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Hearing Instability in Children with Congenital Cytomegalovirus: Evidence and Neural Consequences

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Objective/Hypothesis: Sensorineural hearing loss (SNHL) is a common sequela of congenital cytomegalovirus (cCMV), potentially exacerbating neurocognitive delay. The objectives of this study were to assess: (1) age at which SNHL in children with cCMV; (2) stimulability of the auditory system in children with cCMV following cochlear implantation (CI); and (3) whether features of magnetic resonance imaging (MRI) potentially are predictive of hearing outcomes.

Methods: In this retrospective study of a prospectively acquired cohort, 123 children with cCMV who were referred for hearing loss at a single tertiary referral hospital over 20 years were compared with an unmatched comparative group of 90 children with GJB2-related deafness. Outcome measures were results of newborn hearing screening (NHS), behavioral audiograms, and, in a subgroup of cochlear implant (CI) users, responses from the auditory nerve and brainstem evoked by CI at initial activation, as well as lesional volume of FLAIR-hyperintense signal alterations on MRI.

Results: All but 3 of 123 children with cCMV had confirmed and persistent SNHL. At birth, 113 children with cCMV underwent NHS, 31 (27%) passed in both ears and 23 (20%) passed in one ear (no NHS data in 10 children). At the first audiologic assessment, 32 of 123 (26%) had normal hearing bilaterally; 35 of 123 (28%) had unilateral SNHL; and 57 of 123 (46%) had bilateral SNHL. More than half (67 of 123, 54%) experienced hearing deterioration in at least one ear. Survival analyses suggested that 60% of children who developed SNHL did so by 2.5 years and 80% by 5 years. In the children who passed NHS in one or both ears, 50% developed hearing loss by 3.5 years in the ear, which passed unilaterally ($n = 23$ ears), and 50% by 5 years in bilateral passes ($n = 62$ ears). Hearing loss was significant enough in all but one child with isolated high-frequency loss for rehabilitation to be indicated. Hearing thresholds in individual ears were in the CI range in 83% (102 of 123), although duration of deafness was sufficient to preclude implantation at our center in 13 children with unilateral SNHL. Hearing aids were indicated in 16% (20 of 123). Responses from the auditory nerve and brainstem to initial CI stimulation were similar in children with cCMV-related SNHL compared with GJB2-related SNHL. Characteristic white matter changes on MRI were seen in all children with cCMV-related SNHL ($n = 91$), but the lesion volume in each cortical hemisphere did not predict degree of SNHL.

Conclusions: cCMV-related SNHL is often not detected by NHS but occurs with high prevalence in early childhood. Electrophysiological measures suggest equivalent stimulability of the auditory nerve and brainstem with CI in children with cCMV and GJB2-related SNHL. Hyperintense white matter lesions on FLAIR MRI are consistently present in children with cCMV-related SNHL but cannot be used to predict its time course or degree. Combined, the data show early and rapid deterioration of hearing in children with cCMV-related SNHL with potential for good CI outcomes if SNHL is identified and managed without delay. Findings support universal newborn screening for cCMV followed by careful audiological monitoring.

Key Words: Pediatric, cytomegalovirus, congenital, infection, hearing loss, sensorineural.

Level of Evidence: 3

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INTRODUCTION

Congenital cytomegalovirus (cCMV) infection affects approximately 0.5%–0.6% of pregnancies, making it one of the most prevalent congenital infections. It is the most frequent cause of nonhereditary hearing loss and is more common than all causes of congenital hearing loss, which occur at a combined prevalence of 3 per 1000 births.[1]

Hearing Loss in cCMV Requires Further Definition

Among newborns with cCMV, approximately 10% will have the more severe, symptomatic form of the disease, which is associated with high rates of SNHL (50%–60%).[2] The remaining 90% of children with cCMV are often labeled "asymptomatic." In the absence of routine screening programs, these children are typically not diagnosed with cCMV at birth; however, a noticeable proportion, 10%–15%, go on to develop long-term sequelae, which most commonly consists of isolated SNHL.[1,2] Because asymptomatic cCMV is much more common than the symptomatic form, it is the major contributor to the overall disease burden associated with cCMV.[3] For many children, without formal evaluation, their deficits will never be attributed to cCMV due to the subtlety in presentation, diagnostic challenges, and lack of awareness surrounding this diagnosis.[4]

Many cohorts of children with asymptomatic cCMV have been followed over time and reported in the literature. These studies have provided prevalence rates for development of SNHL and other outcomes in individuals with asymptomatic cCMV. The largest of these studies report long-term follow-up on cohorts as large as 420–651 children, showing cumulative incidence for the development of SNHL that ranges from 6.9% to 11.3% by 5–8 years of age.[3] An additional study with the longest follow-up (18 years) reports a cumulative incidence of 25%.[5] Because of the small numbers of children in these cohorts that develop SNHL (range 29–75 children), as well as the heterogeneity in the presentation of SNHL in cCMV, there are still questions about the use of rehabilitative methods and hearing outcomes of children with cCMV who develop SNHL. In addition, because the children in these studies were identified through routine screening for cCMV in the newborn period, they are privy to early, intensive, and repeated evaluations including monitoring of hearing. Their outcomes therefore may not be reflective of children who experience cCMV-related SNHL in areas where universal CMV screening is currently unavailable. While subject to its own biases, focusing on a larger cohort of children with cCMV-related SNHL as is the case in the current study may better display the natural history of the hearing loss itself including the diagnostic challenges that are at play for these children in a real-world setting. This is particularly relevant given the very few jurisdictions in which universal screening for cCMV is currently available. By focusing on a large group of children known to have cCMV-associated SNHL in the present study, we aim to further define the time course and degree of hearing loss, assess stimulability of the auditory system, and determine the potential predictive effects of cortical white matter lesions on hearing thresholds. Meeting these objectives would both add and complement data from the large asymptomatic cohorts currently reported in the literature.

Potential Consequences for Delayed Identification of cCMV in the Auditory System

A referral on newborn hearing screen (NHS) may be the only sign that an otherwise asymptomatic child has cCMV. However, many children with asymptomatic cCMV will pass their NHS but proceed to develop SNHL over time.[5,6] The progressive and at times partial (i.e., unilateral) nature of the SNHL, as well as the diagnostic challenges of detecting SNHL in prelingual children without identified risk factors, sets these children up for delayed diagnosis and ultimately, even further delayed, rehabilitation.[7] It is well known that early sensory deprivation has a substantial impact on development and that early intervention is important for allowing children with SNHL to best develop oral communication.[8] Without NHS, diagnosis of bilateral SNHL may not occur until 2–3 years of age and present with language delay.[9] If the hearing loss is unilateral, it is unlikely to be detected prior to school entry.[10] In all instances, the benefit that can be obtained through rehabilitation as well as the development of language are time-sensitive.[11]

Children with cCMV-related SNHL are at risk of profound SNHL either beginning at birth or developing during childhood. These children may benefit from rehabilitation with CI. Outcomes following CI are best in young children who have limited duration of auditory deprivation, but variability in CI outcomes remain, particularly in children with significant neurocognitive delay.[12] Stimulability of the auditory system following CI provides insight into future use of the device.[13] Responses from the auditory nerve and brainstem at initial CI use provide a measure of pre-implant hearing development, thereby defining the degree to which auditory development has been arrested.[14,15] Prior studies indicate clearer responses from the auditory nerve in infants who receive CIs compared with older children[16] and confirm that neural conduction along the auditory brainstem pathway requires stimulation for increasing efficiency.[14]

Children with cCMV are at Risk of Delays in Neuro-Cognitive Development

Children with cCMV are at risk for neurocognitive delays that extend beyond their sensory deficits alone. Many of the cohort studies in the literature also measure and report neurodevelopmental outcomes using a number of assessment tools. A recent systematic review notes that the cumulative incidence of neurodevelopmental impairments in children born with symptomatic cCMV is high and ranges from 30.7% to 66.7%.[3] In contrast, the prevalence in children with asymptomatic cCMV is lower, in the range of 0%–9.1%, and may differ significantly from the general population.[3] When evaluating neurocognitive outcomes in children with cCMV, it can be difficult in

these cohorts to untangle the negative impact of cCMV on central nervous system (CNS) processing from the impact of the SNHL and its rehabilitation, particularly when the diagnosis of SNHL and its treatment are delayed. Several studies have examined and separately reported on the neurocognitive outcomes of children with asymptomatic cCMV who did not have SNHL at birth. In these studies, the cumulative incidence of neurodevelopmental delays ranged from 2.9% to 9.1% over follow-up periods of 18 months–6 years; however, even these outcomes were impacted by the development of delayed-onset SNHL in the cohort, which ranged in incidence from 2.9% to 24.2% over the same follow-up periods. A thorough understanding of the characteristics of hearing loss and the details of its rehabilitation is therefore required to control for its impact on neurocognitive outcomes.

Potential Cortical Consequences for Delayed Identification of cCMV

The impact of cCMV extends beyond the inner ear. There are a number of radiologic features associated with cCMV. MRI findings occur along a spectrum with severe CNS anomalies including polymicrogyria, lissencephaly, hippocampal dysplasia, ventriculomegaly, cerebral atrophy, and cerebellar hypoplasia.[17] Some of the above imaging findings, such as polymicrogyria, represent disorders of cortical development, which contribute significantly to neurocognitive delay. Children with cCMV who had at least two of the classic brain imaging abnormalities demonstrated both a higher risk of clinical symptoms and neurodevelopmental impairment.[18] White matter changes with areas of signal hyperintensity on T2-weighted or FLAIR MRI sequences as well as germinolytic cysts are also part of this spectrum of CNS anomalies but are considered mild changes.[17] The significance of these less severe neuroimaging findings on neurocognitive outcomes is less well defined. In one study, volumetric assessment of such white matter lesions has been associated with lower intelligent quotient scores.[19] However, taken on a whole, the presence of milder changes has failed to demonstrate a consistent relationship with neurodevelopmental outcomes including SNHL.[20] This lack of consistency may be due to the inclusion of relatively small and heterogeneous cohorts of children with cCMV as well as methodologies based on a primarily descriptive assessment of CNS changes. Although the use of neuroimaging to predict outcome in children with cCMV requires further study, MRI has been demonstrated to be useful in supporting or suspecting a diagnosis of cCMV.[17,20] In fact, in many cases in children who develop SNHL, such findings on imaging may provide the first and only clue that a child's SNHL may be due to cCMV. Although CMV testing is without question more cost-effective than MRI, it requires the availability of a sample obtained in the early postnatal period. In the absence of an early suspicion for cCMV within the first weeks of life or the presence of universal screening for cCMV, imaging may be the only diagnostic tool available to assess for the possibility of cCMV in a child presenting with SNHL in jurisdictions where retrospective access to the child's neonatal dried blood spot (DBS) sample is not available.

The goal of the current study is to observe the clinical characteristics and natural history of a large prospectively acquired cohort of children who were followed for cCMV-related SNHL over an extended period of follow-up. This study evaluates: (1) age of diagnosis of cCMV-related SNHL; (2) stimulability of the auditory system in children with cCMV following CI; and (3) features of MRI potentially predictive of hearing outcomes.

To achieve these aims, the following hypotheses were tested: (1a) clinical characteristic of SNHL in children with cCMV will be heterogeneous with the largest burden of SNHL developing in infancy and childhood (<5 years of age); (1b) progressive deterioration of hearing will occur early, often and precipitously; (1c) a significant proportion of children with cCMV will not have hearing loss at the time of NHS and thus will experience delays in diagnosis and rehabilitation of later onset hearing loss; (2) cCMV-related SNHL may have more variability in damage to the cochlea leading to nonuniform survival of spiral ganglia cells and thus differences in the electrophysiologic responsiveness along the cochlea compared with children with other forms of congenital SNHL (i.e. homozygous GJB2 mutations); and (3) degree of white matter lesions, as measured by volumetric assessment, and their hemispheric distribution will predict clinical characteristics of the SNHL, specifically severity or differences in the laterality of presentation.

Identifying the challenges of diagnosis and rehabilitation in children presenting with cCMV-related SNHL by observing this prospectively acquired cohort with hearing loss will inform how to better minimize sensory deprivation in these children who are already at risk for developmental delay. Any predisposition that these children have toward neurocognitive impairment will be further compounded by their sensory deficits particularly if they go undetected and/or unrehabilitated. Instituting and improving methods for newborn CMV screening carries the potential to impact outcomes in this population.

METHODS

Study Design and Participants

This study was conducted at a pediatric tertiary care hospital. Institutional approval was obtained from the hospital research ethics board (REB# 1000064309, 1000007199, 1000002954). A clinical database allowed for identification of all children who received diagnostic testing for SNHL between January 1, 2011, and July 15, 2020, and were assessed by an otolaryngologist who investigated the etiology of their deafness. Given that the sample of children seen in the clinic and tested for cCMV between 2011 and 2020 was cross-sectional and included not only those who presented with a newly detected SNHL but also those who were being followed for SNHL, many had audiometric data that preceded CMV being implicated as the underlying etiology. Therefore, the audiometric data available for this cohort extended over a 20-year period from June 7, 2000 to July 15, 2020. In most cases, diagnosis of cCMV was based on polymerase chain reaction (PCR) detection of CMV DNA on the birth DBS. Retrospective testing of a child's DBS for

CMV DNA by PCR became a widespread practice at our institution in 2011.[21] DBSs are kept indefinitely after birth in our jurisdiction and can be used to retrospectively confirm a diagnosis of cCMV. In 2018, province-wide NHS was expanded to test all infants who referred on their NHS for CMV (PCR for CMV DNA on DBS) along with a number of other common genetic risk factors (i.e., common variants of GJB2 and SLC26A). In August of 2019, this screening further expanded with parental consent such that all infants were tested both for CMV (PCR for CMV DNA on DBS) and the common genetic risk factors irrespective of NHS results. In March of 2020, at the onset of the COVID-19 Pandemic, separate consent for DBS screening for cCMV was replaced by the consent obtained at the time of obtaining the DBS uncoupling it from the NHS. This was important given that in some jurisdictions, NHS was put on hold at the onset of the pandemic. Where the DBS was not available, the presence of SNHL combined with MRI findings consistent with cCMV was the basis for cCMV diagnosis (described below).

Of the 1117 children referred with hearing loss who underwent testing for cCMV, 123 (11%) were diagnosed with cCMV and included in the study (62 female, 61 male). In 111 of 123 cases (90%), the diagnosis of cCMV was based on detection of CMV DNA by PCR on the birth DBS, including 104 (94%) who presented with SNHL and had retrospective CMV PCR testing of their DBS and 6 (5%) who were detected through cCMV screening tied to the universal NHS Program (April 2018–July 2019) or the universal cCMV Newborn Screening Program (August 2019–2020). One child was diagnosed soon after birth by CMV PCR testing of urine and was followed due to the risk of developing SNHL. In the remaining 12 children, cCMV diagnosis was established clinically on the basis of both SNHL and presence of brain MR imaging findings characteristic of cCMV ($n = 3$ [2%] no neonatal DBS available for testing; $n = 9$ [8%] negative DBS for CMV). We considered the limitations posed by including these children as having cCMV based on their imaging and hearing loss findings alone. Although the characteristic findings of cCMV on MRI as outlined above are deemed nonspecific, the combination of imaging findings characteristics of hearing loss and prevalence rate support cCMV being the most likely diagnosis. Additionally, PCR testing of DBS is known to have a significant false-negative rate, making it feasible that a proportion of children with cCMV will test falsely negative on their DBS. That being said, there remains a possibility of overlap with other diagnoses such as RNaseT2 mutations, which share similar radiologic and clinical features but are significantly less common than cCMV and have a phenotype that consistently includes seizures (which were not found in any of our patients). In addition, the number of children whose diagnosis was dependent on their MRI findings was small relative to the larger cohort and therefore would be unlikely to significantly impact the findings.

