complex of central nervous system sequelae, with SNHL a frequently occurring abnormality (Hanshaw, 1976; Stagno et al, 1977; Pass et al, 1980; Ramsay et al, 1991; Boppana et al, 1992). The large majority (90–95%) of infected newborns are asymptomatic, although they are at risk for developing SNHL (Hanshaw et al, 1976; Williamson et al, 1990; Fowler et al, 1997).

Early identification of hearing loss in infants with CMV is hampered by the fact that, for many children, the infection leads to latent damage to inner ear structures that may not appear for months or years following birth, and the loss of hearing may fluctuate and/or progress in severity (Dahle et al, 1979; Hickson and Alcock, 1991; Williamson et al, 1992; Fowler et al, 1997, 1999). Given the long-term effects of congenital CMV infection on the auditory system, it is important to document hearing status over an extended period of time. To accomplish this, serial audiologic evaluations were performed as part of an ongoing

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longitudinal multidisciplinary investigation of children infected with congenital CMV.

METHOD

Subjects for this study consisted of 860 children who had congenital CMV infection identified by isolation of the virus in urine or saliva in the first weeks of life (Reynolds et al, 1973; Boppana et al, 1992; Balcarek et al, 1993). All children were seen as part of an ongoing longitudinal investigation of CMV over a 24-year period at the University of Alabama at Birmingham. Children were followed in an interdisciplinary clinic established for this study, which included serial medical, psychometric, vision, and hearing evaluations. The majority (651) of children had no clinically apparent symptoms and were classified as having asymptomatic CMV infection. The remaining children (209) were documented as having symptomatic CMV infection. At the time of their last audiologic evaluation, chronological age for all subjects ranged from 1 month to 19 years with a median age of 5 years.

Audiologic evaluations during the course of the study were performed according to a standard protocol under the direction of the lead author. Depending on the child's age, audiologic evaluations consisted of assessment with auditory brainstem response audiometry (ABR), otoacoustic emissions (OAEs), immittance measures of middle ear function, and/or pure-tone and speech audiometry as appropriate for the child's developmental level. During the latter years of the study, children routinely received an initial ABR evaluation between 3 to 8 weeks of age and re-evaluations at 3, 6, and 12 months of age. Behavioral audiometric evaluations using visual reinforcement procedures were performed beginning at 9 months of age, with follow-up assessments every 6 months until valid pure-tone thresholds via play audiometry could be obtained for each ear, which usually occurred between 2½ to 3 years of age. Thereafter, children were seen annually unless test results or parental concern revealed a need for additional audiologic assessment. At each evaluation, middle-ear function was assessed using immittance measures and otoscopic examination performed by a clinic physician. Children exhibiting middle-ear dysfunction were rescheduled for audiologic testing after resolution of middle-ear problems. Whenever possible, pure-tone bone-conduction thresholds were obtained to confirm type of hearing loss. A child was considered to have a SNHL if air-conduction thresholds at one or more frequencies were greater than 20 dB HL in conjunction with normal middle-ear function as evidenced by normal tympanograms, normal otoscopic findings, and/or normal bone-conduction thresholds. ABR testing was conducted while children were asleep following sedation with chloral hydrate. Air-conduction thresholds were routinely obtained for clicks and 500- and 4000-Hz tone bursts; thresholds for bone-conducted stimuli were also obtained if air-conduction thresholds were greater than 25 dB nHL; a child was judged to have SNHL if ABR air-conduction thresholds were greater than 25 dB nHL in conjunction with normal bone-conduction thresholds and normal middle-ear function. Classification of type of loss for children with mixed conductive/sensorineural impairments was deferred until the conductive components were resolved.

