Hearing loss is the most common sensory disability in infants and young children. Undiagnosed, it can hamper acquisition of speech and language and lead to adverse effects on social, emotional and cognitive development. In response to the recognized need for early diagnosis and timely intervention, screening of newborn infants for hearing loss has become almost universal across the United States.

In Washington state, babies in newborn nurseries are given a hearing test whose results are reported to the state Department of Health, along with results of a checklist of risk factors that can presage future hearing loss. While newborn hearing screening is not mandated by law in Washington as it is in some states, some 80 percent of babies born in the state now receive a hearing test before hospital discharge.

Screenings are valuable but not foolproof, says Richard C. Folsom, Ph.D., University of Washington professor of speech and hearing sciences and a research affiliate at the Center on Human Development and Disability. He is evaluating the usefulness and cost-effectiveness of tracking children up to age 3 who, despite passing an initial screening, are at risk for hearing loss.

The three-year study, funded by the federal Centers for Disease Control (CDC) through the Association of University Centers on Disabilities (AUCD), will look at data from an estimated 210,000 newborns who will be screened in Washington state over the life of the grant. It is a collaborative effort between the University Center of Excellence in Developmental Disabilities at the UW Center on Human Development and Disability, Children’s Hospital and Regional Medical Center, and the Washington State Department of Health.

Susan Norton, Ph.D., UW professor of otolaryngology/head and neck surgery, is co-principal investigator. She is director of research and audiology at Children’s Hospital and Regional Medical Center and a CHDD research affiliate, Debra Lockner-Doyle, M.S., state coordinator for genetic services for the Department of Health, is also an investigator. She manages the state database that tracks newborn metabolic and hearing screenings.

“Our partnership takes advantage of decades of experience in developmental disabilities, pediatric audiology and newborn hearing screening,” said Folsom. “Our long-term goal is to improve the quality of life for infants and young children with hearing loss through appropriate intervention. While universal newborn screening should detect most hearing losses at birth, some progressive or late-onset hearing losses are missed. We don’t have a mechanism for screening babies once they leave the hospital, so it is up to parents and the primary care provider or others who observe the baby to determine whether there may be a problem.”

Hearing impairment that is mild to moderate, limited to one ear, or confined to specific frequencies may be very difficult to detect without testing. “The incidence of significant hearing loss at the time of birth is only about one to three babies in 1,000 screened,” said Folsom. “In older children the incidence goes up six-fold. These are clearly late-onset cases not identified through newborn screening. We want to learn to identify and follow children with risk factors for later-onset hearing loss. The average age at which hearing loss is identified is 12 to 25 months. When detection is delayed, critical opportunities for developing speech and language are lost.”

In Washington state, failing the screening test in the well-baby nursery—usually a test called evoked otoacoustic emissions or OAE, which evaluates the functioning of the cochlea in the inner ear—triggers an action letter from the Department of Health to the baby’s primary care physician, requesting that the child be referred to a pediatric audiology center, where more extensive diagnostic testing is performed.

Washington’s newborn screening program includes a hearing screening and a checklist of risk factors for possible future hearing loss.
Hearing screening . . . from page 1

and, if necessary, treatment prescribed, such as hearing aids or cochlear implants.

In addition to those identified at birth, the focus of the study is the baby who passes the initial screening but who has one of five general risk factors for future hearing loss and thus should be monitored until at least age 3. Developed in the year 2000 by the national Joint Committee on Infant Hearing (JCIH, of which Folsom was a member), the risk indicators are the following:

- Any illness or condition requiring admission of 48 hours or more to a neonatal intensive care unit (NICU)
- Findings associated with any syndrome known to include hearing loss
- Family history of permanent childhood hearing loss
- Craniofacial anomalies
- In utero infections such as cytomegalovirus (CMV, a major cause of late-onset hearing loss), herpes, rubella, syphilis and toxoplasmosis.