The mean age of the children with cCMV-related SNHL included in this study at the time of their last diagnostic audiometric assessment was 6.0 (4.3) years. In comparison, the mean (SD) age of the children with cCMV-related SNHL included in this study at the time of analysis (July 15, 2020) was 8.7 (4.9) years. This difference reflects the many children who went on to receive cochlear implants as thresholds following the insertion of a cochlear implant were not included in data analysis. Nine children (8/123, 6.5%) with cCMV-related SNHL had additional diagnoses, which included achondroplasia, microtia with aural atresia, Beckwith–Wiedemann, neuroblastoma, branchio-otorenal syndrome, severe combined immunodeficiency disorder (SCID), autism, and genetic variants of uncertain clinical significance for mutations that code for Type 1 Usher syndrome. In all of these children, cCMV was likely the primary factor responsible for SNHL. This assumption was based on the characteristics of the hearing loss (i.e., unilateral, progressive) as well as the presence of MRI characteristics consistent with cCMV infection. In future work, if other nonauditory outcomes were to be examined, we would again need to consider the risks these additional diagnoses may pose in confounding the results.

A comparative group comprised of children with deafness due to homozygous Connexin 26 mutations (GJB2) was identified. Children with GJB2-related deafness were chosen as an unmatched comparative group for the following reasons: (a) they provide a large and homogeneous group of children typically with congenital onset, nonprogressive, severe to profound SNHL; (b) GJB2-related hearing loss is non-syndromic in nature and therefore the prevalence of developmental delay beyond that associated with SNHL is generally equal to that of the general population; (c) onset of hearing loss is typically at an early age. Other studies have also used a comparative group of children with GJB2-related SNHL to compare outcomes to those children with cCMV-related SNHL.[2223] The GJB2-related SNHL comparator group consisted of 90 children (35 female, 55 male). The mean (SD) age of this cohort at the time of the analysis (July 15, 2020) was significantly older ($p > 0.001$) than the cCMV-related SNHL group at 15.3 (5.0) years of age; they were a historical cohort in whom electrophysiologic data had been collected. About half (44 of 91) of the cohort with GJB2 related SNHL underwent retrospective DBS testing for CMV and were negative. One child initially considered for inclusion in the GJB2 group had a DBS positive for CMV; this patient was one of two deaf siblings who shared homozygous mutations for pathogenic variants in the GJB2 genes and had no findings suggestive of cCMV on MRI. Despite the likelihood that the etiology of deafness was due to mutations in the GJB2 genes, data from this child were excluded from further analysis. DBS was also unavailable in one patient in the GJB2 group. DBS testing for CMV was not routinely done for children with hearing loss in our program at that time and was thus not performed in 46 of 91 of the GJB2 cohort. The negative cCMV-status of 46 of 90 subjects was therefore uncertain; however, the imaging results were not suggestive of cCMV in any of the children in the GJB2 cohort.

Outcome Measures

Once our cohort was identified, electronic medical records were reviewed and patient demographics, NHS status, audiometric testing results, CNS imaging, and hearing rehabilitation records were collected.

Natural history and characteristics of hearing loss in children with cCMV

HEARING THRESHOLDS. In our jurisdiction, NHS for children without risk factors for SNHL is by protocol completed using automated otoacoustic emissions (AOAE) that include the frequency spectrum between 1 and 4 kHz. When risk factors for SNHL are present, an automated auditory brainstem response (AABR), which consists of a broadband click at 35 dB, is used. For the purposes of this study, referral on NHS testing was considered an indicator of hearing loss at that time point. Confirmative testing was carried out. Hearing loss was defined as a diagnostic test result where the average of all available frequencies was >25 dB HL. The nature of the hearing loss was defined as conductive if bone conduction thresholds were ≤ 25 dB HL, and all other losses were defined as having a sensorineural component. Middle ear status was assessed using tympanometry and/or otoscopic confirmation of the presence or absence of middle ear pathology by a pediatric otolaryngologist. Although conductive hearing losses were noted and excluded from assessments for progression, bone conduction thresholds were not available in many. Thus, we cannot rule out a conductive component in many time points, which could have contributed to

improvements or progression of hearing loss in all children. Moreover, including these potential conductive component fluctuations in hearing reflects a part of the natural medical history for these children. Nonetheless, the variability due to transient conductive hearing loss due to OME would be smaller than the progression of hearing loss identified in the cCMV group.

The configuration of the child's hearing loss (i.e., bilateral, unilateral, or asymmetric) was noted. The primary unit for the majority of the analysis was individual ears. For all children with suitable ear-specific audiologic thresholds, three measures of SNHL severity were calculated: (1) a 4-ton average (PTA) (500 Hz, 1, 2, and 4 kHz); (2) an average of all frequencies available; and (3) a 4-ton PTA plus thresholds for 6 and 8KHz where available. There were no significant differences between ear-specific means for each of the calculated measures (right ear: $F(2, 1843) = 0.05$, $p = 0.95$; left ear: $F(2, 1873) = 0.02$, $p = 0.98$); therefore, in all subsequent analyses, the average of all available frequencies[2] were used as a measure of the severity of ear-specific hearing loss.

HEARING LOSS PROGRESSION. Hearing loss progression by ear was defined in two ways: (1) significant change in hearing as defined by (1a) > 10 dB HL difference between the mean of all available ear-specific thresholds on the first and last audiogram; or (1b) development of SNHL in an ear that had previously passed NHS; or (2) by using for each child the averages of all available ear-specific thresholds over time to calculate the regression slope of change in thresholds with age (dB HL/year) for each ear ($n = 120$ children, 239 ears). For the latter analysis, an ear that passed its NHS was given a value of 25 dB HL at age 0, whereas for ears that referred on their NHS, the first diagnostic audiometric assessment was used. While numerically a slope of 0 would indicate a lack of change in hearing thresholds, this does not account for error and the degree of variation around the mean. Therefore, to be conservative in our estimates of progression, slopes >5 dB HL were defined as progression, slopes ≤2 dB HL defined as improvement in hearing, and slopes <5 dB HL but ≤2 dB HL representing stable hearing (i.e., stability of hearing was defined as no more than a 5 dB HL drop per year and no more than a 2 dB HL improvement per year).

Both definitions of progression do pose some limitations, which is why two methods were included as defining the characteristics of progression is meaningful in cCMV-related hearing loss. For example, in the setting of method (1a) when examining the mean of all hearing thresholds over time. It is possible that a different number of thresholds are available on the most recent audiometric assessment compared with the first, which may lead to an assumption of progression, which may be due to hearing loss not having been detected in the first assessment instead. Despite this risk, we elected to use the mean of all available hearing thresholds as there is significant session-to-session variability as well as variability over time in children as they develop.

CATEGORIES OF SNHL OVER TIME. Based on this model, several categories of SNHL over time were defined including (1) bilateral progressive HL defined as the slope of the averaged thresholds over time >5 dB HL in both the left and the right ear, (2) unilateral progressive where the slope of the averaged thresholds over time of either the left or right ear >5 dB HL while that of the contralateral ear were <5 dB HL, and (3) stable bilateral where the slope of the averaged thresholds over time of both the right and the left ear were <5 dB HL.

Electrophysiologic responses to implantation. Children with bilateral cCMV-related SNHL were felt to be CI candidates if they had hearing thresholds in the severe to profound range and were unlikely or unable to obtain or maintain oralism with conventional hearing aids. For those with unilateral or asymmetric SNHL, the poorer ear was considered a CI candidate if hearing thresholds were severe to profound and the child was felt to be receiving less benefit from a conventional hearing aid than they would receive from a CI. In cases of unilateral SNHL, the duration of deafness needed to be less than 4 years, to be considered a CI candidate at our institution. Ear-specific measures of aided and unaided speech discrimination scores were also used to determine candidacy when a child was able to participate in this aspect of the evaluation.

The electrophysiologic responses following CI were measured and reviewed for our cohort of children with cCMV-related SNHL. Outcome measures included (1) amplitude growth, (2) maximum amplitude, and (3) threshold of the evoked compound action potential (ECAP) and evoked auditory brainstem response (EABR) on electrodes 3, 9, and 20. Additionally, wave and inter-wave (waves III–V and II–III) latencies of the EABR were measured. While all responses can either be recorded in an awake child or under anesthesia, ECAPs were recorded in the operating room, while EABR responses were recorded on day 1 of CI activation given that they are lengthier to record and would have incurred considerable additional anesthetic time. These electrophysiologic responses in children with cCMV-related SNHL were compared with a group of children with GJB2-related SNHL to explore whether hearing status at birth, progression of hearing loss, or other characteristics related to etiology of deafness may impact these measures. Additionally, these electrophysiologic measures have been previously studied in children with GJB2-related SNHL.[15] The methods for EABR recordings have been previously published.[14]

Volumetric assessment of white matter lesions: MRI acquisition, data retrieval, image segmentation. Variables that were considered when deciding whether to obtain MRI in children with SNHL included, (1) severity of SNHL and diagnostic need during evaluation for CI candidacy (2) as part of an etiologic workup in a child who was either old enough (typically >6 years) or young enough (typically <6 months for scanning during natural sleep) to undergo imaging without the need for general anesthesia. For some children, imaging was ordered at an outside institution and transferred for review.

All patients scanned at our institution underwent brain MRI at 1.5 T or 3 T across various vendors (Signa, GE Healthcare, Milwaukee, Wisconsin; Achieva, Philips Healthcare Best, The Netherlands; Skyra, Siemens Healthineers, Erlangen, Germany). An SNHL protocol was performed (i.e., brain and internal auditory canal views) with surface and head coils. The sequences acquired included a 2D axial T2 FLAIR (TR/TE, 7000–10 000/140–170 ms; 3–6 mm slice thickness; 3–7.5 mm gap) as part of the standard departmental protocol. All images were stored on Picture Archiving Communication System (PACS), for accessible viewing and measuring on workstations. All MRI data were extracted from the PACS and were de-identified for further analyses. White matter lesion segmentation was performed by a board certified radiologist (MS) using 3D Slicer (ver. 4.10.2)[24] (http://www.slicer.org). Semi-automated lesion segmentation on FLAIR images was performed with the Level-Tracing-Effect tool. This semiautomatic approach had been found superior to multiuser manual delineation with regard to reproducibility and robustness of results.[25] Final and proper placement of regions of interest (ROIs) was confirmed by a fellowship-trained pediatric neuroradiologist with 6 years of neuroradiology research experience (MWW). Right hemispheric and left hemispheric white matter lesional volumes were extracted from the ROIs on FLAIR images (Fig. 1). Comparisons were made between both total lesional volumes as well as lesional volumes by hemisphere, relative to age at scan, severity of hearing loss. Additional comparisons were made to measure the presence or absence of an effect of asymmetric hearing thresholds on lesion lateralization.

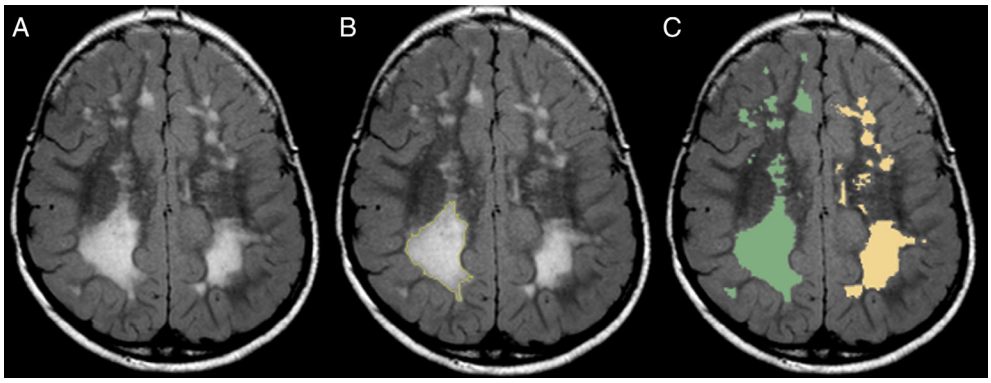

Fig. 1. Axial fluid-attenuated inversion recovery (FLAIR) sequence in a 2-year old with cCMV. Bi-hemispheric FLAIR hyperintense white matter lesions are displayed before (A), during (B), and after (C) the segmentation. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Statistical Analysis

Descriptive statistics were calculated for the overall sample as well as within the subgroups based on NHS. Means and standard deviations were computed for continuous variables. Between-group comparisons were conducted using Student's *t*-tests. Repeated measures ANOVA was used for within-group comparisons. Linear mixed effects regressions were conducted using the lmer4 package.[26] Model effects were described by Type III analysis of variance tables using Satterthwaite's method. Least-squares means were used for post hoc comparisons of factors in the mixed models with Satterthwaite method for correcting degrees of freedom. Using this method, a regression model was developed for the purpose of generating slopes that are conditional modes of the random effects by participant from the associated fitted mixed model. Definitions of slope criteria were chosen based on clinic criteria where stability in hearing was defined for each individual, which could then be used to categorize progression of hearing loss and provide predicted mean hearing threshold values over time as outlined above. In addition, Kaplan–Meier survival analysis was used to estimate the proportion of children with SNHL by age for both the group of children with cCMV- and GJB2-related SNHL. The pattern of hearing loss development over time was also estimated using a survival analysis among children who initially passed their NHS. For all comparisons, $p < 0.05$ was considered statistically significant. RStudio (Version 1.0.153 – © 2009–2017 RStudio, Inc.) statistical software was used for all analyses.

RESULTS

Natural History and Characteristics of Hearing Loss in Children with cCMV

Newborn hearing screen results. The majority of children who were diagnosed with cCMV had undergone NHS (113 of 123, 92%), Table I. Ten children (8%) had either not received NHS or the result was unknown. The most common recorded reason for not receiving NHS was having been born in a jurisdiction in which NHS was not available. Of the 113 children with a recorded result, 31 (27%) passed their NHS bilaterally and 23 (20%) passed in one ear (15 right, 8 left). More than half of the cohort (59 of 113, 52%) referred bilaterally. Out of a total of 226 screened ears, more than one-third (85 of 226, 38%) passed their NHS.

Over a 20-year period, a total of 732 diagnostic audiometric assessments were reviewed for the 123 children with cCMV. On average (SD), each child with cCMV received 6.6 (5.5) diagnostic assessments, with the majority (88%, 108 of 123) having two or more assessments. Those who had a single available diagnostic assessment (22%, 15 of 123) had normal hearing (3), were implanted immediately following the single assessment (2), were followed elsewhere after coming to our center specifically for vestibular evaluation (1) or CI evaluation (9) and either did not wish or fit criteria for implantation, or who had developmental delay that precluded meaningful results beyond their initial ABR (1), despite having multiple attempts at behavioral assessments. A total of 1152 diagnostic audiometric assessments were reviewed for the 90 children with GJB2-related hearing loss. The mean age at which a confirmed diagnosis of SNHL was made was significantly lower in children who were referred on their NHS in at least one ear (mean age = 1.84 years, SD 1.8, Range 0.1 to 7.9 years) than in either children who passed their NHS in both ears (mean age = 4.2 years, SD 2.7, Range 1.3 to 15.4 years) ($p < 0.001$) or children who did not receive NHS (mean age = 5.9 years, SD 2.2, range 3.2 to 9.6 years) ($p < 0.001$). It is important to note that the mean age at diagnosis for children who passed their NHS was not significantly different than that of children who did not receive NHS ($p = 0.08$). To capture and model what happens in the interval between a passed newborn hearing screen in one or both ears and subsequent detection of SNHL in children with cCMV, Kaplan–Meier survival analysis was used with the measured occurrence being the detection of hearing loss in an ear following a passed NHS in that same ear. By this method, we estimated that among children who develop unilateral cCMV-related SNHL, 50% of ears that passed NHS ($n = 23$ ears), will develop SNHL detected by 5 years of age (Fig. 2). For those children with cCMV-related SNHL whose ears passed NHS bilaterally ($n = 62$ ears), 50% will develop SNHL detected by 3.5 years of age, increasing to more than 70% of ears by 7 years of age (Fig. 3). In many cases, the true age of onset of SNHL is unknown and may be very different than the age at diagnosis, and this is

TABLE I.
Newborn Hearing Screening (NHS) Results

Received NHS	Number ($n = 123$)	NHS Result	Number ($n = 113$)
Yes	113 (92%)	Pass	31 (25%)
		Bilateral	8
		Unilateral	23
		Refer	83 (67%)
		Bilateral	59
		Unilateral	23
Unknown/No Screen	10 (8%)		

particularly relevant for children who did not receive or who passed their NHS.

