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A World's First Addition to Ontario's Infant Hearing Program

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Let's Get Some Context First

The value of Early Hearing Detection and Intervention programs (EHDI) has been well established and is considered standard of care. Since 2002, Ontario's Infant Hearing Program (IHP), funded by the Ministry of Children, Community and Social Services, coordinates hearing screening and follow-up audiology assessment. The aim is to identify babies with permanent hearing loss (PHL) as early as possible so that they can be connected with the supports and services they need to develop language. The IHP also offers hearing surveillance to infants identified with a risk factor for developing hearing loss later in childhood. This surveillance component is an important piece of any EHDI program. While approximately 2-3 out of 1,000 babies will have PHL at birth, another 2–3 out of 1,000 will develop PHL by the age of 5.

Finding At-Risk Babies Is Hard

One of the major challenges with any EHDI program is identifying babies at risk. While PHL has a variety of environmental and genetic causes, by far the most common causes are congenital cytomegalovirus (cCMV) infection and genetic risk factors. Variants in the *GJB2*, *GJB6* and *SLC26A4* genes and cCMV explain ~25% and ~20% respectively of congenital hearing loss and ~30% and ~25% of hearing loss by 4 years of age. The problem is that these genetic causes are autosomal recessive (i.e., no family history) and non-syndromic (i.e., no other indicators) making them difficult to ascertain. Additionally, most babies with cCMV, up to 90%, are asymptomatic and the infection usually goes undetected in the newborn.

More On cCMV and Genetic Risk Factors

Cytomegalovirus (CMV) is a common virus and most healthy people will not have any signs or symptoms of infection. When a pregnant woman is infected there is a risk of transmitting the infection to the baby. *Congenital* CMV (cCMV) applies when a baby is infected prenatally, not if infection occurs after birth. cCMV can affect a baby's growth, and the development of the brain, cochlea, and eyes. The most common permanent problem is hearing loss. The hearing loss may be present at birth or develop later in childhood. It may be unilateral, bilateral, mild to profound, asymmetrical, and is often progressive.

Genetic causes account for about half of all childhood PHL. Many different genes are known to be associated with hearing loss. Risk factor screening looks for some of the most common pathogenic variants, or genetic mutations, in the genes *GJB2*and*GJB6*, and *SLC26A4* that can cause DFNB1 and DFNB4-related hearing loss, respectively. These three genes provide instructions for the production of proteins that are important to the development of the cochlea; pathogenic variants cause the genes to either not work, or to work differently.

Forming a Partnership

The IHP has partnered with Newborn Screening Ontario (NSO) to expand screening to include testing for risk factors for PHL. While IHP continues ***to screen babies for hearing loss*** using otoacoustic emissions (OAE) and automated auditory brainstem

response (AABR), parents can now consent to have NSO ***screen for risk factors*** for hearing loss on their infant's dried blood spot (DBS). The goals of the risk factor screening are to improve surveillance by finding those most at risk, improve etiological information for babies with PHL, and as a backup for both missed and false-negative hearing screenings.

A Primer On Newborn Screening Ontario and the Dried Blood Spot Screening

Newborn Screening Ontario is the provincial program that coordinates newborn dried blood spot (DBS) screening. Shortly after birth, a small amount of blood is collected from all infants by pricking the heel. The blood is spotted and dried on a special filter paper card (DBS) and sent to the NSO laboratory, located at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa. DBS are screened for treatable diseases that usually show no symptoms in the newborn period; including metabolic diseases, endocrine diseases, sickle cell disease, cystic fibrosis, and severe combined immune deficiency. Like hearing screening, newborn DBS screening is considered standard of care and strongly recommended for all infants.

Introducing Risk Factor Screening for PHL

Since July 2019, all babies who have hearing screening are now offered screening for cCMV and common variants in the *GJB2/6* and *SLC26A4* genes using the DBS collected by the hospital or midwife for routine newborn screening. Risk factor screening for PHL is a consented test offered to parents by the IHP either at the time of the baby's physiologic hearing screening or when that screening is booked. Consent is then submitted to NSO where testing is requested and results are processed. Screening results are returned to the regional IHP lead agency.

What Happens with cCMV Screen Positive Results?

NSO communicates the positive cCMV screening results to a dedicated nurse practitioner working in each of the Pediatric Infectious Diseases clinics in the Pediatric Academic Health Sciences Centres. The regional nurse practitioner (NP) informs the parents and primary care provider of the positive screening result then refers the baby to

a community pediatrician who is partnered with the screening program. The community pediatrician performs a medical evaluation to assess for signs and symptoms of cCMV infection. The IHP simultaneously refers to the baby for a diagnostic audiology assessment. Any infants with symptoms of cCMV identified on medical or audiology assessment are referred to an infectious disease specialist for consideration of antiviral treatment. All babies identified with permanent hearing loss are offered intervention including amplification, language development, and family support services through their local IHP lead agency.

Continued Surveillance Is Essential

Infants with no PHL at birth and no other sequelae of cCMV infection have a ~10% risk of developing non-congenital PHL by six years old. These asymptomatic children are offered audiologic surveillance through the IHP at 10 months, 15 months, 18 months, 3 years and 5 years of age. Any infants with no PHL but with other symptoms of cCMV infection have a ~30% risk of non-congenital PHL and are consequently offered more intensive surveillance with two additional assessments at 3-month intervals after the initial ABR, followed by the same surveillance as for asymptomatic infants. All children with cCMV are followed by a pediatrician for developmental surveillance throughout early childhood.

What Happens with Genetic Risk Factor Screen Positive Results?

An audiologist and genetic counsellor from the IHP and NSO inform the parents and primary care provider of the results and the IHP coordinates a diagnostic audiology assessment. The majority of the genetic variants included on the NSO screening panel have a strong association with congenital or early-onset PHL and many will have already received a refer results on their physiologic hearing screening. If PHL is identified, NSO refers the baby to an otolaryngologist and intervention including amplification, language development, and family support services are offered to the family through the local IHP lead agency. If no PHL is identified at the audiology assessment, audiology surveillance is arranged by the IHP at 3-month intervals for the first year, and at 15–18 months, and 3 years of age.

How NSO and IHP Know the Program is Working

The audiologists, pediatricians, ENT surgeons, or infectious diseases specialists who see these babies with PHL risk factors, complete a diagnostic and initial outcome report that is returned to NSO and the IHP. This ensures the program is meeting its objectives to identify children at risk for PHL and connect them with appropriate care to optimize their developmental outcomes.

This Novel Program Has Been Well Received

Consent uptake for the hearing loss risk factor screen has been >98.5%. Anecdotal experience has revealed that most parents of screen-positive infants want to be engaged in a heightened surveillance program for their children at risk for PHL, and are grateful to have an etiology for those with hearing loss detected at birth. We look forward to sharing program outcomes at a later date.

Overall, risk factor screening for PHL has strengthened the level of screening and care provided to infants at risk for PHL. This collaboration between the Infant Hearing Program and Newborn Screening Ontario is a “first of its kind” endeavour that will place Ontario at the international forefront of early detection and intervention for early childhood permanent hearing loss. Benefits of this collaboration include: more children being identified and provided with services earlier due to recognition of genetic and environmental causes, improved access to ENT, improved understanding of etiology, and improved surveillance.