The study will analyze data compiled over the next three years in Washington state’s surveillance and tracking system, known as EHDDI, Early Hearing Loss Detection, Diagnosis and Intervention, to determine the prevalence of late onset and/or progressive hearing loss and to assess the utility of evaluating according to the JCIH risk factors. “EHDDI not only tracks newborn hearing screening,” said Folsom. “It tracks the whole process of early detection, diagnosis and intervention, using software developed with funding from the CDC. We expect to ask many questions of the database. It’s a wonderful opportunity to have access to a wealth of information.”

Once statistics are compiled from the more than 200,000 screenings, a state health care economist will help determine if it is feasible to continue such tracking and whether it is worthwhile to invest in such an effort. “Until we know how many babies such a screening effort uncovers, we won’t know the real cost to society to track and identify these children,” said Folsom.

The grant will also fund a continuing education program aimed at people on the frontlines of screening, said Folsom. “The education effort will focus on risk indicators. We think we can improve the quality of the data—the risk indicators being checked off at birth—by educating the screeners and hospital nursery staffs charged with reviewing charts and evaluating risk factors.”

It will also be aimed at primary care providers, said Folsom. “We want to know how primary care physicians respond when they receive an action letter from the state, alerting them to a potential hearing problem in a child in their care. Are they acting on it? Do they see the importance of following up on the information contained in the letter?”

This study seeks to determine whether there are better means of screening babies to take into account risk factors for hearing loss, said Folsom. “Is there something about a baby that we could see at the time of birth that might predict whether he or she is susceptible to late-onset hearing loss? There is an unknown population of babies who develop hearing loss after birth, and we don’t currently have a mechanism for screening them. That’s what this study is all about.”

Early diagnosis and treatment of hearing loss helps prevent developmental problems.
Using new technologies to study the p53 gene’s role in neurodegenerative and neurodevelopmental disorders

ongoing research by Richard S. Morrison, Ph.D., is increasingly clarifying the important role that a gene with the unassuming name of p53 plays in the clinical course of a number of neurodegenerative and neurodevelopmental disorders, as well as in traumatic brain injury and stroke. Morrison is a University of Washington professor of neurological surgery and a research affiliate at the Center on Human Development and Disability.

p53, a tumor suppressor gene, has long been known to fulfill a positive function in suppressing the growth of many types of cancer cells by initiating apoptosis, or programmed cell death, in genetically damaged cells. However, p53’s more sinister role in the neurons of the central nervous system was less clearly defined until Morrison’s investigations, which incorporate cutting-edge research methods to gain a fuller understanding of the gene’s myriad functions.

The p53 protein works in the cell nucleus and functions as a regulator of DNA repair, cell-cycle progression and apoptosis. It accomplishes this task by stimulating or repressing the expression of other genes, each with its own unique function.

To understand the range of genes regulated by p53, scientists including Morrison are pursuing the new science of proteomics. Just as genomics, or the study of the genome, identifies all the genes in a particular organism, proteomics involves studies to uncover all the proteins in a proteome: a particular genetic pathway, cellular structure, cell, tissue, organ or organism. The goal is to determine how the proteins respond to each other and their environment, to advance understanding of the mechanisms of disease processes. “Proteomics gives us a broad view of the changes in protein expression that take place in neurons destined to die, as occurs in a number of neurodegenerative disorders as well as brain trauma,” said Morrison.

“p53 is one of the major regulators of cell death in neurons. We know that p53 promotes apoptosis, but we’re finding that it may also compromise cell function without pushing the cells over to cell death. They’re sick, but they’re not dead yet. There is good evidence that neurons exist in a sick, dysfunctional state in neurodegenerative diseases prior to showing a significant degree of apoptosis. Understanding how p53 compromises function prior to the change in viability is very important, since we may be able to intervene before the cells die.”

The neurodegenerative and neurodevelopmental disorders and conditions associated with over-expression of the p53 protein in neuronal cells constitute a long list: Alzheimer’s disease, amyotrophic lateral sclerosis (ALS or Lou Gehrig’s disease), Angelman syndrome, Down syndrome, HIV-associated dementia, Huntington’s disease, seizures, stroke, and traumatic brain injury. In laboratory mice, experimental removal of the adrenal gland, exposure to ionizing radiation, methamphetamine-induced neurodegeneration, and photochemical injury of the brain are also associated with p53 over-expression.