More than one-third of children (48 of 123, 39%) experienced delays in diagnosis. Many of these were either children who missed their NHS or were born in a jurisdiction in which NHS was not available (10 of 48, 21%) or children who passed their NHS who then went on to develop progressive SNHL (28 of 48, 58%). For this latter group, the assumption of delay was an uncertain one and often based on parental observation or the presence of a language delay suggesting that the onset of the SNHL occurred prior to actual presentation and formal diagnosis. Children who experienced a delay in diagnosis were, by definition, on average significantly older (mean age = 4.5 years, SD 2.6) at the time their SNHL was diagnosed compared with the cohort that did not experience a delay in diagnosis (mean age = 1.6 years, SD 1.5) ($p < 0.01$). Delays still occurred in children who were referred on their NHS initially but were lost to follow-up (10/48, 21%), highlighting that NHS systems remain imperfect.

Severity and configuration of hearing loss. Of the 123 children in the cCMV cohort, 120 of 123 (98%) had a diagnostic assessment consistent with SNHL at the time of analysis and 3 of 123 (2%) had bilaterally normal hearing thresholds at the time of analysis. Of these three, one referred unilaterally on NHS but normalized by the time diagnostic testing was performed, one had early hearing assessments that revealed hearing loss confirmed over time to be entirely conductive in nature, and one was referred for speech delay whose subsequent testing revealed normal hearing. We opted to keep these three children in the cohort as they are representative of the reality and limitations of hearing screening and assessment in the pediatric population.

The mean age at the time of data analysis for the cCMV-related SNHL cohort was 8.8 years (SD 4.9, Range 0.9–23.9 years) and the mean duration of follow-up since the onset of SNHL was 7.9 years (SD 4.9, Range 0.9–20.4 years). Mean age at recognition of SNHL was 1.1 years (SD 2.2, Range 0–15.4 years) for all ears with SNHL. Mean age of the child at recognition of SNHL in either one or both ears was similar at 1.0 years (SD 2.1, Range 0–15.4 years). Congenital SNHL was present in 143 of 246 ears (58%), whereas 40 of 246 (16%) of ears

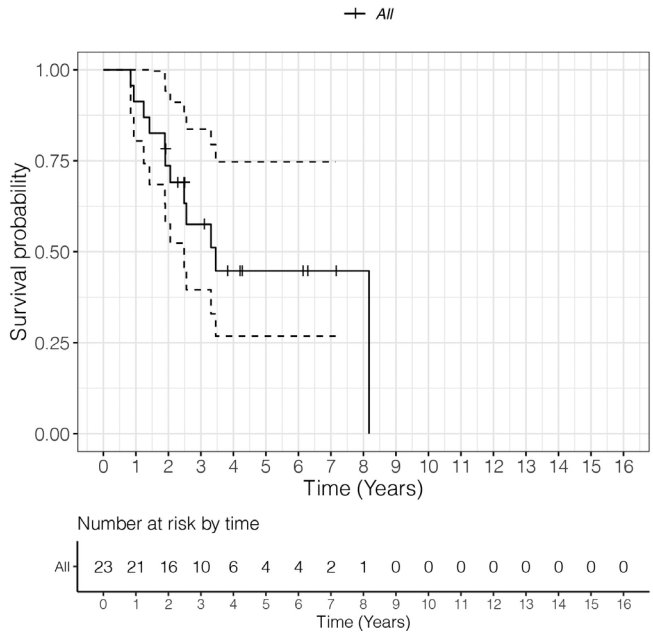

Fig. 2. Survival analysis predicting development of hearing loss in children who passed NHS in one ear demonstrates that 50% of ears that individually passed NHS ($n = 23$ ears) develop SNHL detected by 5 years of age.

had normal hearing and 63 of 246 (26%) of ears had non-congenital SNHL (Table II). The mean age at time of the first diagnostic audiologic assessment available was 2.8 years (SD 2.5). At the time of the first audiologic assessment, 26% (32/123) of children had normal hearing, 28% had unilateral SNHL, and 46% had bilateral SNHL (Table III). Kaplan–Meier survival analysis was used, with the occurrence defined as the detection of bilateral SNHL in children with cCMV. Using these methods, we estimated that among children who develop bilateral cCMV-related SNHL ($n = 87$), more than 50% will do so at birth, increasing to 75% by 2 years of age and 90% by 5 years of age (Fig. 4). One-third of children were born with profound SNHL in at least one ear (80 of 248, 32%).

Progression of hearing loss. When comparing the first audiologic assessment to the last available audiologic assessment where progression was defined as a change in the mean of all available ear-specific thresholds of >10 dB HL, nearly half of the ears (104 of 246, 42%) experienced progression, and overall, more than half of the children experienced progression in at least one ear (66 of 123, 54%), (Table IV). Of the 123 children in the cohort, 3 (2%) had bilaterally normal hearing thresholds at the time of analysis and were thus not assessed further for progression, leaving the denominator of children assessed to be 120. Children with cCMV-related SNHL demonstrated progression across all configurations of SNHL. For example, 40% of those with unilateral SNHL initially progressing to bilateral SNHL over time (14 of 35) (Table III). More than half of the ears (80 of 145, 55%) with congenital SNHL had profound SNHL at the outset, and therefore further deterioration of thresholds in this cohort would not alter treatment options or outcomes. Of

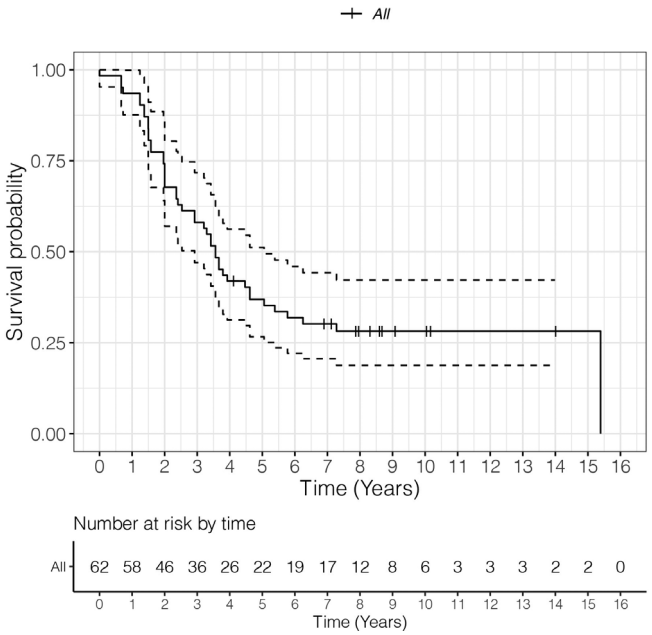

Fig. 3. Survival analysis predicting development of hearing loss by ear in children who passed their NHS bilaterally demonstrates that 50% of children whose ears passed NHS bilaterally ($n = 62$ ears) will develop SNHL detected by 3.5 years of age, increasing to more than 70% of ears by 7 years of age.

those remaining ($n = 65$ ears), two-thirds demonstrated progression (44 of 65 ears, 68%), with only a third demonstrating stable SNHL (21 of 65 ears, 32%) (Table III).

The frequent progression in their hearing thresholds that children with cCMV-related SNHL experience over time was demonstrated by a mixed model regression to display the change in hearing over time for each ear (left ear data from 119 children, right ear data from 120 children). Regression slopes (dB HL/year of age) within the "worsening" criteria defined for CMV (slope >4 dB decline/year) are shown in Figure 5 to display the change in hearing over time for each ear. Using these regression slopes, children were placed into three categories of hearing over time: (1) stable bilateral (43 of 119, 36%); (2) bilateral progressive (38 of 119, 32%); (3) asymmetric progressive (38 of 119, 32%). Using these classifications, well over half of children who had or developed cCMV-related SNHL went on to progress over time (76 of 119, 64%). Pure tone averages for the children in the cCMV group are shown in Figure 6. For children with stable SNHL bilaterally (Fig. 6A), there appear to be two separate groups, (1) those with bilateral severe to profound loss without residual hearing and (2) those with mild to moderate thresholds, which remain stable over the time of the study. As shown in Figure 6B, bilateral progressive loss in 38 children with cCMV was often precipitous with declines of 11.5 (6.6) dB HL/year in the left ear and 10.6 (6.7) dB HL/year in the right ear. Of the 38 children with asymmetric progression (Fig. 6C), 17 had left ear progression of 7.5 (6.4) dB HL/year and 21 had right ear progression of 7.8 (5.9) dB HL/year. In comparison, children with GJB2-related SNHL experienced little progression in their hearing thresholds over time, as demonstrated by regression slopes (dB HL/year of age) within the "stable" criteria defined for CMV (slope <4 dB decline/year) (Fig. 7).

TABLE II.
Ear-Specific Severity and Configuration of Hearing Loss

	Right Ear	Left Ear
Normal	23	17
Congenital	65	78
Profound	34	46
Progressive	21	21
Stable	10	11
Non-congenital progressive	35	28
Progressive to profound	12	8

TABLE III.
Change in Configuration of Hearing Loss by Child Over Duration of Follow-up

Configuration of Hearing Loss	First Test ($n = 123$)	Last Test ($n = 123$)
Normal	32 (26%)	3 (2%)
Unilateral	35 (28%)	32 (26%)
Bilateral	57 (46%)	89 (72%)
Normal → normal		4 (3%)
Normal → unilateral		10 (8%)
Normal → bilateral		18 (14%)
Unilateral → unilateral		21 (17%)
Unilateral → bilateral		14 (11%)
Bilateral → bilateral		57 (46%)

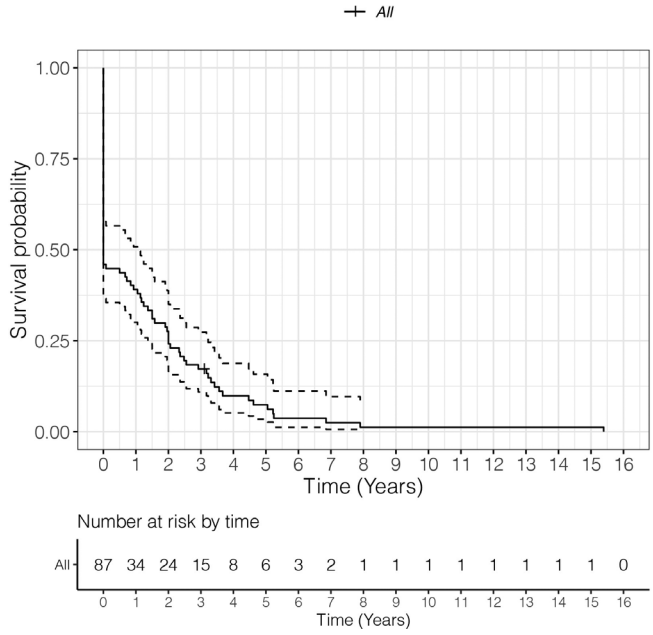

Fig. 4. Survival analysis predicting time to development of bilateral hearing loss.

TABLE IV.
Prevalence of Ear-Specific Progression

Progression ($n = 123$)		
	Yes	No
Right ears	55 (45%)	68 (55%)
Left ears	49 (40%)	74 (60%)
Overall (at least one ear)	66 (54%)	57 (46%)

Access to sound for our cohort diminished at a very early developmental age, with, on average, thresholds (SD) becoming moderately severe by 6 months of age (61.6 (26.1) dB HL), and severe by 2 years of age (68.7 (30) dB HL). In comparison, children with SNHL from GJB2 on average start with profound thresholds, which remain profound over time. Specifically predicted thresholds in the GJB2 group were on average 96.5 (9.5) dB HL at 6 months of age and, on average, 96.5 (8.7) dB HL at 2 years of age (Table V). This model further supports the above assumption that it is likely many children who passed their NHS and went on to develop cCMV-related SNHL did so early with a gap occurring prior to actual detection.

Progression can also be predicted using survival analysis, which allows us to determine not only proportion of those effected but adds the ability to examine time course to progression. Using survival analysis, we estimate that, among children with cCMV who develop SNHL, 50% of ears have SNHL identified at birth. Among children who develop hearing loss, the proportion of ears with identified SNHL increases to nearly 70% by 2.5 years of age and reaches over 80% by 5 years of age (Fig. 8). In comparison, we estimate that in children with GJB2-related deafness, more than 60% of ears are identified as having SNHL at the time of birth, increasing to close to 100% by age 2.5, with all ears identified with SNHL by 3 years of age (Fig. 8). When SNHL developed asymmetrically in the cCMV group, the mean duration between the detection of SNHL in the first ear and the progression of SNHL in the contralateral ear was 3.4 years (SD 2.4, Range 0.1–7.9 years).

All methods for defining progression yielded similar proportions of children experiencing progression. Exactly 55% of children were defined as having progression due to change in threshold or development of SNHL subsequent to a passed NHS, 64% experienced progression by the slope of the mixed model regression, and survival analysis suggests that 50% of children who developed hearing loss did not experience a congenital loss.

Rehabilitation of hearing loss due to cCMV. Of the 134 children in the cohort, 3 (2%) had bilaterally normal hearing thresholds at the time of analysis and did not require any form of hearing rehabilitation. As outlined in detail above, these children displayed concern for

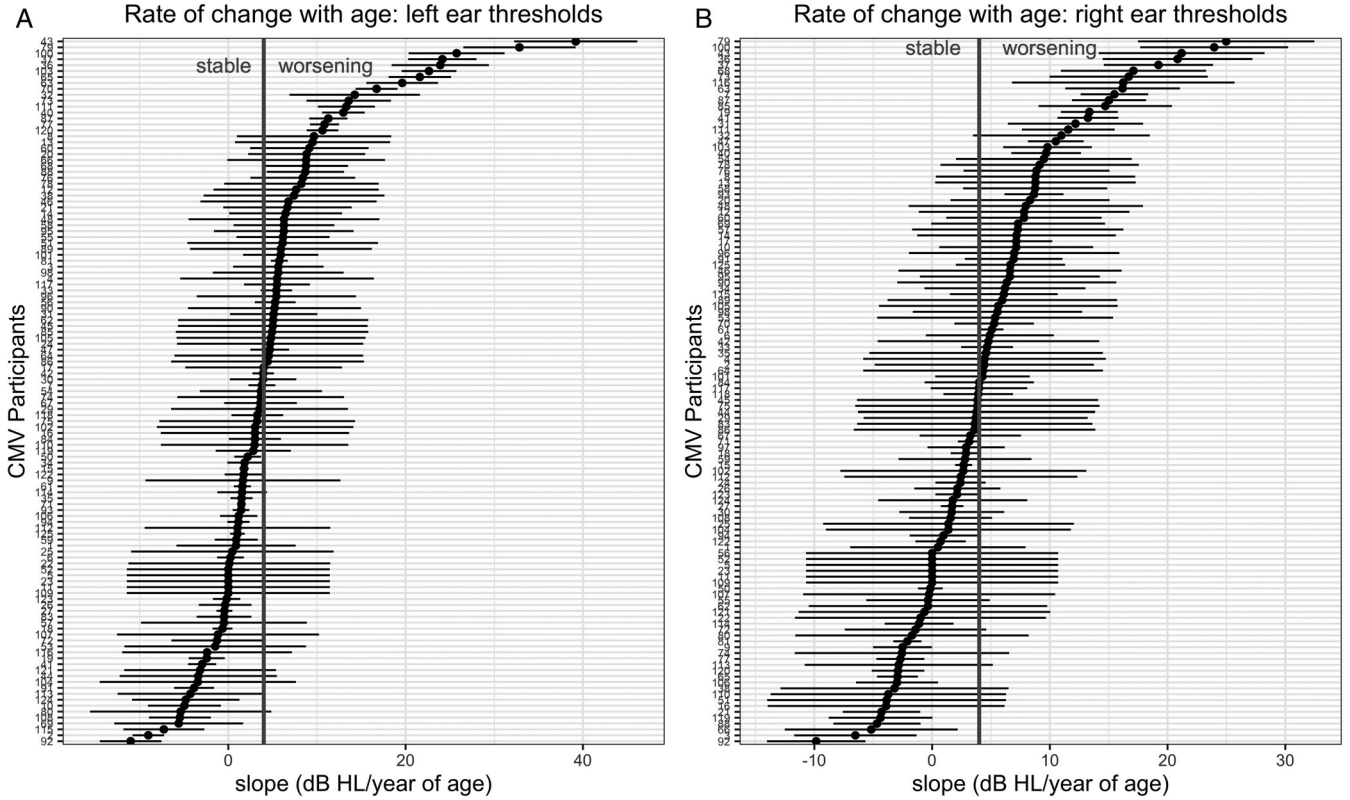

Fig. 5. Ear-specific rate of change of hearing thresholds (mean of all available frequencies) over time as displayed by the slope of a mixed model regression for children with cCMV-related SNHL. Criteria for progressive deterioration of hearing versus stable hearing are shown at 4 dB HL/year

