Hearing Loss and Ophthalmic Pathology in Children Diagnosed Before and after the Implementation of a Universal Hearing Screening Program

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ABSTRACT: **Background:** Ophthalmic pathologies may further complicate the sensory input of patients with congenital hearing loss; however, data on children with coexisting impairment of vision and hearing is outdated, from before universal implementation of hearing screening programs.

Objectives: To examine the different ophthalmic pathologies among children with congenital sensorineural hearing loss (SNHL) before or after the introduction of a universal newborn hearing screening program (UNHSP).

Methods: Retrospective cohort study was conducted of 91 children diagnosed with congenital SNHL between 2005 and 2016 in a tertiary pediatric hospital. All patients completed an ophthalmologic examination, including assessment of visual acuity, refraction, ocular motility, slit lamp examination, and indirect funduscopy. Radiological assessment and genetic analysis were offered to all caregivers.

Results: Average age at diagnosis was 4.1 years. Nineteen children (21%) were diagnosed with an ophthalmic condition, of which the most common were refractive pathologies. Diagnosis of an ophthalmic pathology was twice as likely in the pre-UNHSP era (14 children, 27%) compared to the post-UNHSP era (5 children, 13%). Out of 91 children, 57 (63%) underwent a computed tomography scan and/or magnetic resonance imaging. Imaging was positive for structural abnormalities in 23 children (40%). There was no correlation between imaging and ophthalmic conditions. Genetic analysis was performed in 67 patients (74%).

Conclusions: The ophthalmic assessment of babies and children with congenital SNHL may yield in significant numbers of children with concomitant ophthalmic pathologies. Implementation of a UNHSP allows early diagnosis and treatment of coexisting ophthalmic and hearing conditions.

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The prevalence of congenital sensorineural hearing loss (SNHL) is considered between 1 and 3 per 1000 live births [1]. Different newborn screening programs are routinely performed worldwide, and hearing loss is the most commonly diagnosed congenital pathology [1,2]. Visual and auditory channels are responsible for approximately 95% of the information humans gather from their surrounding [2], hence the importance of early diagnosis of concomitant visual and auditory pathologies. Early diagnosis of ophthalmic pathologies in congenital SNHL may help cognitive and emotional development and allow compensation for lack of auditory inputs [3,4]. It may also help uncover syndromic causes of SNHL, which may present with concomitant auditory and visual deprivation such as Usher syndrome.

This study describes the different ophthalmic pathologies associated with congenital hearing loss in a large pediatric cohort and the evolving incidence of ophthalmic disorders before and after the implementation of a universal newborn hearing screening program (UNHSP).

PATIENTS AND METHODS

The study was approved by the local Auckland District Health Board ethics committee. Ethics approval reference 16/NTA/19.

A retrospective cohort study of 91 children diagnosed with SNHL between January 2005 and January 2016 was conducted in a tertiary-level pediatric institution in Auckland, New Zealand. All caregivers of newly diagnosed children were counseled by a pediatric otolaryngologist. An ophthalmological assessment was performed as part of the clinical workup.

A UNHSP was implemented in some areas in New Zealand starting in July 2007. Since April 2010, all New Zealand-born babies have been screened. Automated auditory brainstem response (ABR) is the first-line screening tool in our program. Babies who do not pass screening for one or two ears are referred to the audiology services and formal ABR testing is conducted. Babies who are confirmed to have hearing loss are referred to our pediatric otolaryngology unit. Babies and

children in this study were diagnosed either before or after the implementation of a UNHSP.

Age-appropriate audiometry with air and bone thresholds were available for all patients included in this cohort. ABR potentials were obtained for children who were either too young or unable to cooperate with behavioral audiometry.

Ophthalmological assessment was performed for all 91 children by pediatric ophthalmologists, which included visual acuity assessments with a Snellen chart or vision estimation by assessing centration, steadiness, and maintenance of fixation in uncooperative children. Additional testing included slit-lamp examination, ocular movement, assessment of refraction, and indirect funduscopy.