In order to monitor the stability of their hearing impairment, children who exhibited SNHL were evaluated more frequently than children with normal hearing sensitivity. Children with SNHL received audiologic assessments every 3 to 6 months up to 3 years of age and every 6 to 12 months thereafter. Pure-tone thresholds were routinely obtained at the standard audiometric frequencies from 250 to 8000 Hz. Degree of hearing impairment, based on the mean pure-tone thresholds for 500, 1000, and 2000 Hz, was defined as follows: mild loss 21 to 45 dB HL, moderate loss 46 to 70 dB HL, severe loss 71 to 90 dB HL, and profound loss greater than 90 dB HL. In cases where hearing loss was present outside the 500- to 2000-Hz range (e.g., high-frequency impairments at 4000 and 8000 Hz), the threshold of the affected frequencies determined the classification for degree of impairment. If SNHL was determined by ABR measures, hearing thresholds were categorized based on nHL as follows: mild (30–45 dB), moderate (50–70 dB), and severe (>70 dB). In addition to severity, SNHL loss was categorized by time of onset (congenital vs delayed onsets), audiometric configuration, and threshold variability.

Audiometric configuration was analyzed in a subgroup of children with SNHL who had complete audiograms with pure-tone thresholds from 250 to 8000 Hz. Analysis was based on the most current audiogram using a classification system reported by Brookhouser et al, (1994). Configuration was classified by the slope in the low-mid frequencies (250, 500, and 1000 Hz) and in the high frequencies (2000, 4000,

Table 1 Summary of Audiologic Results for Children with Congenital Cytomegalovirus Infection

	Asymptomatic	*Symptomatic*
Total number of children	651	209
Number (%) of children with sensorineural hearing loss at one or more audiometeric frequencies	48 (7.4%)	85 (40.7%)
Characteristics of loss		
Unilateral loss	25 (52.1%)	28 (32.9%)
Bilateral loss	23 (47.9%)	57 (67.1%)
High-frequency loss only (4000–8000 Hz)	18(37.5%)	11 (12.9%)
Delayed-onset loss	18 (37.5%)	23 (27.1%)
Median age (range) of delayed onset	44 mo (24–182)	33 mo (6–197)
Progressive loss*	26 (54.2%)	46 (54.1%)
Median age (range) of first progression	51 mo (3–186)	26 mo (2–209)
Fluctuating loss*	26 (54.1%)	25 (29.4%)
Improvement of loss*	23 (47.9%)	18 (21.2%)

* Since threshold variations were categorized on changes in sensitivity at each audiometeric frequency, it was possible for a child to have more than one type of threshold variation.

and 8000 Hz). Slopes within each frequency region were classified as flat (slope < 10 dB/octave), rising (upward slope > 10 dB/octave), or sloping (downward slope > 10 dB/octave). This classification system resulted in nine possible audiometric configurations: (1) sloping-sloping, (2) sloping-rising, (3) sloping-flat, (4) flat-sloping, (5) flat-rising, (6) flat-flat, (7) rising-sloping, (8) rising-rising, or (9) rising-flat.

Thresholds at each pure-tone frequency exhibiting SNHL were analyzed for variability across time. Possible categorizations included (1) stable thresholds, (2) nonprogressive threshold fluctuations, (3) improvement of hearing sensitivity, or (4) progression of loss. The analysis of threshold variability was confined to a subset of children who had pure-tone audiograms from at least three consecutive evaluations in which middle-ear function was documented as normal as indicated by type A tympanograms and normal otoscopic findings. Categorization was based on the following criteria adapted from Brookhouser et al (1994):

Stable: No threshold varied by more than 5 dB from the initial threshold recorded for that frequency.

Progressive: Final audiometric threshold was poorer by 10 dB or more than the initial audiometric threshold for that frequency.

Fluctuating: Final threshold differed by 5 dB or less from the initial threshold for that frequency, but thresholds obtained during intervening evaluations varied by 10 dB or more from the initial threshold.

Improvement: Final audiometric threshold was better by 10 dB or more than the initial threshold for that frequency.

Table 2 Degree of Sensorineural Hearing Loss Based on Average Pure-Tone Thresholds at Last Audiologic Evaluation (Percentage of Ears)

*Degree of Loss**	*Asymptomatic (%)*	*Symptomatic (%)*
Mild (21–45 dB HL)	17.0	11.8
Moderate (46–70 dB HL)	14.9	13.4
Severe (71–90 dB HL)	17.0	30.7
Profound (>90 dB HL)	51.1	44.1

*If sensorineural hearing loss was determined by auditory brainstem response, hearing thresholds were calculated based on nHL as follows: mild (30–45 dB), moderate (50–70 dB), severe (>70 dB).