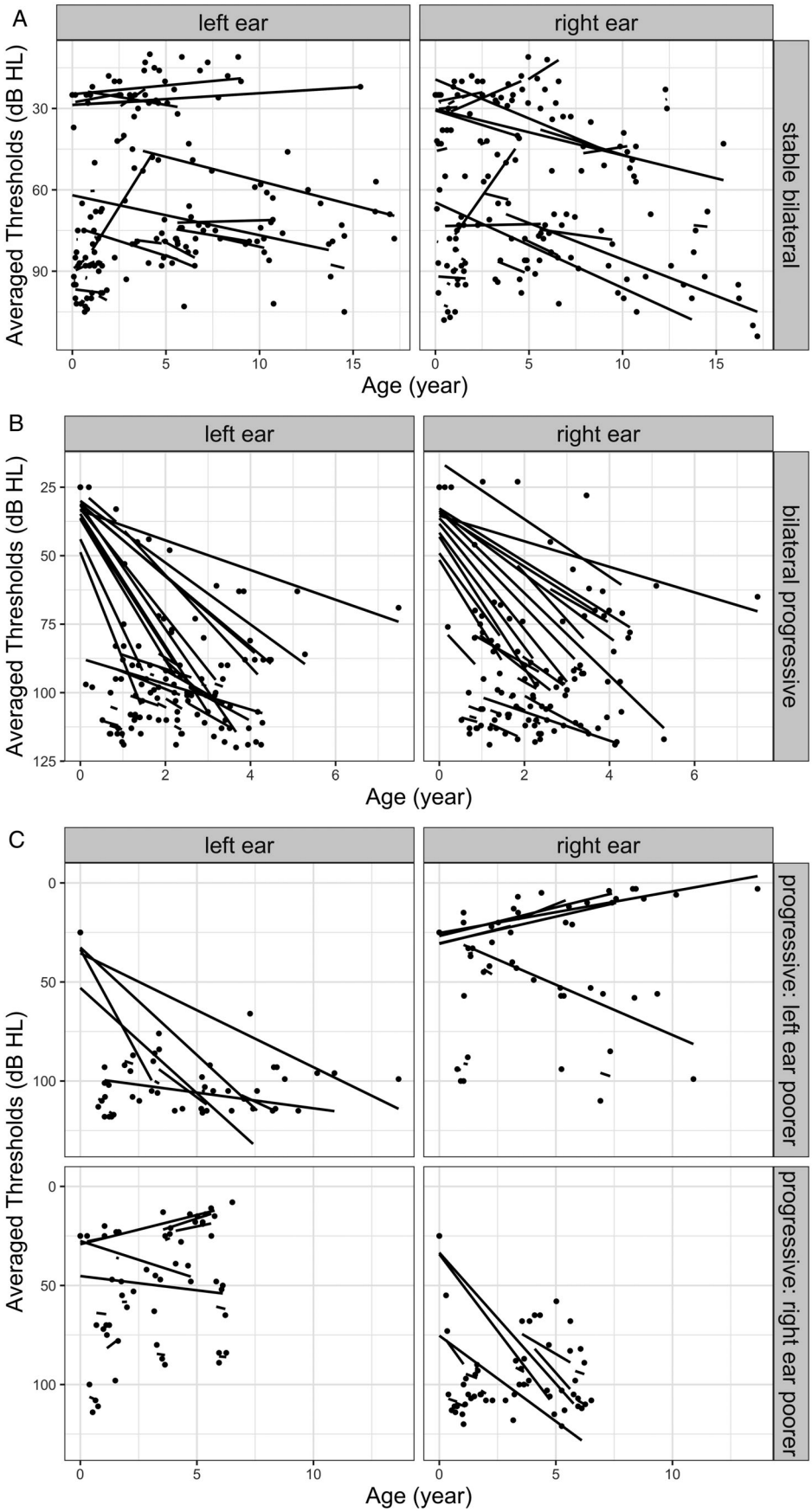

Fig. 6. Categorical classification of types of ear-specific changes in hearing thresholds (mean of all available frequencies) over time as displayed by the slope of a mixed model regression for children with cCMV-related SNHL.

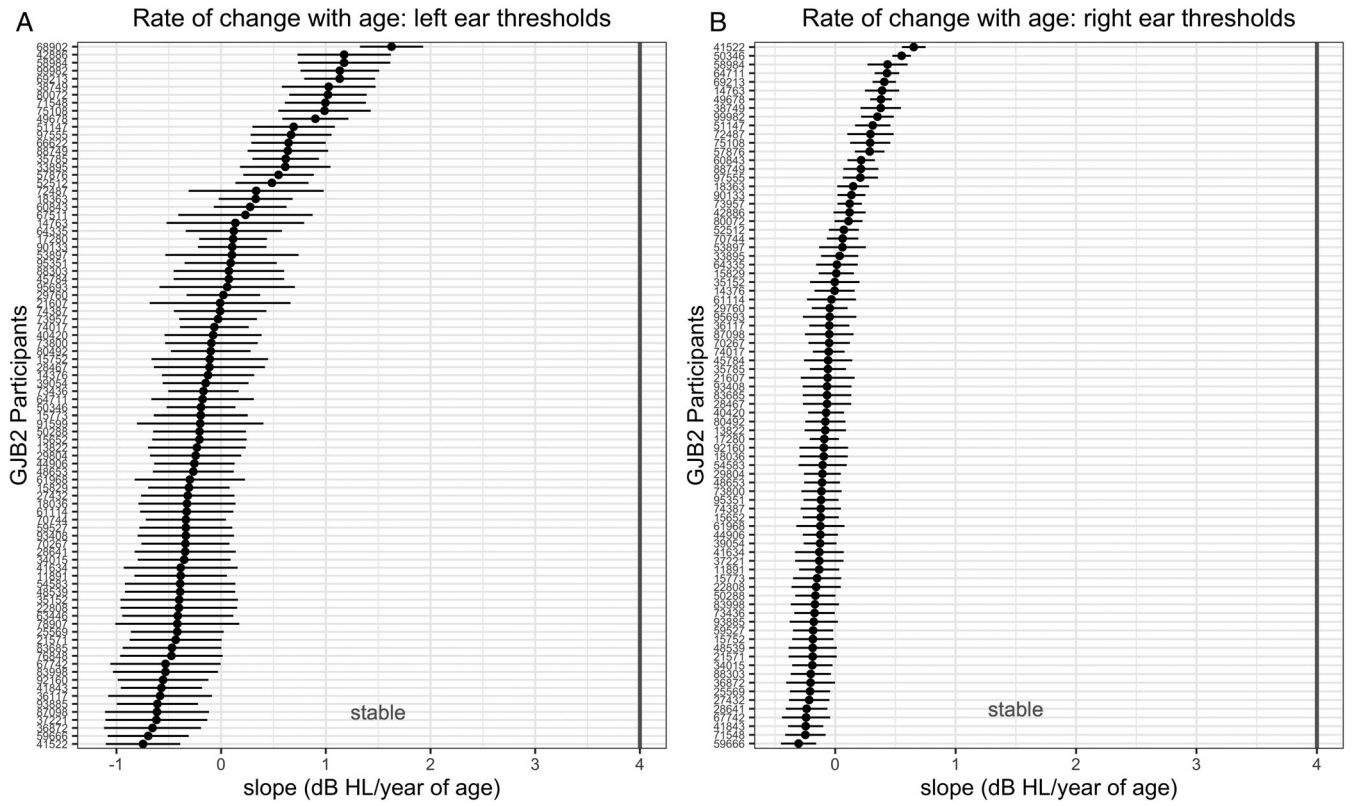

Fig. 7. Ear-specific rate of change of hearing thresholds (mean of all available frequencies) over time as displayed by the slope of a mixed model regression for children with GJB2-related SNHL. Criteria for progressive deterioration of hearing versus stable hearing are shown at 4 dB HL/year

hearing loss at an early time point that was not confirmed with subsequent diagnostic testing (i.e., temporary conductive hearing loss). Additionally, a single child had isolated bilateral high-frequency loss where a hearing aid was not felt to be indicated at the time of analysis. In 54% of the cCMV cohort (20 of 37), hearing aids were indicated either bilaterally (16 of 20, 80%) or unilaterally (4 of 20, 20%). However, a number of children did not wear their hearing aids despite being indicated (8 of 20, 40%), with 6 of 8 (75%) not wearing aids bilaterally and 2 of 8 (25%) not wearing them unilaterally. A third of this cohort (13 of 37, 35%) had single-sided deafness where the degree of SNHL is too significant for a hearing aid to be beneficial. When we consider this group specifically, using survival analysis, we estimated that among children with cCMV who are born with unilateral profound SNHL ($n = 41$), that more than 40% will develop contralateral hearing loss detected by 5 years of age, increasing to almost 65% by age 8 (Fig. 9).

TABLE V.
Predicted Mean Ear-Specific Hearing Thresholds by Age and Etiology

Predicted Hearing Thresholds (dB)	Left					Right				
Age (years)	*n*	Mean	SD	SE	CI	*n*	Mean	SD	SE	CI
Congenital cytomegalovirus										
0.5	118	66.64	26.86	2.47	4.90	118	61.64	26.16	2.41	4.77
1	118	68.96	27.22	2.51	4.96	118	63.99	27.07	2.49	4.94
2	118	73.59	29.50	2.72	5.38	118	68.70	29.90	2.75	5.45
3	118	78.23	33.45	3.08	6.10	118	73.40	33.77	3.11	6.16
GJB2										
0.5	80	96.53	9.46	1.06	2.10	80	93.65	10.13	1.13	2.25
1	80	96.52	9.20	1.03	2.05	80	93.65	10.02	1.12	2.23
2	80	96.50	8.69	0.97	1.93	80	93.65	9.81	1.10	2.18
3	80	96.48	8.18	0.91	1.82	80	93.65	9.60	1.07	2.14

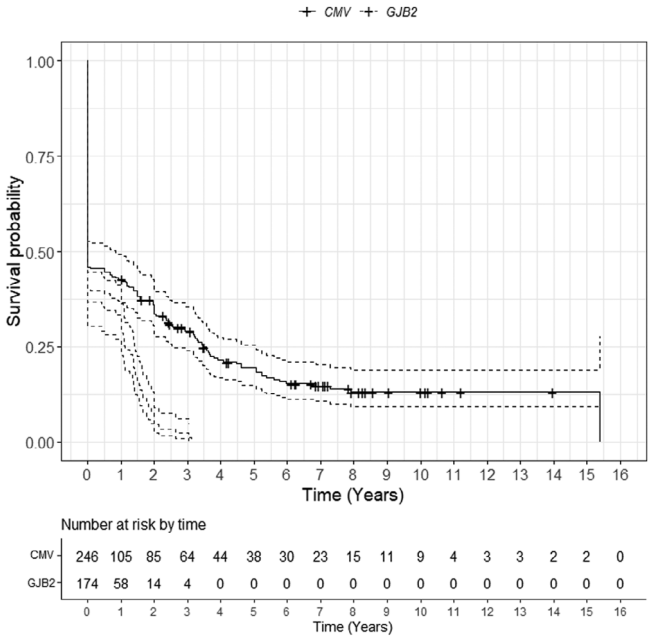

Fig. 8. Survival analysis predicting the development of ear-specific hearing loss for children with cCMV-related SNHL and GJB2-related SNHL.

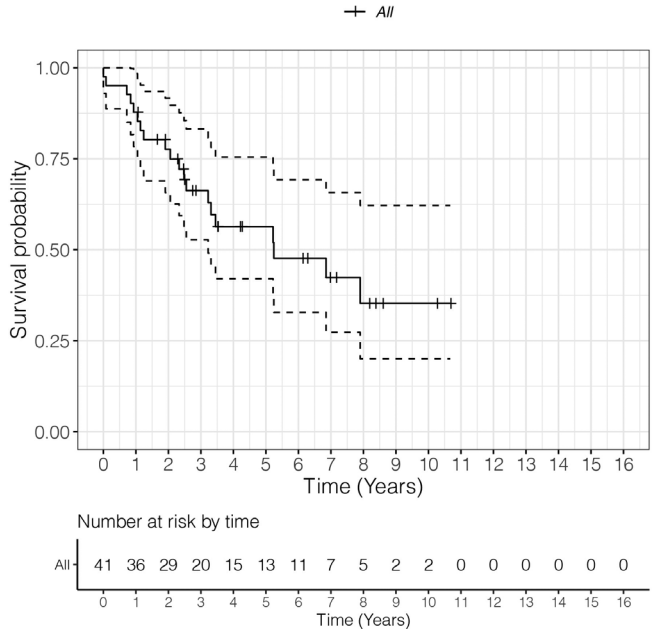

Fig. 9. Survival analysis predicting the development of contralateral hearing loss in children with cCMV-related SNHL who are born with or have early acquired unilateral profound SNHL.

Seventy percent of the children with cCMV-related SNHL (86 of 123) underwent CI. In 48 of 123 children (39%), bilateral CI was indicated, with the majority (39 of 48, 81%) receiving simultaneous bilateral CI and the remainder (9 of 48, 19%) receiving sequential bilateral CI. Exactly four of nine children (44%) receiving sequential CI were, by today's criteria, candidates for bilateral CI at the time of their first implant; however, 3 of 4 were implanted at a time where bilateral CI was not performed, whereas for the fourth patient it was parental preference to proceed only with unilateral implantation initially. The remaining 5 of 9 (56%) progressed into sequential candidacy, with the mean (SD) inter-implant interval being relatively brief (2.8 (2.4) years; range: 0.5–6.9 years). An additional 38 of 123 children (31%) received unilateral CI, with 17 of 38 (45%) receiving them for the rehabilitation of SSD while the remaining 21 of 38 (55%) wore contralateral amplification. At the time of analysis, three additional children were undergoing assessment for CI for SSD. Roughly equal numbers of children received unilateral CI for single-sided deafness (17 of 38, 45%) and asymmetric SNHL (21 of 38, 55%). All children with asymmetric SNHL wore a hearing aid on the better hearing ear and thus received bilateral access to sound through this bimodal fitting.