Recent biotechnological advances are enabling Morrison and his colleagues to make rapid strides in their understanding of p53. One is the ability to measure changes in gene expression using microarray analysis. Microarrays are ordered sets of DNA molecules, fixed to DNA chips. Microarray analysis allows scientists to detect the expression levels of thousands of genes simultaneously. They can also examine tissue microarrays, surveying a single gene in thousands of different tissue specimens, to analyze the relationship of individual genes to disease. “With the advent of microarray analysis, it’s now possible to measure changes in mRNA expression on a global scale,” said Morrison. “You can measure expression of every gene known.”

Intriguingly, in a significant number of cases—about 30 percent of the time in Morrison’s studies—there is no change in a gene at the mRNA level, but there is a significant change in the abundance of the protein that the gene expresses. “There are many important genes relevant to cell death or dysfunction that you might miss if you draw conclusions solely on the basis of mRNA expression,” said Morrison. “You have to look at the proteins as well.”

Studies at the protein level are a significant challenge. Complex protein samples are first broken into smaller peptide fragments using protease enzymes such as trypsin. These peptide mixtures are separated on the basis of charge, size and polarity and run through a mass spectrometer, an instrument that determines the mass of the peptides and their relative concentrations.

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When bigger isn’t necessarily better: brain imaging studies may help unravel some of autism’s mysteries

Researchers affiliated with the Center on Human Development and Disability have observed through neuroimaging studies that preschool-aged children diagnosed with autism spectrum disorder have larger brains than either typically developing children or those whose developmental delay originates from other causes. Other studies indicate that children who subsequently develop autism do not have a history of especially large head circumference at birth. These findings are prompting investigations into when and why unusual brain growth occurs in children later diagnosed with autism, and how alterations in brain structures relate to clinical characteristics of the disorder.

Stephen Dager, M.D., University of Washington professor of radiology and a research affiliate at the Center on Human Development and Disability, is investigating how brain anatomy, brain chemistry, and behavior and cognition relate to each other and how these factors evolve as children with autism grow and develop. Dager is principal investigator on two important imaging studies of autism.

One, Neuroimaging in Autism, sponsored by the National Institute of Child Health and Human Development (NICHD), is the third phase of a long-term study that initially focused on 3- and 4-year-olds, evaluated them at age 6 and 7, and is currently re-examining them as 9-year-olds.

The second investigation, titled Brain Development in Autism, is sponsored by the National Institute of Mental Health (NIMH) and based on the earlier study of 3-year-olds. Dager and colleagues are evaluating toddlers aged 18 to 24 months, currently the youngest age range at which autism can be diagnosed. The toddler study is a project of the National Institutes of Health’s STAART Network: Studies to Advance Autism Research and Treatment.

“We’re using innovative imaging methods to try to understand the progression of brain development and what goes awry in children with autism spectrum disorders,” said Dager. “Such an understanding may help to point the way to earlier diagnosis and more effective interventions, both pharmacological and behavioral.”

Imaging techniques include two-dimensional and three-dimensional magnetic resonance imaging (MRI) to systematically characterize brain anatomy, and two-dimensional proton echo-planar spectroscopic imaging (PEPSI), a radiation-free technology for quantitatively measuring brain chemistry, developed at the University of Washington in collaboration with Stefan Posse, Ph.D., a research scientist at the NIH. Neuropsychological measures of behavior and cognition are also taken.

The longitudinal study of the now-9-year-olds involves 45 children with autism, 25 with developmental delay of unknown origin, and 25 typically developing children. “It’s a challenge to do longitudinal imaging studies of youngsters,” said Dager, “but they and their parents have been very much committed to the research. One family had moved to Amsterdam, but on a brief return visit to Seattle made sure their child came in for a repeat imaging study.”

Included in the toddler study are 48 children with autism, 25 with developmental delays of unknown origin, and 25 typically developing children. Those with autism and developmental delays are being clinically assessed over time, to relate the course of their symptom development and behavioral performance to subtle alterations of brain structure.