Table 3 Cumulative Percentage of Sensorineural Hearing Loss According to Age

Age	*Asymptomatic (%) (N = 48 Children)*	*Symptomatic (%) (N = 85 Children)*
Birth–1 month	25.5	43.5
3 months	31.4	55.3
6 months	43.1	67.2
2 years	47.1	82.4
3 years	58.8	88.2
4 years	72.5	89.4
6 years	86.6	95.3
7–15 years	100.0	100.0

Hearing sensitivity was measured by either auditory brainstem response (ABR) or pure-tone audiometry depending on the child's age and developmental level. The criteria for hearing loss for pure-tone audiometry was the presence of thresholds greater than 20 dB HL at one or more frequencies; for ABR, hearing loss consisted of thresholds greater than 25 dB nHL.

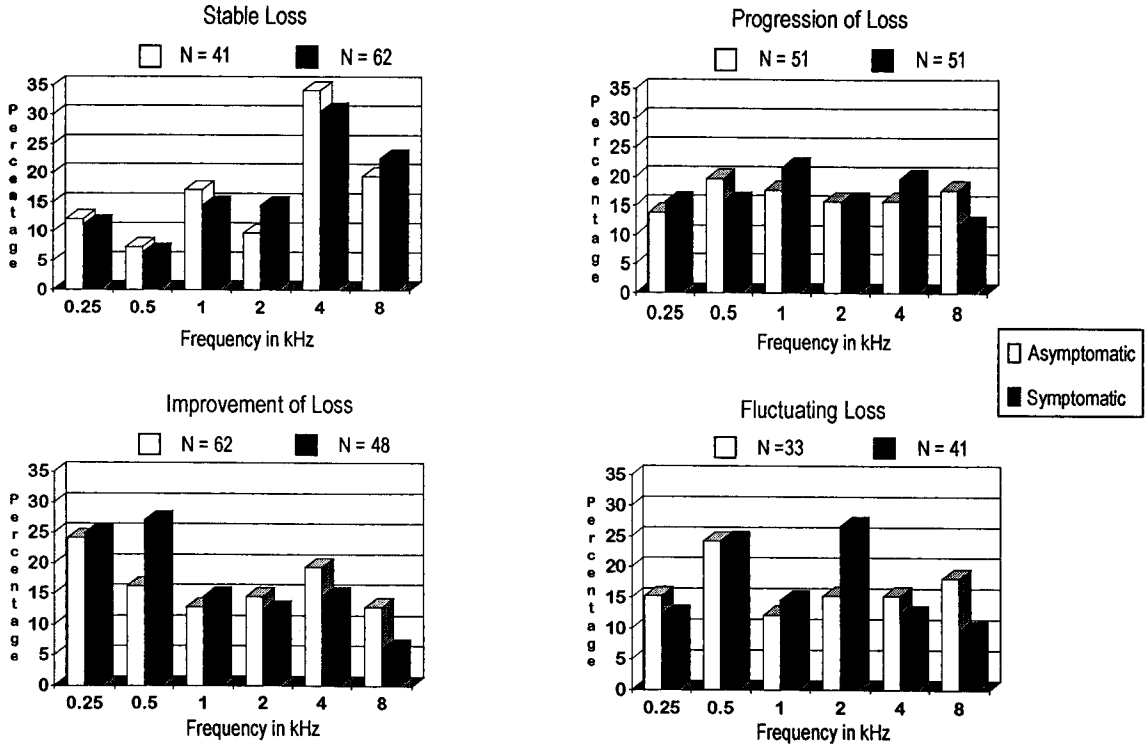

Figure 1 Threshold variability in relation to audiometric frequency. N = number of occurrences of each type of variation (since threshold variations were categorized by changes in sensitivity at each audiometric frequency, it was possible for a child to have more than one type of threshold variation).

RESULTS

Table 1 displays a summary of the findings from the longitudinal audiologic assessment of the 860 children with congenital CMV infection. It includes all children who were determined to have SNHL by either ABR or pure-tone audiometry. As indicated, SNHL occurred in 48 (7.4%) of the children with asymptomatic infections and in 85 (40.7%) of those with symptomatic infections. The loss was bilateral in 47.9% of the asymptomatic children with hearing loss compared to 67.1% of the symptomatic children who had hearing impairment. SNHL was confined to the high frequencies (4000–8000 Hz) for 37.5% of asymptomatic children with loss versus 12.9% for children with symptomatic CMV infection.