Electrophysiologic Responses to Implantation

For the cohort included in the ECAP analysis, mean age (SD) at the time of ear-specific implantation for the cCMV group ($n = 54$) was 4.0 (3.5) years (range 0.45–16.9 years) and not significantly different ($p = 0.31$) that of the GJB2 group ($n = 61$) at 4.3 (4.3) years (range 0.7–17.8 years). For the cohort included in the EABR analysis, mean age (SD) at the time of ear-specific implantation for the cCMV group ($n = 41$) was 3.7 years (SD, range 0.5–16.9 years) and was not significantly different ($p = 0.31$) than that of the GJB2 group ($n = 67$) at 4.3 (4.3) years (range 0.7–17.8 years).

ECAP responses. There were no significant differences in either the amplitude growth ($F(1, 111) = 0.55$, $p = 0.46$) (Fig. 10) or the maximum amplitude ($F(1, 114) = 0.13$, $p = 0.72$) of the ECAP responses between the groups of children with deafness due to cCMV versus GJB2 (Fig. 11). By contrast, ECAP amplitude growth was steepest for the apical electrode and most shallow for the mid-array electrode ($F(2, 3087) = 342.15$, $p < 0.00001$) and was significantly affected by the type of implanted electrode array used ($F(6, 611) = 16.7$, $p < 0.0001$). The maximum amplitude model similarly demonstrated largest ECAP amplitudes were evoked from the apical electrode ($F(2, 383) = 22.0$, $p < 0.0001$) and that the type of implanted cochlear array interacts with the location of the electrode being stimulated ($F(12, 384) = 2.74$, $p = 0.001$). An effect of ear (higher amplitudes in the left ear: $F(1, 257) = 5.2$, $p < 0.02$) was found as well as an interaction between ear and type of array ($F(6, 336) = 3.7$, $p = 0.001$) (Fig. 11). ECAP thresholds (level at ECAP amp = 0 + 5 CU) were significantly higher in the children with cCMV than those in children with GJB2 ($F(1, 106) = 7.6$, $p = 0.007$) but only by 11.3 (SE = 32.0) CU as estimated by the model (Fig. 12). There was no effect of the degree of SNHL at young ages (averaged thresholds across frequencies predicted at 6 months) (Left ear: $F(1, 87) = 0.001$, $p = 0.97$; Right ear: ($F(1, 88) = 0.06$, $p = 0.81$) or whether children's hearing remained stable or progressed (slope >4 dB HL/year) in one or both ears on maximum ECAP amplitude ($F(2, 87) = 0.22$, $p = 0.81$) (Fig. 13).

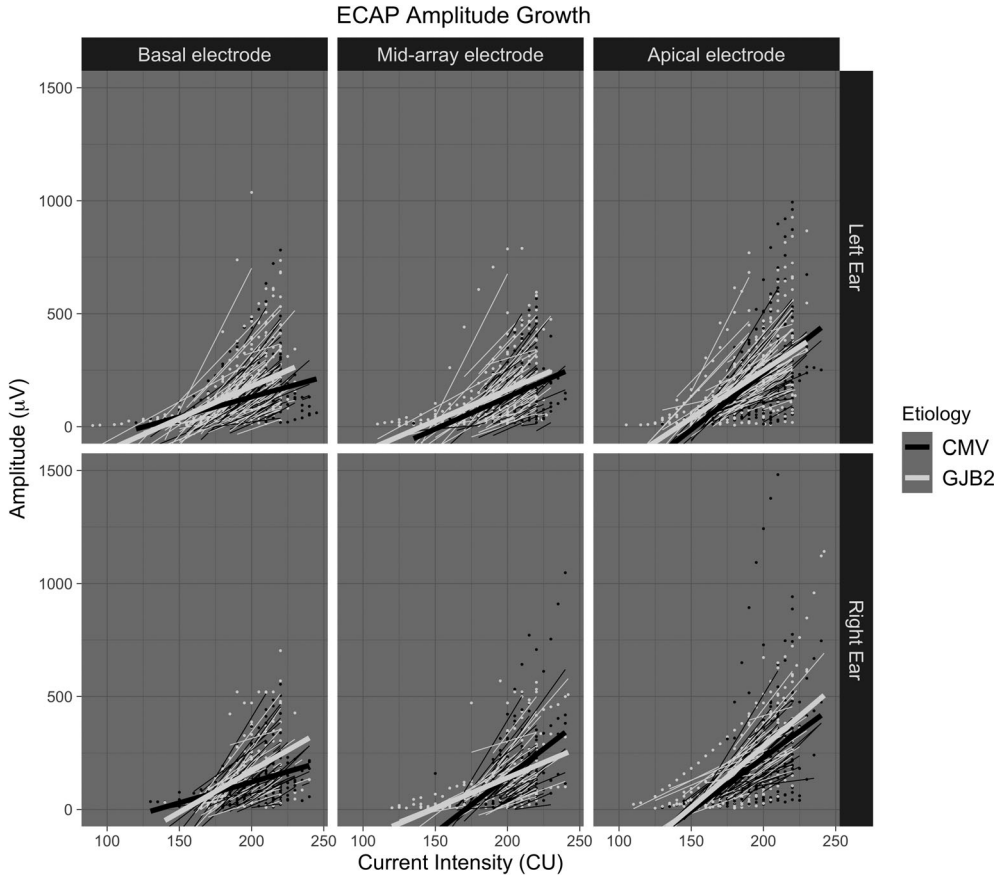

Fig. 10. Ear-specific amplitude growth of the ECAP response in children with cCMV-related SNHL compared with those with GJB2-related SNHL.

EABR responses. As expected, amplitude increases ($F(1, 1649) = 269.4$, $p < 0.0001$) and latency decreases ($F(1, 1592) = 24.3$, $p < 0.0001$) with stimulus intensity as shown in Figure 14. A trend for higher EABR wave amplitude growth ($F(1, 107) = 3.26$, $p = 0.07$) (Fig. 14A) and maximum EABR wave amplitudes ($F(1, 106) = 3.27$, $p = 0.07$) (Fig. 15) was observed between implanted children with cCMV-related deafness and those with GJB2-related deafness. There were no significant effects of etiology (cCMV vs. GJB2) on EABR absolute latencies ($F(1, 112) = 0.07$, $p = 0.80$) (Fig. 16) or thresholds ($F(1, 104) = 0.04$, $p = 0.84$) (Fig. 17) nor were there any effects of type of implanted cochlear array (Latency – $F(6, 314) = 1.40$, $p = 0.21$); Threshold- $F(6, 275) = 1.10$, $p = 0.36$). EABR peak amplitudes were larger ($F(1, 492) = 55.89$, $p < 0.0001$) and latencies were reduced ($F(1, 521) = 49.07$, $p < 0.0001$) for apical electrodes compared with basal electrodes across etiologic groups (Figs. 15 and 16).

The inter-wave (II–III) latency at maximum amplitude, a measure of development in caudal brainstem, was not significantly different between groups (cCMV vs. GJB2) ($F(1, 35) = 0.6$, $p = 0.45$) (Fig. 18A). There was a trend for shorter II–III latency at apical than basal electrodes ($F(1, 28) = 3.2$, $p = 0.08$).

The inter-wave (III–V) latency at maximum amplitude, a measure of development in rostral brainstem, was not significantly different between groups (cCMV vs. GJB2) ($F(1, 86) = 0.16$, $p = 0.69$) (Fig. 18B) and there were no electrode differences on the III–V latency ($F(1, 151) = 1.32$, $p = 0.25$).

Effects of the degree of hearing loss in early life (predicted thresholds at 6 months of age) and whether hearing remained stable or progressed (>4 dB HL/year of age) in one or both ears on EABR parameters were assessed. There were no significant effects of degree of hearing loss in the left or right ears on EABR amplitudes (left ear: $F(1, 60) = 0.12$, $p = 0.73$; right ear: $F(1, 59) = 0.08$, $p = 0.78$) or EABR wave V latency (left ear: ($F(1, 62) = 0.05$, $p = 0.82$); right ear: $F(1, 59) = 0.05$, $p = 0.83$). Similarly, there were no significant effects of stability/progression of hearing loss on EABR amplitudes ($F(2, 54) = 0.19$, $p = 0.83$) or EABR wave V latency ($F(2, 54) = 1.55$, $p = 0.22$).

Volumetric Assessment of White Matter Lesions

Imaging studies had been completed in 96 of 124 (77%) children with cCMV. These 96 children underwent a total of 102 scans. Mean age at the time of scan was 3.0 years (SD 2.7, Range 0–15.9 years). All scans demonstrated white matter changes consistent with cCMV. Areas of signal hyperintensity on T2-weighted or FLAIR imaging are known to be associated with a

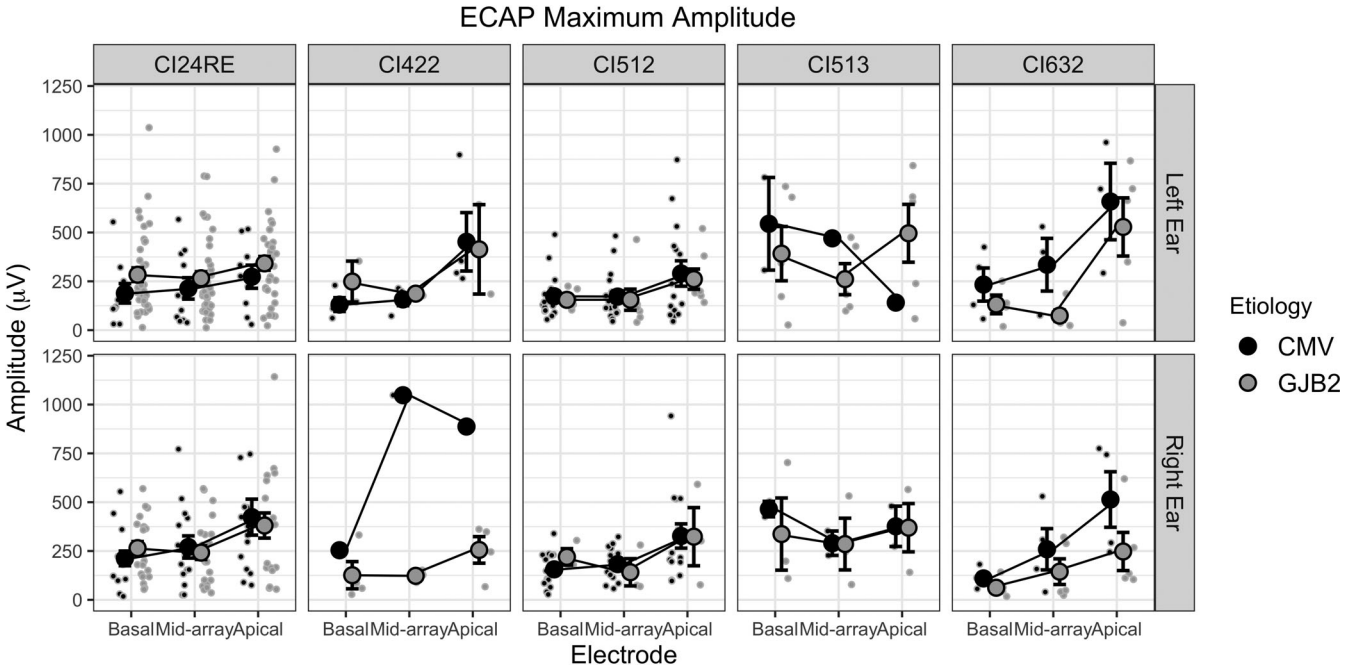

Fig. 11. Ear-specific maximum amplitude of the ECAP response by electrode type in children with cCMV-related SNHL compared with those with GJB2-related SNHL.

congenital exposure to CMV. The mean (SD) volume of such lesions within both left (6380 (9445) mm^3) and right (5740 (8534) mm^3) hemispheres significantly decreased with increasing age at the time of imaging ($F(1, 84) = 7.8$, $p = 0.007$) (Fig. 19). There was a trend toward larger lesions in the left hemisphere ($F(1, 252) = 3.1$, $p = 0.08$). Lesional volumes did not significantly predict whether SNHL will progress ($F(3, 84) = 0.65$, $p = 0.58$), the ear of SNHL ($F(1, 254) = 0.003$, $p = 0.96$) or the degree of SNHL at the age at scan ($F(1, 254) = 0.0006$, $p = 0.98$) (Fig. 20). Figure 21 plots asymmetries in hearing thresholds (puretone averages in right–left ears) against asymmetries in lesion volumes between hemispheres (right–left) against, revealing the limited value of relative

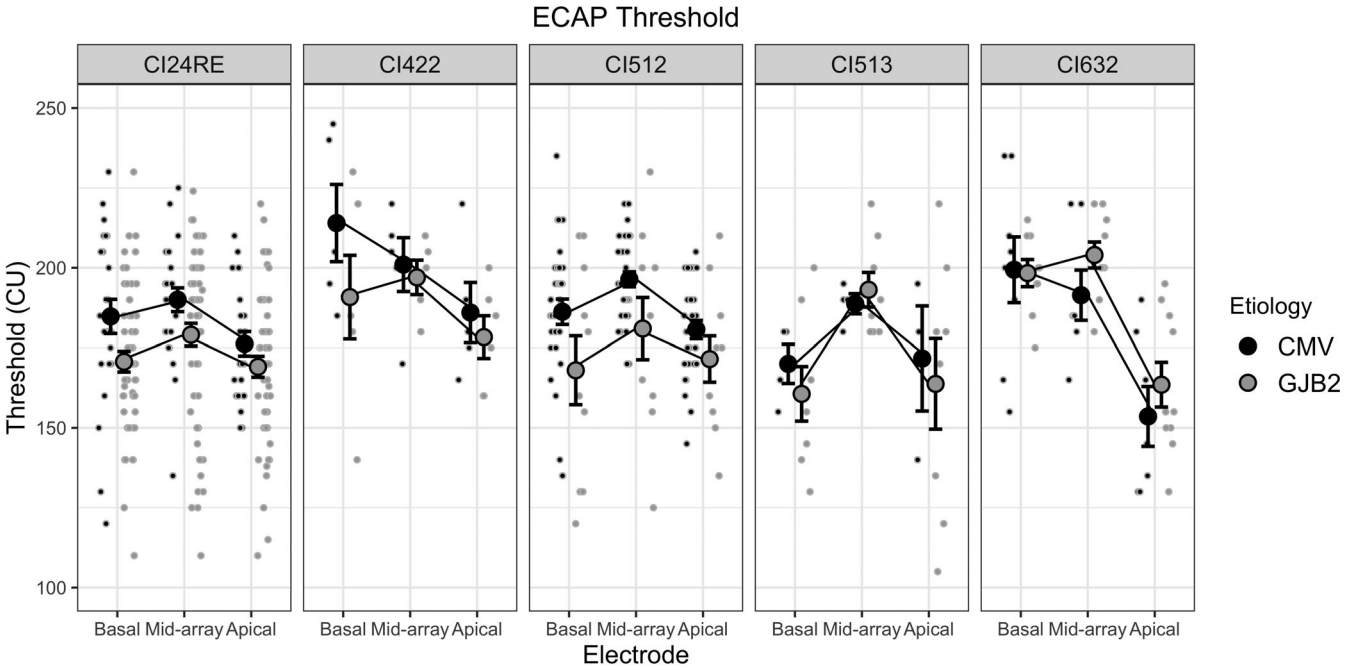

Fig. 12. Ear-specific threshold of the ECAP response by electrode type in children with cCMV-related SNHL compared with those with GJB2-related SNHL.