Demographic data were collected and included age at diagnosis and ethnicity. Prenatal and postnatal risk factors were assessed, including maternal alcohol and/or drug abuse, gestational diabetes mellitus, and gestational hypothyroidism, as well as gestational toxoplasma, rubella, cytomegalovirus (CMV), Herpes virus (TORCH) exposure, prematurity, birth weight < 1500 grams, jaundice, ventilation > 4 days, ototoxic medication exposure, and a family history of hearing loss. Parental consent for genetic evaluation was obtained in 67 children and was performed using a multi-gene screening panel for 11 possible genetic abnormalities. Blood samples were taken from the child at our institute and one sample from each child was sent for testing. The genotyping was conducted at ASPER Biotech laboratories (Tartu, Estonia).

Imaging was part of the routine workup and included computed tomography (CT) scan and/or magnetic resonance imaging (MRI) of the temporal bones and brain. In some of the cases, a decision was made to perform the imaging at an older age to avoid general anesthetics. Inclusion criteria was any newly diagnosed child with SNHL, who was 0–15 years of age. Exclusion criteria was mixed SNHL and conductive hearing loss, inconsistent audiometry results, and lack of ophthalmological review.

SNHL was defined as bone conduction hearing thresholds > 20 dB in any three consecutive frequencies.

SEVERITY OF HEARING LOSS

Hearing loss was classified as mild (20–45 dB HL), moderate (46–70 dB HL), severe (71–90 dB HL), or profound (< 90 dB HL). High frequency hearing loss was considered if the lowest abnormal frequency was > 2000 Hz. Low frequency hearing loss was considered if the highest abnormal frequency was < 2000 Hz.

GENETIC TESTING

SNHL can follow a pattern of autosomal dominant, autosomal recessive, X-linked recessive, or mitochondrial inheritance. Targeted mutation analysis was performed using DNA microarray for genotyping 11 different genes [3] known to be correlated with non-syndromic SNHL, including *GJB2 (OMIM 121011), GJB3 (OMIM 603324), GJB6 (OMIM 604418), KCNQ4 (OMIM 603537), MYO7A (OMIM 276903), MYO15A (OMIM 602666), MTRNR1 (OMIM 561000), MTTS1 (OMIM 590080), SLC26A4 (OMIM 605646), SLC26A5 (OMIM 604943),* and *TMC1 (OMIM 606706)*; 249 detectable mutations were tested from each sample.

Criteria for assigning a variant as pathogenic or benign are based on scientific publications and data, which are available from relevant databases (e.g., ClinVar, EXac, Ensembl). All detected variants were confirmed by Sanger sequencing. The software used for analyzing the data was Genorama Basecaller, PicDb, and PicDb Autoscan.

This specific array for SNHL was used for the analysis of 1282 samples. Seven false negatives (FN) and 0 false positives (FP) were detected with the particular array.

Sensitivity and specificity of this method is as follows (TP = true positive, TN = true negative):

- Sensitivity (TP/[TP + FN]) = 1275/1282 = 0.9945 (99.4 %)
- Specificity (TN/[TN+FP]) = 1282/1282 = 1 (100%)

RESULTS

The average age at diagnosis was 4.1 years. A pediatric ophthalmologist completed evaluation of 91 children. Nineteen children (21%) were diagnosed with an ophthalmic condition, and the most common problems were refractive pathologies (11 children, 55%). Refractive pathologies included myopia, hyperopia, and astigmatism (which causes blurred vision due to irregular curvature of the cornea or lens). See Table 1 for a list of the different pathologies. Of the children included in the evaluations, 68 (75%) and 23 (25%) had either bilateral or unilateral SNHL, respectively. We found no correlation between bilateral versus unilateral SNHL and ophthalmic conditions. The spectrum of hearing loss was mild to profound and 60 children (66%) of this cohort use hearing aids. Seven children (8%) had a cochlear implant surgery.