Degree of sensorineural hearing impairment (Table 2), based on the most recent test results, varied from mild to profound, with the majority of both asymptomatic and symptomatic children falling within the severe to profound range. Several children developed hearing loss so profound that they fail to respond to pure-tone or speech stimuli, even when presented at maximum intensity levels. It should be noted that the severity of a child's loss frequently changed over time. For example, some children progressed from a mild to profound loss during the course of this study.

As indicated in Table 1, children in both groups (27.1% and 37.5%) experienced delayed onset of their hearing impairment. The delay in onset occurred over a wide age range from 6 months to 16.4 years. Although not statistically significant, the age at which delayed onset of loss occurred tended to be younger for children with symptomatic infections than for children with asymptomatic infections (median age at time of onset of 33 vs 44 months). Table 3 displays the cumulative percentage of SNHL according to age. Clearly, both groups exhibited a consistent increase in percentage of children with hearing loss with increasing age, reflecting the delay in onset of loss that is characteristic of children with congenital CMV infection.

Following the onset of loss, a majority (approximately 54%) of children in both groups who had SNHL experienced a progression in the severity of their hearing impairment at one or more frequencies. There was a wide range of age (2–209 months) at which progression of loss was first documented and, although not statis-

Table 4 Mean dB (SD) Change in Hearing Sensitivity Associated with Improvement, Progression, and Fluctuation of Hearing Impairment

	Test Frequencies (Hz)					
	250	*500*	*1000*	*2000*	*4000*	*8000*
Improvement	18.3 (8.6)	17.8 (7.1)	15.5 (5.9)	15.8 (7.9)	17.1 (6.9)	15.0 (6.1)
N	12	16	10	12	12	5
Progression	22.1 (13.9)	28.5 (19.3)	31.4 (15.5)	30.5 (21.2)	25.6 (13.7)	17.5 (6.6)
N	17	22	18	18	19	19
Fluctuation	18.0 (6.7)	15.0 (5.2)	18.1 (10.9)	17.1 (7.2)	16.7 (9.3)	23.8 (11.1)
N	5	12	8	12	6	4

N = number of ears at each frequency.

tically significant, the initial progression of loss tended to occur earlier in children with symptomatic infections (median age of 26 months) than for children with asymptomatic infections (median age of 51 months).

During the course of the study, the investigators noted that some of the children with SNHL experienced considerable fluctuation in their hearing threshold levels. That is, pure-tone thresholds might decrease (become worse) at one evaluation and improve at the next, despite the lack of any apparent intervening factors (e.g., middle-ear dysfunction). Although hearing-impaired children from both groups experienced fluctuations in hearing sensitivity, the phenomenon was more prevalent among the children with asymptomatic infections (54.1% vs 29.4%) than the children with symptomatic infections.

Some children with SNHL experienced an improvement in hearing sensitivity from their initial to final thresholds, frequently in conjunction with threshold fluctuations. Improvement in threshold levels at one or more frequencies occurred in 23 (47.9%) of the children with asymptomatic infections compared with 18 (21.1%) of the children with symptomatic infections.

Figure 1 charts the occurrence of threshold variations in relation to audiometric frequency. Except for a much higher percentage of fluctuations among asymptomatic children at 2 kHz, both groups exhibited relatively similar patterns of threshold variability. The audiometric frequencies 250 and 500 Hz tended to be the least stable, whereas 4000 Hz was the most stable. Additionally, hearing improved more often at 250 and 500 Hz than at higher frequencies. Progression of loss occurred more uniformly across all frequencies. Threshold fluctuations were seen at all test frequencies but did not appear to follow any pattern in terms of affected frequencies.

Table 4 lists the frequency-specific mean dB changes in hearing sensitivity associated with improvement, progression, or fluctuation of pure-tone thresholds for both CMV groups combined. The mean values for improvement of hearing from initial to final tests ranged from 15.5 to 18.3 dB. The mean dB change in threshold from initial to final tests for progressive impairments covered a wider range from 17.5 to 31.4 dB, with the largest mean progression occurring at 1000 and 2000 Hz. Nonprogressive fluctuations were measured as the difference in dB between the minimum and maximum threshold levels occurring over the course of serial audiometric assessments. The magnitude of fluctuations was similar across frequencies except for a tendency for slightly larger fluctuations at 8000 Hz.