Using MRI, the researchers are taking detailed anatomical measurements of various brain structures and examining the composition and distribution of the brain’s gray and white matter. “We find that the children with autism have cerebral enlargement of about 10 percent compared with children who are typically developing when they are imaged at age 3 to 4,” said Dager. “By age 6, their brains are only about 2 percent larger. We don’t think this is merely a regression to the mean. There may be something in the brain’s growth trajectory that is more rapid in children with autism but plateaus earlier.”

Perhaps more intriguing is that at age 3 to 4, children with more severe clinical expression of autism also exhibit disproportionate enlargement of the amygdala, the almond-shaped brain structure that plays an important role in motivation and emotional behavior. The enlargement becomes even more striking when the imaging studies are repeated at age 6. “This observation may have clinical relevance, as those with enlarged amygdala volumes tend to do less well in terms of social growth and communicative skills,” said Dager. “Our findings suggest that these abnormalities in the amygdala are tied to the severity of autistic symptoms, and may be predictive of some aspects of neuropsychological development. It seems that bigger is not always better, although some of these children...”
The peptide sequence is then determined for developing epilepsy, Dager and colleagues are adding an additional imaging modality to the study of the 9-year-olds: FLAIR, or fluid-attenuated inversion-recovery imaging, an MRI technique that enhances the detection of lesions or gliosis in the brain, to determine whether it may be possible to identify brain markers to predict the risk of seizures.

“About a third of children with autism develop temporal lobe epilepsy, usually as they approach adolescence,” said Dager. “Because of behavioral issues with autism, the seizures are often difficult to verify clinically. You don’t want to treat all children with autism as if they have epilepsy, but it’s important to treat those who do. Seizures may bring about a diminution of the ability to interact socially and a step backwards in developmental milestones. We hope to recognize evidence of gliosis or scarring over the temporal lobes that is involved in the development of seizures.”

In collaboration with researchers at Washington University in St. Louis, Dager’s lab is using powerful imaging analytical techniques to study projections on the surface of another brain structure, the hippocampus. “Although these are preliminary findings, we’ve observed that children with more severe autism who are at greater risk for seizure development have characteristic deformation of one region of the hippocampus similar to that in adults with mesiotemporal lobe epilepsy,” he said. “We hope to follow these children over time to see if this structural abnormality persists and whether it can predict which will later develop seizures.” This research is supported by Cure Autism Now (CAN).

Dager’s research collaborators include CHDD research affiliates Geraldine Dawson, Ph.D., professor of psychology, and Dennis Shaw, M.D., associate professor of radiology, as well as Seth Friedman, Ph.D., research assistant professor of radiology, Helen Petropoulos, Ph.D., research scientist in radiology, and Alan Arrtu, MD, professor of anesthesiology.
Bright Futures in Early Childhood enhances efforts to give children a head start toward good health

Bright Futures is a term that aptly describes a national effort to improve health outcomes for children, promote healthy behaviors and develop partnerships among health professionals, families and communities. Based on a philosophy of health promotion, Bright Futures offers materials aimed at professionals in health and education, as well as families, to promote children’s physical, nutritional and social/emotional health.

Launched by the federal Maternal and Child Health Bureau in 1990, Bright Futures programs now exist in most states. The Center on Human Development and Disability is working closely with the Washington State Department of Health’s Office of Maternal and Child Health to promote Bright Futures.

“We started with a small project called Promoting Bright Futures in Washington State,” says Susan Wendel, MS, OTR, occupational therapy coordinator at CHDD, who manages the Bright Futures projects. “We now have an additional focus with a new pilot project called Bright Futures in Early Childhood.”

Involving early childhood programs in 11 communities across the state, Bright Futures in Early Childhood focuses on organizations that offer education, health, nutrition and parent-involvement services to young children from low-income families: Head Start, Early Head Start and ECEAP have mandates to promote children’s health, there can be a wonderful link between these organizations and the tools and materials offered by Bright Futures.”