Table 1. Ophthalmic pathologies

Pathology	Number of children	Bilateral/unilateral SNHL
Myopia (refractive)	6	4B/2U
Hyperopia (refractive)	3	3B
Astigmatism (refractive)	2	2B
Epiphora	2	2B
Squint	2	B/U
Abducens nerve palsy	1	B
Delayed visual maturation	1	B
Congenital cataract	1	B
Exotropia	1	U

SNHL = sensorineural hearing loss

COMPARISON OF OPHTHALMIC PATHOLOGIES BEFORE AND AFTER IMPLEMENTATION OF A UNHSP

A total of 53 children with hearing loss were born after the implementation of a UNHSP, and 39 (74%) were referred to ophthalmologists. Before the implementation of a UNHSP a total of 52 children were referred to ophthalmologists. Diagnosis of an ophthalmic pathology was more than twice as likely in the pre-UNHSP period (14 children, 27%) compared to the post-UNHSP era (5 children, 13%). Spectrum of pathologies was similar in both subgroups and ophthalmic conditions during the post-UNHSP time included one case each of myopia, exotropia, hypermetropia, bilateral hyperopia, and abducens nerve palsy.

RISK FACTORS FOR HEARING LOSS

Risk factors for hearing loss were assessed in all patients, and included low birth weight (< 1500 grams), prematurity, neonatal intensive care unit admittance, family history, ventilation > 4 days, jaundice, and ototoxic exposure. Of the 72 children without ophthalmic conditions, 35 (49%) presented with at least one positive risk factor. In addition, 10 (53%) with ophthalmic conditions had at least one risk factor for hearing loss. Prevalent risk factors among the total cohort were jaundice (21/23%), family history of hearing loss (18/20%), neonatal intensive care unit admission (16/18%), and prematurity (12/13%). Prenatal risk factors were also assessed including TORCH exposure with two children positive for congenital CMV infection, gestational diabetes mellitus in two children, and drugs/ethanol exposure in two children. No child had a history of gestational hypothyroidism. None were diagnosed with prenatal rubella infection. One patient had a history of meningitis. None of the study participants were suspected of having congenital syphilis; however, 14 patients were tested and found negative for this infection. CMV was tested in a retrospective manner using a polymerase chain reaction (PCR) essay using from blood retrieved from the newborn Guthrie card test.

IMAGING

Of 91 children, 57 (63%) underwent CT and/or MRI as part of the routine hearing loss workup. Imaging studies were positive in 23 (40%) children. Imaging was considered to be positive if any structural pathology was demonstrated. Imaging was completed in 40 (56%) out of the non-ophthalmic pathology subgroup and 17 (43%) of those presented with positive findings. CT and/or MRI were performed in 14 (74%) patients from the ophthalmic pathology subgroup and positive findings were diagnosed in six (43%) of these children. Hence, the rate of positive imaging findings was similar for children with or without ophthalmic conditions. The common positive imaging findings were vestibulocochlear dysplasia, enlarged vestibular aqueduct, and cochlear nerve absence. Imaging findings among the group of children with positive ophthalmic conditions seemed to be arbitrary and we did not find a correlation between imaging findings and ophthalmic conditions. See Table 2 for detailed imaging findings.

GENETIC ANALYSIS

Genetic analysis was offered to all families, but was eventually performed in only 67 patients (74%) from the overall cohort. Fifty-four children (75%) from the non-ophthalmic pathology subgroup completed genetic analysis and 22 (41%) of this subgroup had positive genetic findings. Of the 19 with positive ophthalmic findings, 17 were non-syndromic. The two syndromic patients had Stickler and Kabuki syndromes. Thirteen (76%) patients with non-syndromic hearing loss from the ophthalmic subgroup completed genetic evaluation, and four were diagnosed with heterozygous mutations to Connexin 26 (two children), SLC264A/Pendrin (one child), and SLC26A5/Prestin (one child).

Some children tested positive for more than one heterozygous mutation. Homozygous mutations are clinically more important. We did not uncover any mutations for non-syndromic hearing loss with ophthalmic conditions compared to four positive mutations in non-syndromic hearing loss without ophthalmic conditions. See Table 3 for genetic findings among the overall cohort.