As stated previously, hearing loss was classified according to nine possible audiometric patterns based on the slope of pure-tone thresholds in the 250 to 1000 Hz and the 2000 to 8000

Table 5 Configuration of Hearing Loss at Most Recent Evaluation (Percentage of Ears)

*Configuration**	*SS*	*SR*	*SF*	*FS*	*FR*	*FF*	*RS*	*RR*	*RF*
Asymptomatic (N = 49 ears)	6.1	0.0	18.4	28.6	0.0	38.8	2.0	2.0	4.1
Symptomatic (N = 77 ears)	5.2	0.0	24.6	11.8	1.3	55.8	1.3	0.0	0.0

*SS = sloping-sloping, SR = sloping-rising, SF = sloping-flat, FR = flat-rising, FF = flat-flat, RS = rising-sloping, RR = rising-rising, RF = rising-flat.

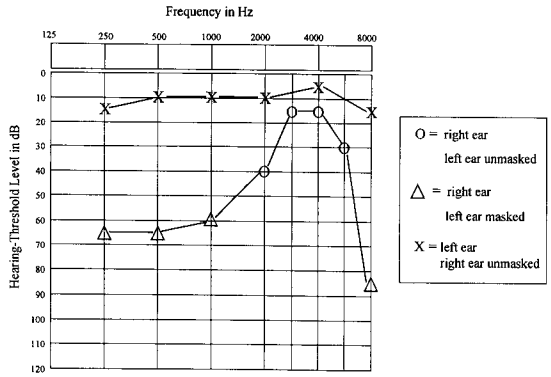

Figure 2 Peaked sensorineural hearing loss occurring at age 5 years.

Hz ranges. Table 5 displays the percentage of ears falling in each classification of audiometric configuration at the time of their most recent audiogram. In general, the percentage of ears in each category followed a similar pattern for children in both groups. A flat audiometric configuration (i.e., flat-flat) was the most common pattern of loss. The next most frequently occurring configurations consisted of impairments that sloped downward in the higher frequencies (i.e., flat-sloping) or sloped downward in the low frequencies (i.e., sloping-flat).

At some point during the course of their audiologic evaluations, 15 children exhibited an audiometric configuration that did not follow the flat or sloping patterns. This configuration consisted of SNHL in the low- and high-frequency range with peaks of normal or near-normal hearing at 2000 and/or 4000 Hz. An example of this pattern is illustrated in Figure 2. This child, who had asymptomatic CMV infection, had normal hearing bilaterally until age 5 years when she complained of a loss of hearing in her right ear. Tympanograms were normal, but pure-tone audiometry revealed a unilateral SNHL with a peak of normal hearing at 3000 and 4000 Hz. A subsequent otologic evaluation and temporal bone computed tomography scan were normal. Of the 15 children with this audiometric pattern, 10 were primarily unilateral impairments. The loss was delayed onset for all ears with this configuration, with age of onset ranging from 18 months to 14 years.

DISCUSSION

The results of this longitudinal study confirm and extend the findings of previous investigators by documenting the pervasive effects of congenital CMV infection on hearing sensitivity. Clearly, there is a high probability that children with symptomatic CMV infection will develop bilateral moderate-to-severe SNHL. Although asymptomatic CMV infection is associated with a much lower prevalence of hearing loss than symptomatic CMV infection, the resulting impairments are equally severe, and the larger total number of children born with asymptomatic CMV infection arguably makes it the leading cause of SNHL in children (Fowler et al, 1997). In addition to a high prevalence of SNHL, congenital CMV infection frequently exerts latent effects on hearing, resulting in delayed onset of loss, which may not appear until months or years following birth. Additionally, the majority of infected children will, at some time, experience progression of their hearing impairment, leading, in some cases, to a complete lack of response to auditory stimuli; in our experience, hearing usually diminishes gradually, although sudden decreases in hearing sensitivity may occur. In some instances, sudden decreases in hearing due to congenital CMV infection have been reversed by treatment with steroids (McCollister et al, 1996). In contrast, some children with congenital CMV infection exhibit threshold fluctuations without progression of their loss and, in some cases, may experience improvement in their hearing sensitivity. Unfortunately, we cannot predict which children may be susceptible to the latent effects of congenital CMV infection on the auditory system.