Also working on the 17-month pilot project are Jean Myers, MPH, PT, also of the Center on Human Development and Disability; Karen Zeribi, MHS, of the UW Child Health Institute, in charge of data evaluation and monitoring; and Peggy King, MA, RN, of Kids Northwest, who has an extensive background working with early childhood programs. CHDD is also collaborating with an interagency steering committee of statewide stakeholders.

Each of the 11 participating programs has designated a Bright Futures team that includes health coordinators, family services coordinators and education coordinators. Team members attended one-day training sessions in February and April, and returned to their home programs to provide training to their own staffs. A third session in the fall will bring the group together and may involve onsite visits.

“Early childhood educators are in a good position to offer health information to children and families,” said Wendel, “but some may feel reluctant to talk about such issues if it’s not part of their educational backgrounds. While most programs have a health and nutrition coordinator, he or she may be just one person in a rather large agency, and may have little direct contact with families.”

The 11 participating programs range in size from one to 15 education centers, and serve from 70 to 690 children, for a total of almost 2,500 children in 65 centers across the state. “We wanted representation from urban and rural communities, small and large programs, and with cultural and geographic diversity,” said Wendel. For example, in rural northeastern Washington, the Spokane Tribe of Indians Head Start program has one center with 70 Native American children enrolled. In urban northwestern Washington, the Snohomish County Head Start, Early Head Start, and their associated childcare programs involve 12 centers serving some 540 children from various ethnic backgrounds.

Following the first training session, participants developed Bright Futures work plans for their centers. First, they devised ways to use Bright Futures materials to promote well-child visits and ensure that
children and families have a primary care provider, know the reasons for routine dental and health checks, and attend well-child visits. Secondly, each program chose and promoted a specific health issue, such as nutrition and obesity, physical activity, oral health, or mental health. Participants utilize Bright Futures’ wide variety of resource tools, including separate workbooks on various health promotion topics, and determine how best to use the materials to address their chosen topics in their particular situations.

At the second training session, participants returned for a “show and tell” to demonstrate how they began training their staffs and implementing the use of Bright Futures teaching aids. Examples included designing bulletin boards to promote specific health issues, producing weekly menus for children that incorporate healthy eating messages for families, and promoting physical activity with an activity pyramid on which children’s photos were posted for their families to see.

Participating programs received tool chests containing a wide variety of Bright Futures materials, such as colorful activity books for children and families. During home visits, the teacher or health educator might introduce a particular topic like teeth brushing or family meals, or respond to concerns raised by the parents.

“The materials have visual appeal and offer clear and direct information,” said Wendel. “The idea isn’t to bombard the family with hundreds of messages, but to pace and repeat them.” A curriculum is being developed for training parents to use a tool called the Bright Futures Health Organizer and other family health-promotion materials.

At the conclusion of the pilot period, three outcomes will be measured, said Wendel: the improvement that individual centers achieve in meeting the health promotion requirements of their programs; the improved knowledge, skill and confidence of staff in working with families on health promotion practices; and the degree to which participating families’ knowledge of health promotion practices is enhanced.

“As the pilot program draws to a close, we will gather all the clever Bright Futures ideas that our participants have implemented and share them with the other centers,” said Wendel, “and we will determine how this project can be sustained and replicated in other early childhood programs. While we have funding at present, that may not always be the case, so we need to devise ways to extend the program with less financial support. In our final report, we hope to document a model that may be of interest not only statewide, but nationally. Our federal administration is emphasizing early learning and school readiness, and our message is that good health is essential for learning.”

For more information on the program, visit Bright Futures’ web sites at www.brightfutures.aap.org and www.brightfutures.org. Materials for centers and families may be ordered or downloaded from the web sites.

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Does it tie up proteins that would ordinarily be available to the neuron for processes needed for normal function and survival?”

Using proteomics, the Morrison lab has identified a number of mitochondrial proteins that change in response to injury. “Some of these proteins weren’t previously known to translocate from the cell’s cytoplasm to the mitochondria,” he said. “We want to identify what these mitochondrial proteins interact with that precipitates a decline in mitochondrial function. Once they decline, they lose the ability to make ATP (a nucleotide that is the cell’s major energy currency) and they release other factors that promote apoptosis. The neurons then can’t function or survive.”

