



Eunice Kennedy Shriver
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Frontiers in Down Syndrome Research

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Down Syndrome: An Introduction

We have learned a lot about Down syndrome since it was recognized by Dr. John Langdon Down 150 years ago, when he published a paper in 1866 describing people who shared very similar facial features. We know now that Down syndrome is relatively common: about 250,000 Americans have Down syndrome, and 1 out of 700 babies (nearly 6,000 per year) is born with the condition. Children with Down syndrome often have cognitive impairments and are at risk for a range of health problems. About half of all newborns with Down syndrome have a congenital heart defect, which occurs when the baby's heart does not form properly. Fortunately, with early identification and treatment, including cardiac surgery, many infants do well with this condition.

When Dr. Down first recognized the condition, he had no idea what really caused this "syndrome," suggesting that it might have been caused by maternal tuberculosis. It was not until 1959 that researchers found the link between the cognitive disability and a chromosomal difference, a first in the field of genetics. Typically, people are born with cells that carry 46 chromosomes. However, in 1959, French researchers discovered that cells of people with Down syndrome have 47 chromosomes because they carry an extra chromosome 21, or "trisomy 21." Now, we know of 200 to 300 genes on chromosome 21 that may contribute to the various features of the syndrome. This information has proved valuable in understanding factors associated with health and learning problems in children with the condition and has helped advance development of specific therapies.

This newsletter will highlight some recent advances in Down syndrome research from the [Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers](#) (IDDRCs), a network supported by the National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH). NICHD also supports DS-Connect®: The Down syndrome registry, which is an online health registry to collect basic demographic and health

information about people with Down syndrome. Approved scientists or researchers can view the DS-Connect® de-identified data on the Professional Portal and use this information to develop research projects and to recruit for clinical studies, while still protecting the privacy of those who take part in the registry.

Development of Language in Children with Down Syndrome

People with Down syndrome face many challenges, including difficulties with speech and communication. Because of these challenges, many are interested in research that will improve their daily lives.

For a long time, we have known that children with Down syndrome struggle with developing speech. Indeed, speech problems are often more severe than one might expect, based on cognitive limitations alone. Current research from the Vocal Tract Development Laboratory at the Waisman Center of the University of Wisconsin has helped explain the basis of these difficulties. Headed by Dr. Houri Vorperian, the research team uses a combination of imaging, sound technologies, and computer modeling to understand the basis of speech development and production in people with and without Down syndrome. By carefully imaging the vocal tract, the team found that people with Down syndrome have a normal-sized tongue inside a small mouth and jaw, which may limit the space available for front-to-back tongue movements and affect a listener's ability to understand a person's speech. To overcome this issue, future studies will focus on designing interventions that might include a combination of behavioral training, mouthpiece appliances (orthodontia), and surgery.

For any infant, acquiring language is a complex process that involves interactions between parent and child. Researchers supported by the IDDRC at the University of Kansas Medical Center have used a software program to analyze vocal interactions between infants and children with Down syndrome and their parents. By talking to the infant, an adult demonstrates sounds, which the infant repeats, resulting in a positive reaction from the adult. These interactions form a mutually reinforcing relationship that supports speech learning. Headed by Dr. Steven Warren, the Kansas team had two goals for understanding this relationship: (1) measuring the "language environment" of a child with Down syndrome, compared to that of typically developing infants, and (2) understanding whether this environment changes as the infants grow into toddlers. The researchers found that parents of typically developing infants tended to use more words than parents of infants with Down syndrome. As a result, children with Down syndrome made significantly fewer vocalizations, even though toddlers with Down syndrome demonstrated more vocalizations than infants with Down syndrome. These data may help language specialists and parents better understand the language delays in children with Down syndrome, even in early infancy, and provide opportunities for intervention.