The instability of hearing sensitivity associated with congenital CMV infection appears to vary somewhat depending on audiometric pure-tone frequency, with lower frequencies (250 and 500 Hz) less stable than higher frequencies; improvement of hearing also occurred more frequently at 250 and 500 Hz than for higher frequencies. In contrast, progressive loss occurred at a relatively similar rate across all frequencies.

A flat hearing loss (approximately equal degree of loss at all frequencies) was the predominant threshold configuration for children with both asymptomatic and symptomatic infections. However, due to the unstable nature of hearing sensitivity in this population, auditory threshold configuration may change markedly over time. An impairment characterized initially by a sloping high-frequency loss may gradually progress to include the lower frequencies, resulting in a flat configuration. The configuration characterized by peaks of better hearing at 2000 and/or 4000 Hz (see Fig. 2) also was

highly variable due to fluctuations in hearing and/or progression of loss. For example, children with this pattern frequently experienced fluctuations in hearing and/or progression of loss in the 250- to 1000-Hz range, whereas the high-frequency component remained more stable.

Although the pathophysiology of hearing loss in children with congenital CMV infection remains unclear, there is evidence suggesting that both a localized inflammatory response and direct cytopathic effects in the inner ear play a role in the development of SNHL (Strauss, 1990; Williamson et al, 1992; McCollister et al, 1996). Fluctuations and progression of loss could be due to virus reactivation and immunologic response to infection (Fowler et al, 1997). Certainly, the fluctuations and improvements in SNHL observed in this study suggest that a transient condition, such as inflammation in the cochlea, is a contributing factor for at least some of the children with congenital CMV infection. The adverse effects of CMV-induced labyrinthitis on hearing has been documented in guinea pigs (Harris et al, 1990; Woolf, 1990; Keithley and Harris, 1996). Additionally, endolymphatic hydrops has been suggested as part of the long-term sequelae of congenital CMV infection (Huygen and Admiraal, 1996). Data presented by Horner and Cazals (1991) on their work with guinea pigs suggest that increased endolymphatic pressure of the type associated with hydrops results first in a high-frequency loss, followed in time by a low-frequency loss and then by loss in the middle-frequency range (the 4-kHz region appeared to be somewhat protected from the effects of excess endolymphatic pressure). Interestingly, the pattern of loss reported by Horner and Cazals for increased endolymphatic pressure is similar to the "peaked audiogram" exhibited by the children in this study who had SNHL with peaks of better hearing in the 2- to 4-kHz range and is consistent with our finding that 4000 Hz was the most stable audiometric frequency for children with CMV.

Regardless of the pathophysiology underlying their loss of hearing, it is imperative that newborns infected with CMV be identified at birth and assessed for SNHL. Cost-effective procedures are available for screening newborns for CMV infection (Balcarek et al, 1993), and hospitals have been encouraged to implement newborn hearing screening programs (National Institutes of Health, 1993). We know, however, that newborn hearing screening based on a high-risk registry will miss children with asymptomatic CMV infection (Hicks et al, 1993), and universal hearing screening of all newborns will fail to identify hearing loss in infected children who experience a delayed onset of loss (Fowler et al, 1999). For these reasons, any child suspected of having congenital CMV infection should be routinely monitored for late-onset hearing loss; if possible, children should be assessed every 6 to 12 months during the first 6 years of life. When SNHL occurs, options for amplification with hearing aids must be considered in terms of the likelihood that the impairment may fluctuate or progress in severity. The use of programmable hearing aids is strongly recommended to allow for changes in both the configuration and severity of the hearing impairment. Speech and language therapy must also be tailored to needs of this population (e.g., children with late-onset progressive loss will require therapy to help preserve voice and articulation skills). In summary, health care practitioners face the challenge of implementing programs for identifying, monitoring, and providing appropriate medical, audiologic and educational services for children with congenital CMV infection.

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