Changes in mitochondrial integrity and function are associated with a host of neurological disorders and injuries, said Morrison. “From head trauma to Huntington’s disease to Alzheimer’s disease, mitochondria are a convergent point in some part of the process. This has become a major focus for our lab.”

p53 regulates a host of proteins that likely compromise mitochondrial function and integrity, both in neurons and in non-neuronal cells such as tumor cells. While a number of proteins are known to mediate apoptosis and regulate neuronal survival, Morrison’s lab is finding that p53 may regulate proteins not previously considered in terms of mitochondrial function. Areas of investigation include p53’s effects on mitochondrial fragmentation, repression of healthy proteins resulting in accumulation of damaging free radicals, ATP biosynthesis, and other metabolic processes.

The lab is using proteomics and bioinformatics analysis to characterize the mitochondrial proteome of neurons: that is, to identify every protein present in neuronal mitochondria, in order to understand how the proteins change in response to disease and injury. “This will help immensely in understanding the response of neurons to injury and how injury ultimately promotes cell death,” said Morrison.

Proteomics technology is beginning to have clinical relevance. For example, in collaboration with Dr. Anthony Avellino and Dr. Richard Ellenbogen, chair of the UW Department of Neurological Surgery, a global analysis of the proteins in cerebrospinal fluid before and after surgical removal of certain pediatric brain tumors is allowing Morrison and colleagues to identify which are expressed only when the tumor is present, helping to guide treatment decisions. Such knowledge may also help point the way to tumor markers that will indicate the presence of brain cancers.

“As research members of a clinical department, we never lose sight of the fact that we’re dealing with actual patients,” said Morrison. “We think this new technology will provide an important tool for the study of nervous system disease and injury.”
Faculty members appointed as new CHDD research affiliates

Philip J. Horner, Ph.D., is an assistant professor of neurological surgery. He studies regeneration in the central nervous system, focusing on stem cell and progenitor cell biology, especially molecular controls of neural and glial cell interactions in models of demyelination, injury and degeneration. He uses cellular and molecular techniques to study stem cells and their progeny in the intact and injured CNS. The adult spinal CNS retains a stem cell with the capacity to differentiate into all the major cell subtypes of the mature CNS; the Horner lab is using confocal microscopy and time-lapse imaging to track these cells, labeled with retroviruses, in the brain. Other projects include the discovery and experimental delivery of growth factors that regulate axon regeneration and myelination in models of spinal cord trauma, demyelinating disorders and retinal degeneration.

Hannele Ruohola-Baker, Ph.D., is a professor of biochemistry and adjunct professor of genome sciences. Her work is focused on how genes that are implicated in neurodevelopmental and neurodegenerative disorders play an important role in fundamental biological processes. Utilizing the fruit fly, her laboratory is investigating defects in three genes that are known to cause developmental problems in humans. In particular, she is seeking to understand how muscular dystrophy results from defects in the Dystroglycan-Dystrophin gene signaling pathway. In addition, she is investigating how the Notch gene signaling pathway acts as a tumor suppressor and how the microRNA pathway regulates stem-cell division, with an emphasis on understanding molecular interactions underlying establishment of cell polarity and the control of cell fate during development.

Sarah Jane Webb, Ph.D., is a research assistant professor of psychiatry and behavioral sciences. She examines the functional neurobiology and development of information processing and memory in autism spectrum disorders and other developmental disorders, as well as in typical development. Using EEG, event-related potentials, eye-tracking and behavioral measures, she studies how children learn about visual images such as faces, and how developmental disruptions impact learning. She seeks to detect the neural underpinnings of deficits in autism in processing and using information from the face, and studies how the brain perceives part of an item as belonging to a whole. With colleagues, she has developed a model of how over- and under-connectivity in specific neural regions may impair the ability to process and understand complex items and scenes.

Visit the CHDD website at depts.washington.edu/chdd