DISCUSSION

Ophthalmic co-morbidities among children with congenital hearing loss are not uncommon and may cause significant communication difficulties for these patients. The ophthalmic examination of children with congenital hearing loss is essential mainly due to two reasons. First, children with different levels of auditory deprivation rely on their visual input more than their peers. Correction of visual pathologies may help these children

Table 2. Imaging findings

	Ophtalmic pathologies (n=19)		Non-ophtalmic pathologies (n=72)	
	CT	MRI	CT	MRI
Vestibulocochlear dysplasia	1	1	5	
LVA	1		5	1
Hyperintense white matter		1		1
Absent cochlear nerve				7
EAC stenosis			1	
Microcephaly			1	
Mondini	1			
CPA lesion		1		
Vascular loop				1

CPA = cerebello-pontine angle, CT = computed tomography, EAC = external auditory canal, LVA = large vestibular aqueduct, MRI = magnetic resonance imaging

Table 3. Positive genetic results

		Ophtalmic pathologies (n=19)	Non-ophtalmic pathologies (n=72)
Connexin 26 (GJB2)	Homozygous	Nil	4
	Heterozygous	2	11
Connexin 30 (GJB6)		Nil	Nil
Connexin 31		Nil	Nil
SLC26A4 (Pendrin)	Heterozygous	1	3
SLC26A5 (Prestin)	Heterozygous	1	1
GJB3		Nil	Nil
MYO15A		Nil	Nil
MYO7A		Nil	Nil
KCNQ4 (DFNA2)		Nil	Nil
DFNB4		Nil	Nil
Usher syndrome		Nil	Nil
Alport syndrome		Nil	Nil
Branchio-oto-renal syndrome		Nil	Nil
Waardenburg syndrome		Nil	Nil
Stickler syndrome		1	Nil
Jervell and Lange-Nielsen syndrome		Nil	Nil

to communicate better and improve their function in everyday activities. Secondly, diagnosing ophthalmic co-morbidity might help in understanding the possible syndromic basis of a child's condition and promote a genetic diagnosis.

Our results demonstrated that 21% of the children from our congenital hearing loss cohort were found to have an ophthalmic pathology; however, the risk for an ophthalmic condition was significantly lower in babies diagnosed in the era of UNHSP. The previously reported overall prevalence of visual impairment among healthy children 5 years of age and younger is between 7 and 8.2% [5]. Our results emphasize the higher rates of visual problems among infants and children with hearing loss. Previous studies described even higher chances for diagnosing co-morbid hearing loss and ophthalmic conditions and past quotes vary between 30 and 60% [4-6].

Differences may be secondary to selecting specific populations in some studies (such as newborns with suspected Usher syndrome) and to the fact that significant numbers of the children in our study were born in after the initiation of a UNHSP. Current screening programs allow early detection of children with hearing impairment compared to past years when they were identified at a later stage. This change is especially relevant for non-syndromic hearing losses and unilateral or mild loses, which occasionally would go unnoticed and undertreated for years. Bakhshaee et al. [2] described their cohort of 50 Iranian children with congenital SNHL in which 32% of the children in their cohort exhibited at least one form of ophthalmic abnormality while the most common problems were refractive abnormalities. An unusual finding in their cohort was a high degree (24%) of retinal abnormalities including suspected rubella retinopathy and retinitis pigmentosa.

We did not diagnose any retinal pathologies in our cohort and this may be explained by the differences in environmental risk factors such as lack of Rubella infections in our catchment area. Guy et al. [6] published results from a cohort of 110 children with hearing loss who were treated at a child development center in the United Kingdom. These children underwent ophthalmic examinations and were found to be two-three times more likely to have an ophthalmic pathology compared to their peers. The prevalence of eye abnormalities amongst their cohort was 43% and the majority had refractive problems. We believe that the high rates of ophthalmic pathologies may be related to the older ages of their patients as this cohort focused on older children treated at a specialized child development center. The chances for diagnosing a refractive pathology, especially myopia, increase with age.