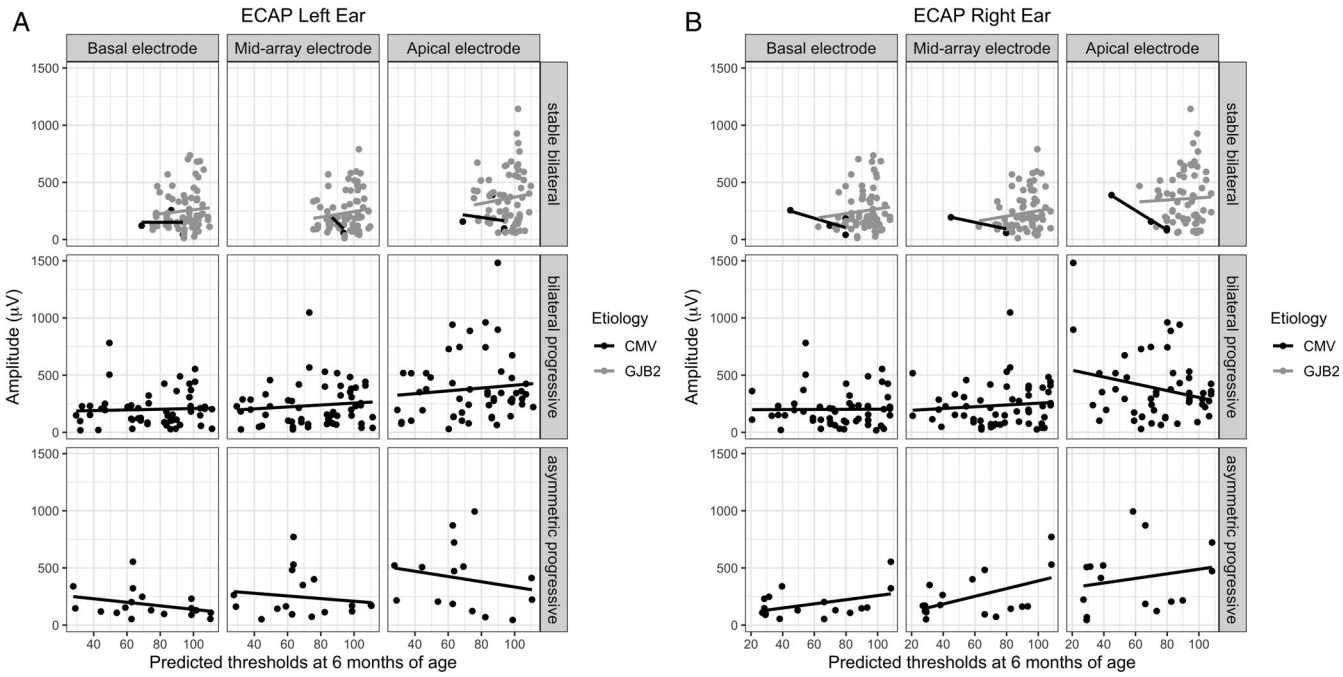

Fig. 13. Ear-specific maximum amplitude of the ECAP response relative to predicted hearing loss severity at 6 months of age, by stimulus location along the electrode array in children with cCMV-related SNHL compared with those with GJB2-related SNHL.

lesion size to predict which ear might have greater hearing loss. The only significant finding in the hemisphere analysis of total lesion volume was a decline in lesional volume relative to age at time of imaging ($F(1, 89) = 5.55$, $p = 0.02$). The mixed model analyses above account for random effects by participant, but a paired analysis was also carried out for children who underwent a repeat scan at an interval with the mean interval (SD) being 3.06 (4.23) years. There was no statistical difference between the total ($p = 0.3$), left ($p = 0.2$) or right ($p = 0.4$) lesional volumes of the repeated scans.

DISCUSSION

The current study demonstrates that there is significant variability in the time course and characteristics of hearing in children who experience cCMV-related SNHL. Many will experience early and rapid deterioration of hearing thresholds, making NHS alone ineffective at capturing these children in a time window that optimizes their access to intervention. A large proportion of children with cCMV-related SNHL will be at risk of delays in diagnosis and treatment that place limits on their developmental outcomes. The ability to study such a cohort is made possible in part due to the ready availability of DBS for PCR testing for cCMV DNA and more recently by the expansion of our provincial newborn hearing screening program to include universal testing of all infants for additional viral (CMV) and genetic (common mutations in GJB2 and SLC26A) risk factors for hearing loss. The general approach to managing cCMV includes (1) early detection and treatment of sensory deficits such as SNHL as well as (2) early treatment with anti-virals for infants presenting with moderately to severely symptomatic cCMV.[27]

Early Progressive Hearing Loss in Children with cCMV is Often Missed by Newborn Hearing Screening

In our cohort, more than a quarter (28%) of children who developed cCMV-related SNHL passed their NHS bilaterally (Table I) and therefore did not receive any routine additional hearing follow-up. In the absence of universal CMV screening, these children are classified as not having any known risk factors and therefore do not receive the frequent and ongoing monitoring that would be required to detect hearing loss as it occurs and to offer rehabilitation without delay.

The average age of detection of SNHL in those who passed their NHS was just over 4 years of age. However, it is possible and even likely that SNHL may have been present in one or both ears well in advance of detection. This hypothesis is supported by prior literature, specifically by the large cohort studies of children with asymptomatic cCMV, where the median age of delayed-onset SNHL ranged from 20 to 44 months.[2,3] Although our study is unable to report the exact age at which these children who passed their NHS went on to develop SNHL, our regression model suggests that hearing loss occurred early. Specifically, the mean (SD) predicted ear-specific thresholds at 6 months of age in children with cCMV who passed NHS bilaterally was 67 (27) dB HL for left ears and 61.3 (26.2) dB for right ears (Table V). This degree of hearing loss would require rehabilitation through hearing aids and therapy for optimal

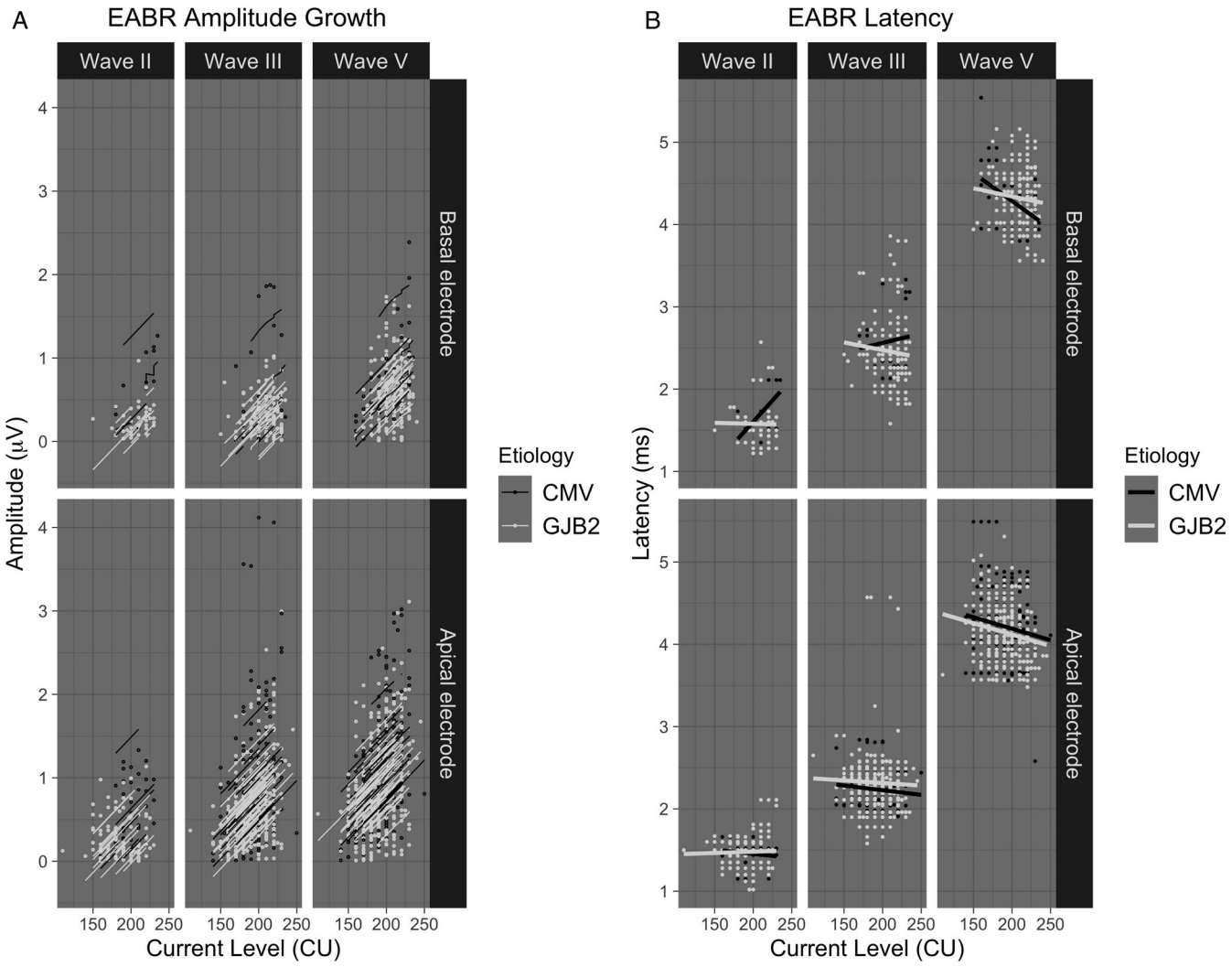

Fig. 14. Ear-specific EABR amplitude growth (A) and EABR latency (B) with change in intensity are plotted for waves II, III, and V evoked by a basal (upper row) an apical electrode (lower row) in children with cCMV-related SNHL compared with those with GJB2-related SNHL.

development, with many progressing to profound loss (Table II), which could benefit from cochlear implantation. Also of note is that the very early onset of their SNHL occurs during an important period for language development. Those children with undiagnosed cCMV who pass their NHS but go on to develop cCMV-related SNHL are vulnerable for delayed diagnosis as well as a significant period of auditory deprivation. In this setting, SNHL is often only diagnosed by parental identification of a language delay, an abnormal school screening result, self-report by a child old enough to articulate dysfunction or concern by teachers, clinicians, or caregivers.[10,28] Additionally, a passed NHS can also provide parents and professionals with false assurances of normal hearing and this may lead to further delay in detecting a slowly progressive or partial hearing loss. Prior to the introduction of NHS programs, the age of detection for bilateral profound SNHL was typically 2–3 years of age.[9] This age of diagnosis is consistent with identification of children with mild to moderate hearing loss prior to screening programs.[29] Although one would expect that bilateral SNHL with a severity approaching 70 dB HL would be detected at a similar age in the form of language delays, unilateral or asymmetric loses would not be as clinically obvious. Additionally, the results presented here are a PTA, and better hearing at one (i.e., low) frequency could provide some audibility and mask the hearing loss. In keeping with this, our study demonstrates that the age of detection of SNHL in children with cCMV who pass their NHS occurs at even older ages likely due to the fact that these losses are partial and slowly progressive and thus more easily missed. The age of detection in this group of children who passed their NHS was only slightly better than those who did not undergo NHS whatsoever. In the latter group, the delay was often compounded by a move from either another country or jurisdiction. This speaks to the limitations of NHS to detect hearing loss or the potential for hearing loss in children with cCMV-related SNHL and undermines the objective of NHS to minimize the duration of deafness at early stages of development.[30]

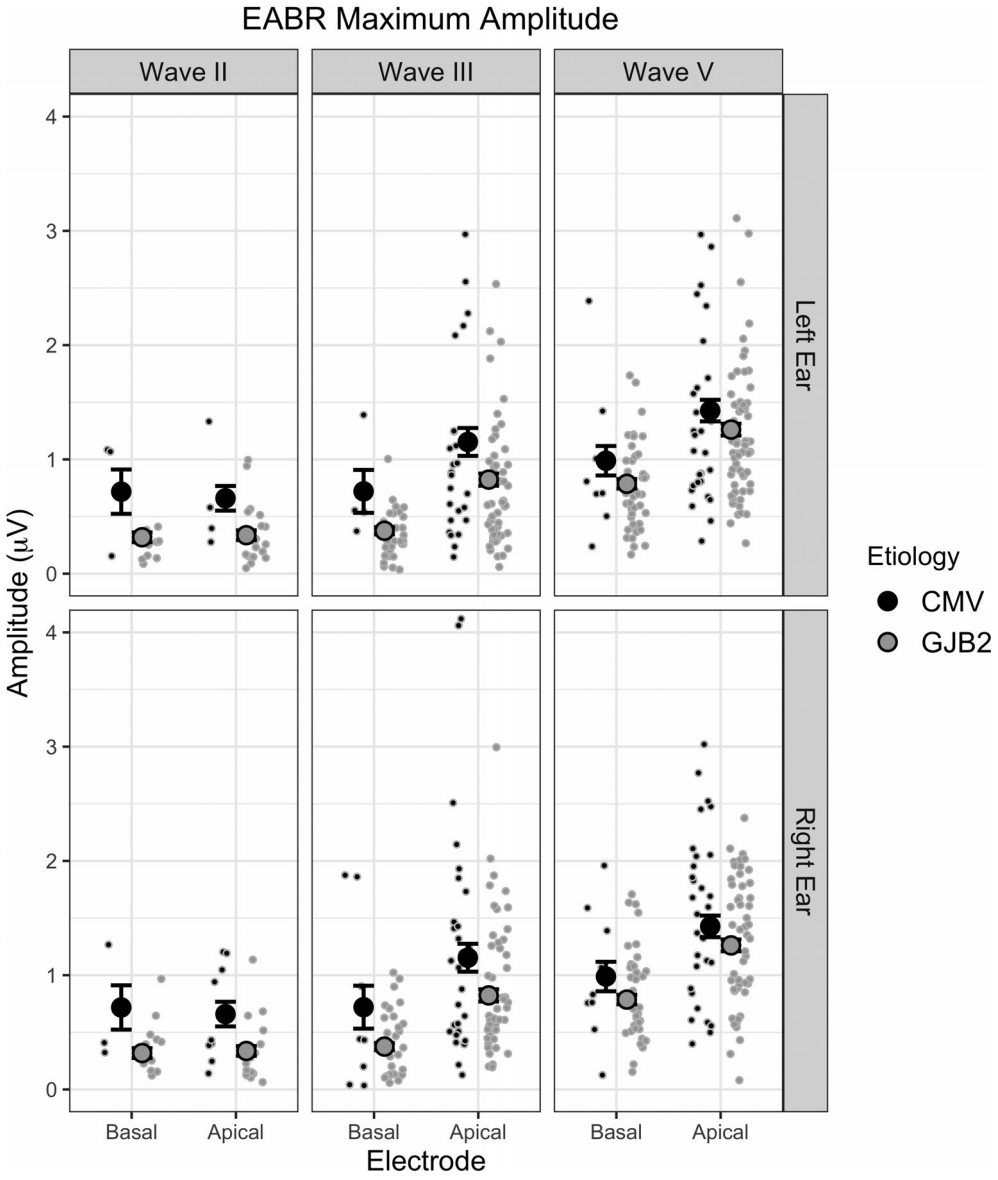

Fig. 15. Ear-specific maximum amplitude of the EABR response by stimulus location for waves II, III, and V in children with cCMV-related SNHL compared with those with GJB2-related SNHL.

In the worst-case scenario, delayed diagnosis could limit the therapeutic options available to the child. This is particularly relevant for interventions such as CI given the known critical period to achieve the optimal benefit from this form of rehabilitation.[31] The appropriateness and criteria for CI in children with SSD remain a topic of debate and study. In our study, 35% of the children who presented with SSD had a duration of deafness >4 years, which by our program's candidacy criteria for implantation in SSD was exclusionary. This left these children with a lifetime of hearing loss and no clear way to access binaural audition.

Some studies report resolution or improvement of hearing in children with cCMV-related hearing loss that occur at rates ranging between 18.2% and 47.9%.[3] We did not see such rates of resolution or improvement in our cohort, although a small number of children in our study did demonstrate positive threshold regression slopes suggesting improvements in hearing (Fig. 5). Most of those children whose hearing improved in our cohort had either near-normal hearing or mild hearing loss (Fig. 6). In addition to reflecting true improvements, other factors may also contribute to perceived improvements over time. Examples include resolution of conductive hearing loss due to otitis media, improvements in test reliability with increased age where measured thresholds go from being suprathreshold to a true measure of threshold. Some children in our study demonstrated ear-specific stability in air conduction hearing thresholds while others experienced fluctuations in hearing thresholds over time; however, the general trend was progression toward worse hearing thresholds. In light of these results, it is

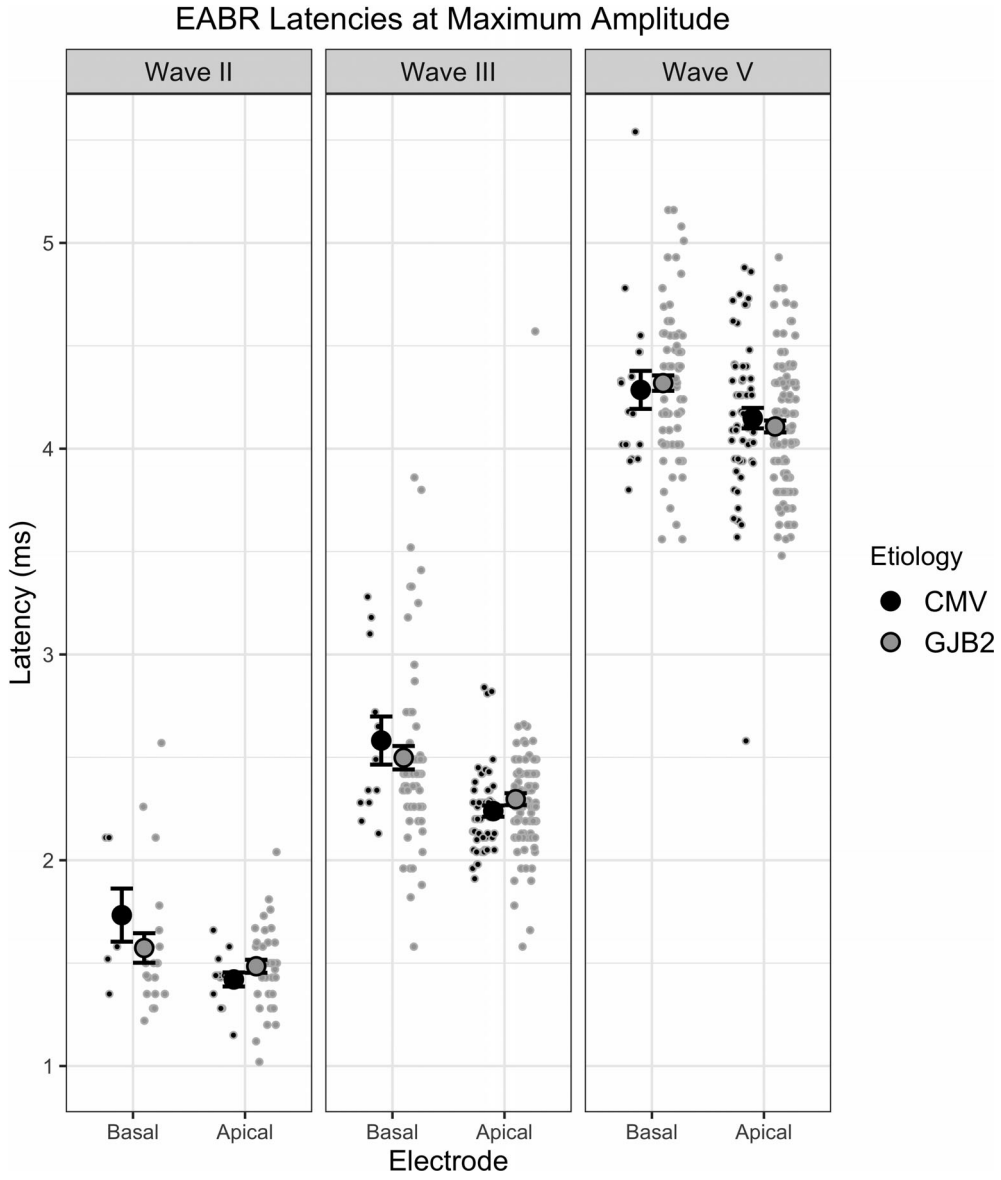

Fig. 16. Latency at maximum amplitude of the EABR response by stimulus location for waves II, III, and V in children with cCMV-related SNHL compared with those with GJB2-related SNHL.

important to consider that, with few exceptions, meaningful and sustained resolution of SNHL from any etiology in the pediatric population is rare in clinical practice. The potentially perceived resolution in these studies may more likely be a reflection of reversible conductive components such as otitis media with effusion, comparison between modalities of testing with different test limits, and poor reliability of behavioral testing, which is impacted both by the child's compliance and the tester's experience with pediatric testing. Most studies use published criteria that define an improvement in hearing as 10 dB improvements in threshold at any of the standard audiometric test frequencies (250, 500, 1000, 2000, 4000, and 8000 Hz).[32] These criteria are derived from a study whose primary goal was to examine deterioration and not improvement of SNHL. What needs to be considered is that these criteria may not represent clinically meaningful changes, particularly in pediatric populations with significant hearing loss. Additionally, many studies classify profound losses as stable over time, and while it is possible for a profound loss to progress, there are limits to the capacity of test equipment as well a question of clinical relevance of a deterioration in a hearing loss that is already severe to profound. Such factors were acknowledged in our study and should be accounted for in studies that assess any treatment effects, such as those of valganciclovir, for example, on hearing outcomes.

Being able to predict SNHL progression has important clinical implications, particularly as it relates to choosing hearing intervention over time. Specifically, in a child with unilateral severe to profound SNHL, the capacity to predict the development of hearing loss in the

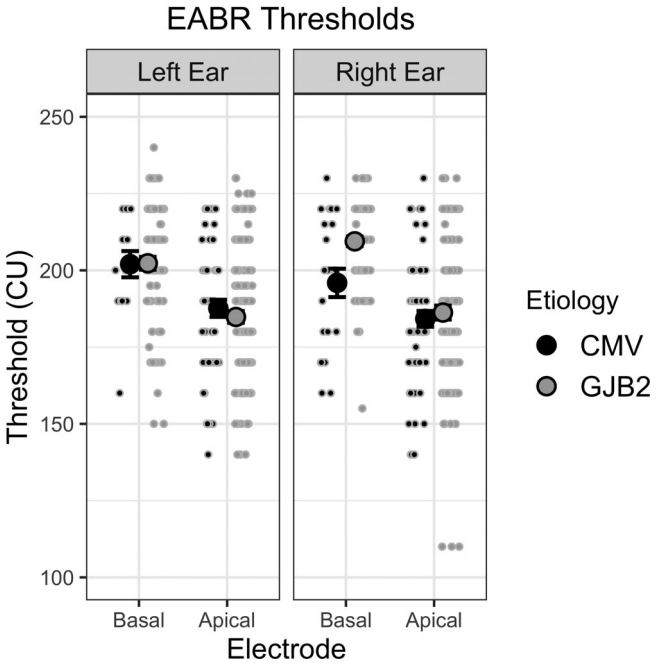

Fig. 17. Ear-specific thresholds of the EABR response by stimulus location in children with cCMV-related SNHL compared with those with GJB2-related SNHL.

contralateral normal hearing ear over time can impact the decision to proceed with unilateral CI. Of 92 children with asymptomatic cCMV in the Congenital Cytomegalovirus Longitudinal Study Group study and 20 who developed cCMV-related SNHL, 65% experienced progression in their poorer hearing ear, whereas 45% experienced progression in the better hearing ear.[5] In this same cohort, of the eight children presenting with either congenital or early progressive SSD, 75% developed bilateral hearing loss by 18 years of age. Progression occurred in a highly variable and, at times, protracted timeline with median time to bilateral hearing loss being 4 years, but

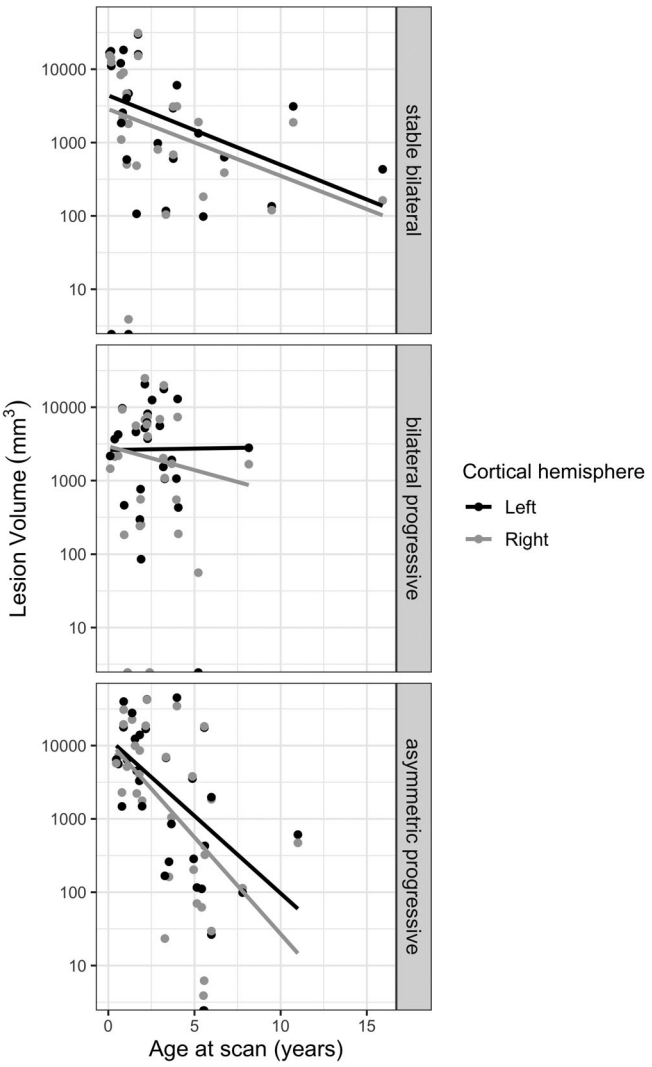

Fig. 19. Hemisphere-specific volume of white matter changes by age at time of scan and categorized by classification of the type of hearing change over time in children with cCMV-related SNHL.

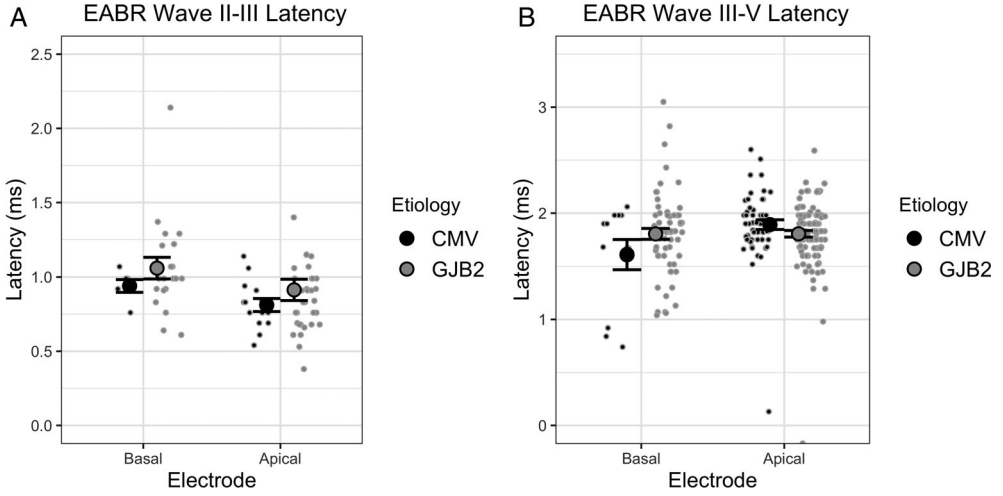

Fig. 18. EABR inter-wave latencies (A) II–III and (B) III–V by stimulus location along the electrode array in children with cCMV-related SNHL compared with those with GJB2-related SNHL.

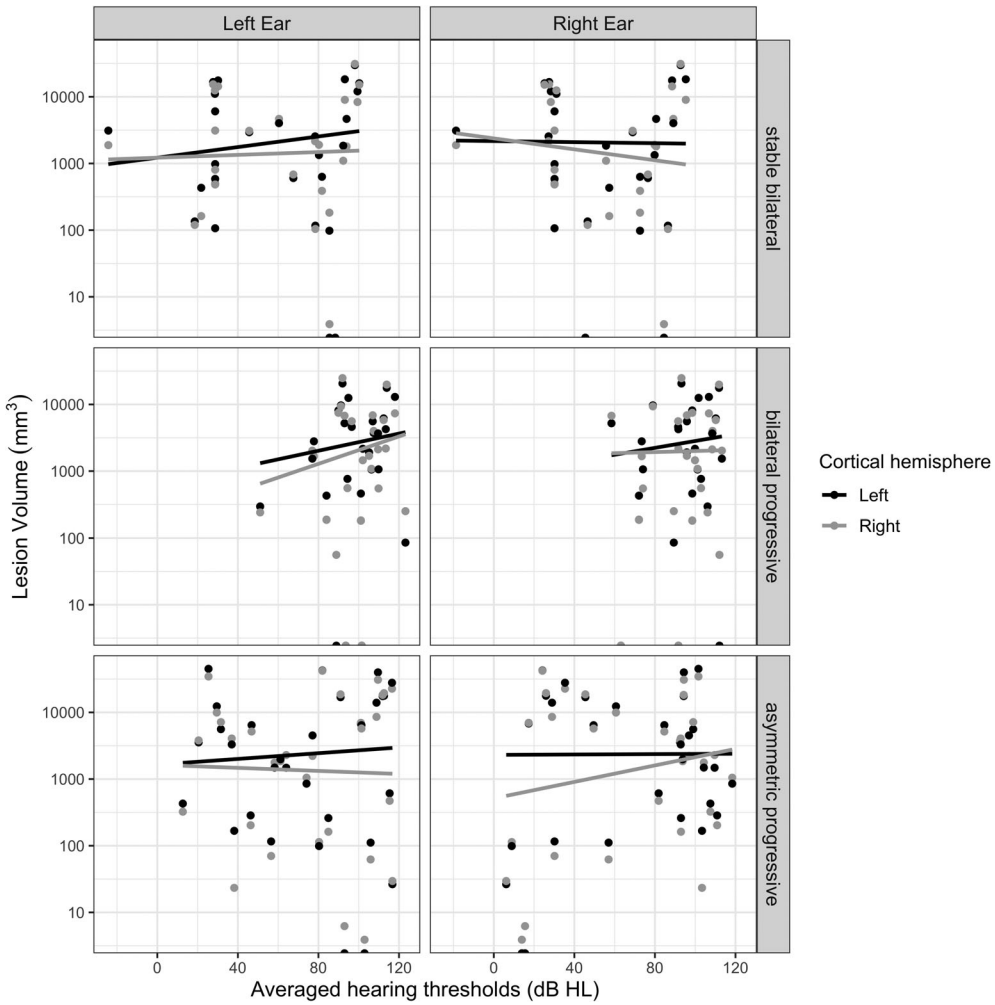

Fig. 20. Hemisphere-specific volume of white matter changes by ear-specific mean hearing thresholds and categorized by classification of the type of hearing change over time in children with cCMV-related SNHL.