Another possible selection bias for this study is that children with milder forms of hearing loss or unilateral losses (like many in our cohort) would probably not be cared for in such a specialized clinic. Mafong et al. [7] described their results of ocular assessments in a cohort of 49 children with SNHL diagnosed in the catchment area of San Francisco, CA, United States. They also showed higher risk for ocular pathologies among children with SNHL with a prevalence of 31% while hyperopia was the most common finding. Their cohort did not include patients with retinal problems and they commented that rubella infection was unlikely among their patient population, which seems to be quite similar to the demographics of our cohort. Among our cohort, like the previous studies mentioned, refractive errors were the main finding with 11 (55%) of the children presenting with those. This finding appears to be the common ophthalmic pathology among all previous studies regardless of date or population.

The diagnosis of retinal abnormalities is not an easy task in babies; however, it may uncover Usher syndrome, which is an important cause for concomitant auditory and ocular deprivation. Electroretinography (ERG) is an important adjunct to the clinical assessment of babies and children suspected for this syndrome although most studies did not include this test as part of their routine [2,3,4,6]. ERG in babies and children frequently requires sedation which often delays its completion. This study is noninvasive and safe although limited by some need for cooperation. We suggest performing this test in high-risk populations for Usher syndrome and geographic areas endemic for Rubella infections. Its potential use may promote diagnosis of early retinal changes and it may be performed in conjunction with CT or MRI which occasionally are done under sedation in this age group.

Performing genetic analysis for children with congenital SNHL is becoming more common [8-12] and in the future

will probably evolve into an integral part of the routine workup for these babies. We were able to complete genetic analysis in 74% of children from our cohort, which includes mainly non-syndromic patients.

Of interest, we did not find any homozygous mutations in the subgroup of children with positive ophthalmic conditions, although some heterozygous mutations with uncertain clinical importance were demonstrated. Among the subgroup of SNHL patients without ophthalmic pathologies, we uncovered four clinically relevant homozygous mutations for *Connexin 26*. These results suggest the possibility that non-syndromic children with hearing loss and ophthalmic conditions are less likely to present with significant genetic findings. Regardless of these results, we do believe that genetic analysis should become a routine part of the workup for congenital SNHL and we always offer this option to parents even though it might not change the course of suggested interventions or clinical decisions.

Strengths of this study rely on its large cohort of young babies and children and the fact that we were also able to complete genetic evaluation and imaging for most of our patients. To the best of our knowledge, this is the first study in the international literature to show up-to-date rates of ophthalmic diagnoses in children diagnosed with congenital hearing loss in the era of the UNHSP. Our data highlights the lower incidence of such disorders in current practice compared to older cohorts. All larger studies so far were based on deaf children who were cared for in special schools or developmental clinics and did not present the typical population that is diagnosed in the era of the universal newborn hearing screening programs. Furthermore, when analyzing the available data it seems that the studies that describe older aged children (i.e., schools and specialized clinics) tend to deviate toward presenting the more severe cases in the spectrum of SNHL as well as the fact that older children harbor more refractive ophthalmic problems due to their older age. Therefore, we presume that the data from the older studies on the high prevalence of ophthalmic problems among children with SNHL presents an overestimation of the prevalence currently.

According to our results, the prevalence of ophthalmic problems among these children is still higher than their peers and we still strongly support routine ophthalmic assessment for all babies and children with congenital SNHL. Limitations of this study are the heterogenic cohort of children as some were diagnosed just after birth (UNHSP) and others at an older age. Another issue is the nature of this cohort, which presents the local demographics and environmental factors of New Zealand and specifically the greater Auckland area.

CONCLUSIONS

The ophthalmic assessment of babies and children with congenital SNHL is still very important in the era of the universal newborn hearing screening programs and a significant percentage of these children will present with ophthalmic pathologies that further complicate their sensory inputs and communication skills.

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"I shall allow no man to belittle my soul by making me hate him"

Booker T. Washington (1856–1915), reformer, educator, and author

"Education is the most powerful weapon which you can use to change the world"

Nelson Rolihlahla Mandela (1918–2013), South African anti-apartheid revolutionary, political leader, and philanthropist who served as President of South Africa from 1994 to 1999; the country's first black head of state and the first elected in a fully representative democratic election