ranging from 4 months to 18 years.[5] In comparison, in our study, of the 41 children with cCMV-related SNHL who were born with unilateral profound SNHL ($n = 41$), more than 40% developed contralateral hearing loss by 5 years of age, increasing to almost 65% by 8 years of age (Fig. 9). Although these percentages could represent an overestimation of contralateral progression, as our clinic is also an implant center and might attract more patients with severe/bilateral losses, the calculated risk is in line with the 75% risk reported for a prospective cohort.[5] When SNHL developed asymmetrically, the mean duration between the detection of SNHL in the first ear and the progression of SNHL in the contralateral ear was similar to that reported in the literature at 3.4 years (SD 2.4, Range 0.08–7.9 years). Considering the risk of progressive deterioration in the better hearing ear,[5] the role of early unilateral CI in the presence of normal contralateral hearing may be viewed as the first stage in preserving consistent bilateral auditory access over a lifetime. Identifying cCMV is thus important in children with hearing loss, particularly those with SSD. Studies of children undergoing CI for SSD have demonstrated that children with cCMV-related SSD make up the largest proportion, nearly half, of all children (20 of 43, 47%) who were candidates for unilateral CI. A high acceptance rate on the part of caregivers was observed with more than 75% of children with cCMV-related SSD going on to receive a CI, much higher than the approximately one-third acceptance among the overall population. This difference in acceptability is felt to be due to the known risk of progression to bilateral deafness in cCMV described above.[33] In fact, early implantation in the setting of SSD due to cCMV may be the only way to preserve a bilateral hearing system in the long term in a child who may progress to bilateral hearing loss. It is possible that children with SSD may benefit from unilateral CI, with the most significant benefit being achieved when the duration of deafness is limited. Although there remains much debate about how long is too long when it comes to auditory deprivation, our center considers unilateral CI in the setting of cCMV-related SSD in children whose duration of deafness is less than 4 years.[34]

The prevalence of cCMV is high and a small number of children had an overlap between cCMV and other conditions, which may have impacted or been an explanation for their SNHL. This is relevant information for clinicians

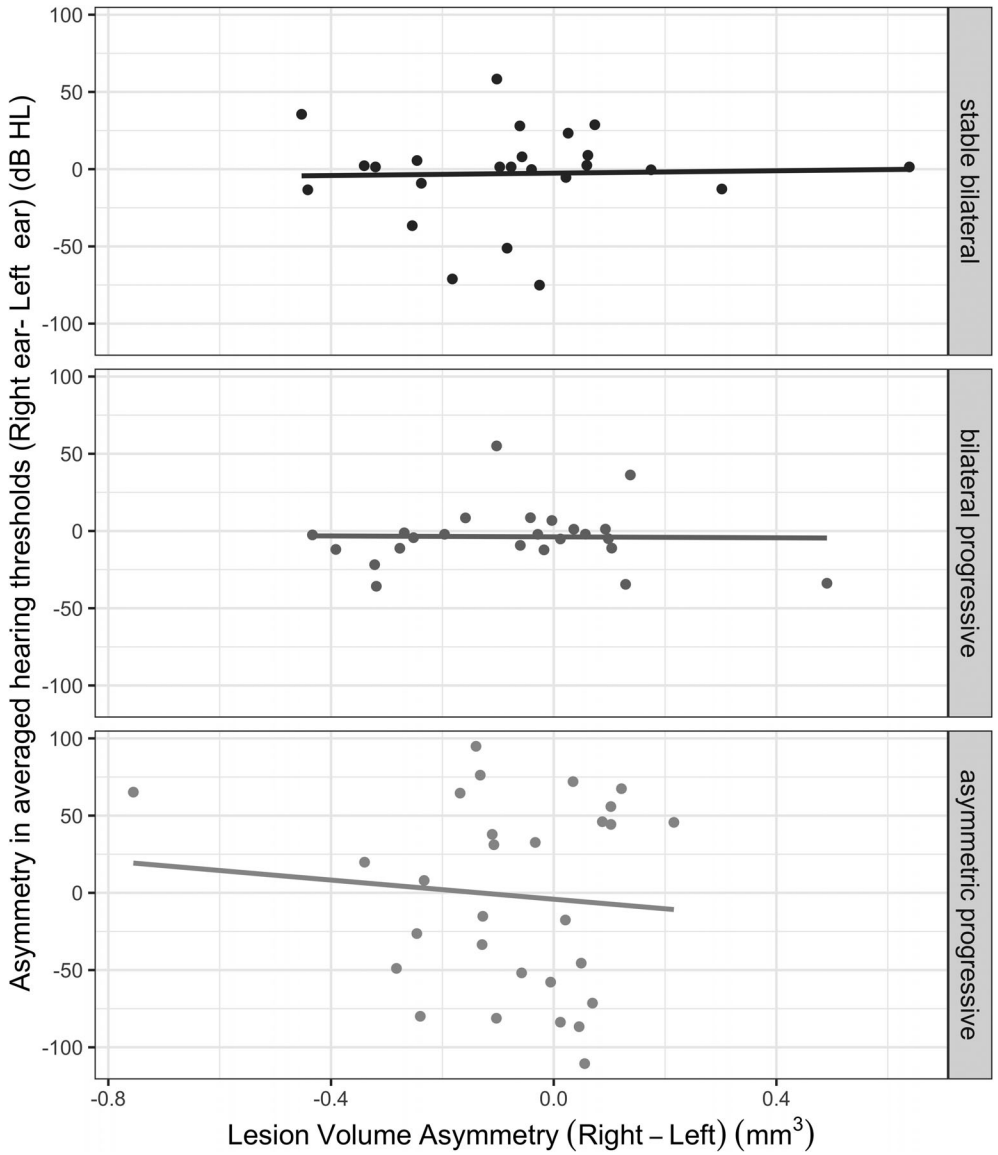

Fig. 21. Hemisphere-specific asymmetry in the volume of white matter changes relative to ear-specific asymmetry in the mean hearing thresholds and categorized by classification of the type of hearing change over time in children with cCMV-related SNHL.

who might narrow their diagnostic focus once a first potential etiology for the SNHL has been identified. In these cases, the important contribution of cCMV to the child's overall development as well as the need for increased frequency of testing to capture the elevated risk of progression might be missed. As such, an assessment for cCMV should be ideally included in all diagnostic algorithms for SNHL in children, with universal screening for cCMV providing the most robust means of doing so.

Precipitous Decline to Profound Deafness in Young Children with cCMV Arrests Development of Auditory Responses, Requiring Cochlear Implantation

The nature and pathophysiology of the injury that CMV inflicts on the inner ear continue to be studied. Murine models demonstrated that deterioration in ABR thresholds over time was paired with evidence of a wide range of cochlear vessel degeneration. Specifically, significant damage to the stria vascularis was observed, and it was inferred that progression of damage occurred from the apex to the base of the cochlea.[35] Similar models found fewer spiral ganglia neurons and inflammatory infiltrates in the spiral ganglion and the stria vascularis with relative sparing of the Organ of Corti.[36] In comparison, in GJB2-related deafness, the pattern of sensorineural damage has been shown to occur uniformly along the cochlea, which is in keeping with its underlying pathophysiology related to gap junctions where the resulting deficits are likely to occur equally in different portions of the cochlea.[15] Other studies examining auditory nerve responses (ECAP) following CI demonstrated that children with GJB2-related deafness demonstrated more uniform neural activity along the length of the cochlea than

children with deafness not due to GJB2.[15] The uniformity of the electrophysiologic responses in the GJB2 group were thought to reflect more uniform effects of spiral ganglion cell survival throughout the cochlea than when deafness was due to other etiologies. Contrary to our hypothesis however, the electrophysiologic characteristics of the ECAP in children with cCMV-related deafness were indistinguishable from those of children with GJB2 related deafness relative to larger effects of cochlear implant electrode position. These findings, shown in Figures 10–13, confirm prior evidence supporting the importance of cochlear implant electrode placement in the cochlea[13] and confirms that viable populations of neurons in the primary auditory nerve are available for stimulation in both children with cCMV and GJB2.

The ability to stimulate the auditory brainstem was also measured in children with cCMV and compared with children with GJB2. The similarities in the electrophysiologic characteristics of EABR measures at initial cochlear implant use, shown in Figures 14–18, suggest that children with cCMV-related SNHL who became CI candidates did not have a significant amount of hearing experience despite the progressive nature of the hearing loss. This is consistent with our predictions suggesting that severe hearing loss occurs by 2 years of age (Table V). Because progression of hearing loss often occurs early and precipitously in many children with cCMV, their early hearing experience is too limited to be protective against the effects of auditory deprivation on the brainstem or to promote significant development.

EABR thresholds can be slightly higher than ECAPs because the children are awake while these responses are being obtained, so the noise floor of response is higher.[37] Furthermore, EABR amplitudes can be 100x smaller than those of the ECAP responses.[37]

The equivalency of these implant-evoked electrophysiologic measures between children with cCMV and GJB2-related SNHL also suggests that, from the perspective of the peripheral auditory system and the brainstem, cochlear implants are an equally effective means of rehabilitation in both clinical groups. A number of studies that look at implant performance in children with cCMV compared with other groups of children with deafness including those with GJB2-related hearing loss and have undergone a systematic review.[38] Overall, they demonstrate that children with cCMV-related hearing loss do benefit from implantation with speech production and perception improving subsequent to implantation, however in general outcomes were not variable.[12,22,38] However, more than half of the studies reviewed (7 of 12) demonstrate poorer performance in children with cCMV-related deafness. Given that in our study, electrophysiological measures suggest equivalent stimulability of the auditory nerve and brainstem with CI in children with cCMV and GJB2-related SNHL, when poorer outcomes are seen in children with cCMV-related SNHL[38] these may be due in part to delays in diagnosis and rehabilitation, older age of implantation in other studies, and combined cochleovestibular loss, which are more common in children with cCMV than other etiologies of deafness. Although our study only included children with cCMV who were otherwise considered asymptomatic, with the exception of their SNHL, neurological sequelae and additional disabilities are known to frequently occur in the setting of cCMV and may also impact outcome.

White Matter Lesions are Universally Present in Children with cCMV-Related Hearing Loss but do not Predict Degree of Impairment

In our cohort, most scans were obtained at relatively young ages, with older children primarily presenting with unilateral or asymmetric progressive SNHL. The impetus for obtaining imaging was in most cases in advance of receiving a cochlear implant. The lower volume of lesions seen with older age may reflect a "milder" degree of hearing loss presentation (i.e., later onset, unilateral or progressive disease). Whereas young infants and children with "severe" hearing loss presentation (congenital, bilateral, profound) would have, by virtue of their candidacy for cochlear implantation, been imaged earlier. The severity of brain lesion on its own does not seem to directly correlate with outcome following CI, but some studies suggest that subtle differences may exist.[39] Specifically, one study in the literature suggests that children with cCMV-related SNHL who did not have cortical lesions detected by MRI performed equally well, with even a trend toward better performance on speech perception tests compared with those with GJB2-related SNHL. The authors suggest that this may be due to a history of progressive SNHL in the cCMV group that allowed them the benefit of some early hearing experience.[23] In this same study, children with cCMV-related SNHL who had cortical lesions detected by MRI exhibited equivalent speech perception measures as children with cCMV-related SNHL without cortical lesions on MRI and children with GJB2-related SNHL.[23] In comparison to the reported literature, in our study cohort, none of the children with cCMV-related SNHL who were imaged had normal scans. Additionally, our study demonstrates that neural responsiveness at device activation, measured by EABR, suggested that these children had not benefited from early hearing access even when the hearing loss had been noted to be progressive. This does not rule out that brief perinatal exposure to hearing may infer an advantage at the cortical level or may relate or contribute to outcomes demonstrated in this population in the literature (i.e., the lag in speech production).

The analysis conducted on the imaging available for children with cCMV-related SNHL was limited to the quantitative assessment of the volume of white matter lesions in the right and left hemispheres. Further analysis of the characteristics of these lesions relative to anatomic location including auditory and speech processing areas, as well as quantification of other imaging changes, is warranted and may reveal the functional implications of the patterns of change on CNS imaging. Likewise, given the differences in volume relative to age at the time of scan seen in our study, further analyses examining the predictive power of imaging done at an early age in a child who subsequently develops prelingual loss may prove insightful. Other studies have used different

severity grades for imaging findings in cCMV and found that this only slightly correlated with neuropsychological disorders and not hearing outcomes.[40] Similarly, neuroimaging evidence of CNS involvement in the neonatal period is associated with the presence of hearing loss in children with a cCMV infection[41,42]; however, imaging abnormalities are not predictive for the development of delayed-onset hearing loss.[42] One of the limitations of the current study is that as macromyelination is not complete until the age of approximately 2 years, lesional volumetric assessment may overestimate lesion load. This needs to be taken into consideration when interpreting the data.

In keeping with the lack of predictive value MRI changes have on hearing outcomes, there does not appear, at this point in time, to be any virologic marker that will predict hearing outcome.[3] The impact of cCMV on the inner ear may therefore occur in a fashion that is idiosyncratic to viral load or the development of white matter disease. This is reminiscent of what happens in the setting of both noise exposure ototoxic medications (i.e. aminoglycosides, platinum-based chemotherapeutics, etc.) where inner ear injury cannot be predicted by the overall dose of noise or serum blood levels alone.[43] In the setting of chemotherapeutics, for example, genetic mutations may impact the susceptibility of the inner ear to damage from these medications[44] and perhaps similar factors or even viral reactivation may be at play in the setting of cCMV-related SNHL.

Universal Screening for cCMV is Likely the Best Way to Impact Outcomes

Many jurisdictions have access to targeted cCMV screening based on NHS results.[45,46] However, the data in the current study are consistent with previous reports demonstrating that this approach misses a large number of children with asymptomatic cCMV who will go on to develop SNHL.[47,48] We thus suggest that the only means of overcoming these limitations of NHS is to add universal screening for cCMV in all newborns. Given that universal screening for cCMV would tie into an intensive audiologic surveillance and monitoring program, SNHL should be identified promptly and managed without delay. Previous studies have found universal screening for cCMV to be cost-effective.[49]

Another benefit of universal CMV screening beyond early detection of and intervention for SNHL is the fact that cCMV is potentially treatable. Valganciclovir may modestly reduce the risk of SNHL progression.[50,51] In addition, early identification of cCMV also allows for health care providers to counsel families on the natural history of cCMV and its associated risks. The identification of SNHL in a child leads to a grief response in caregivers, and denial of the audiologic test results is common. Having an identified etiology such as cCMV that is consistent with the hearing loss diagnosis can, in our experience, help families move through the stages of grief to acceptance where they are best able to provide the support for the interventions that their child needs. Additionally, in our explanations of how this virus is acquired, we as clinicians should be mindful that some mothers do initially feel guilty as they were unaware that they had CMV during pregnancy and clinicians should be ready to provide them with support. There may also be a role for prevention through education to women who are pregnant or are considering pregnancy.

Study Limitations

By virtue of the inclusion criteria, there is an inherent referral bias toward the subgroup of children with cCMV who develop hearing loss. Thus, no estimation of cCMV-related SNHL can be made as children with cCMV who went undiagnosed either because they did not develop hearing loss or because their DBS tested negative for CMV due to low viral load are not accounted for. Furthermore, the hearing rehabilitation of the children included in the study may be skewed by the fact that they have been referred to a pediatric tertiary care hospital with a cochlear implant program.

Additional limitations have also been outlined throughout the discussion where appropriate.

SUMMARY AND CONCLUSIONS

1. cCMV-related hearing loss may be present at birth, but in a substantial subgroup of children is delayed in onset. In addition, progression of cCMV-associated SNHL is common and often occurs early in life and precipitously. Children with an undetected diagnosis of cCMV who have passed their NHS but go on to develop SNHL are therefore at risk of delays in diagnosis, which may impact the initiation of rehabilitation and limit their neurodevelopmental outcomes in the long term.
2. Electrophysiologic responses to CI are equivalent in children with cCMV and GJB2-related hearing loss, suggesting that cochlear implants can overcome the impact of these etiologies on the cochlea and brainstem. Given the immaturity of the brainstem responses observed at the time of device activation, neither group gained benefit from any prior exposure to sound that occurred before the onset of profound deafness.
3. White matter lesions are universally present in children with cCMV-related SNHL but do not predict hearing outcomes.

The findings of the present study thus support early diagnosis through universal screening of newborns for cCMV with aggressive monitoring of hearing. This is the best approach to ensure rapid rehabilitation of all children with cCMV-related SNHL and limit neurocognitive sequelae.

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