IDDRC-supported investigators also are developing strategies to improve speech development in people with Down syndrome. A collaboration between the University of Kansas and the Vanderbilt University Kennedy Center for Research on Human Development found that children with Down syndrome who undergo daily, instead of weekly, speech therapy sessions have

larger spoken vocabularies. These daily therapies helped increase “canonical syllabic communication,” or duplicated syllables (such as “babababa”), and improve the children’s understanding of language. Led by Drs. Paul Yoder (Vanderbilt) and Steven Warren (Kansas), this study was the first to explain why increasing the frequency of speech therapy can improve speech acquisition in children with Down syndrome.

Brain Development in People with Down Syndrome

In addition to speech and communication, people with Down syndrome also may have numerous medical problems, the most challenging of which are associated with behavior and mental abilities. The IDDRCs have long supported research focused on these features.

A prime example comes from the IDDRC at the Kennedy Krieger Institute and Johns Hopkins University, where Dr. Roger Reeves has pioneered the development of mouse models of trisomy 21. Dr. Reeves and his co-investigators have found that, similar to humans with Down syndrome, mice with trisomy 21 demonstrate defects in learning and memory. A study of their brains revealed an abnormally small cerebellum when compared to mice without trisomy 21. The researchers hypothesize that a gene called “sonic hedgehog,” which is critical to normal brain development, might be deficient in people with trisomy 21. When the mice were given a drug that enhanced the activity of the sonic hedgehog gene, they developed a normal-sized and -shaped cerebellum. Their cognitive performance also was indistinguishable from mice without trisomy 21. Remarkably, the drug was given only once, when the animals were newborns. Although their work establishes the exciting possibility of using medications that affect gene action, the sonic hedgehog gene is involved in many key processes, and researchers must test the safety and effectiveness of this drug before it can be used in human trials. Dr. Reeves and his colleagues are continuing this line of research.

By studying mouse models, researchers can better understand abnormal patterns of brain development and test therapies that may improve cognitive performance. For a long time, researchers have known that cognitive and sensorimotor therapy can help the development of children with Down syndrome. At the Children’s National Medical Center, the IDDRC has sponsored research by Drs. Tarik Haydar and Vittorio Gallo that explores the biological basis for this phenomenon. These investigators examined brain growth in the mouse model and found that when young mice (18 days old) were exposed to an enriched environment and a program of regular physical exercise, they had a marked increase in nerve cells (called neurons) and a significant expansion of connections between those cells. Indeed, in some brain areas, these beneficial changes were so dramatic they almost restored the normal growth rate of the mouse’s brain.

The IDDRC at the Waisman Center at the University of Wisconsin also has made advances in better understanding the consequences of trisomy 21 on brain development. In their studies, Drs. Anita Bhattacharyya and Su-Chun Zhang have sampled skin cells from people with trisomy 21 and transformed these cells into neurons to examine human nerve function. While nerve cells normally communicate extensively through connections called synapses, the Waisman

researchers found that neurons with an extra copy of chromosome 21 were much “quieter” and failed to establish the normal communication networks essential for mental functions, such as memory and abstract thought. This impairment may be the failure to develop a specific nerve cell called an interneuron. In addition, the Bhattacharyya group noted that the neurons experienced considerable “oxidative stress,” a form of toxicity that can damage cells. The relationship between oxidative stress and disease is important in medical research, and evidence suggests that treatment with anti-oxidants, such as vitamin C or E, can protect cells from this injury. This line of research is valuable, not only for understanding abnormal brain development in Down syndrome, but also the cognitive decline that older adults often experience.

The Possibility of Pharmacologic Intervention to Improve Cognition

While it is not fully clear why neural pathways lead to cognitive deficits in people with Down syndrome, some evidence points to excessive activity of specialized neurons, called GABA-ergic neurons, that slow down the communication among other neurons. These inhibitory neurons can prevent the formation of complex neural networks responsible for learning and memory. An international, multi-site clinical trial, supported by the IDDRCs at Boston Children’s Hospital and the Waisman Center, tested the effectiveness of a drug intended to decrease the activity of GABA-ergic neurons to improve learning and memory. Although the results indicated that the drug is safe to give to children (age 6-17 years old), the drug did not improve the children’s cognitive performance. Other drugs that decrease the activity of inhibitory neurons may prove more effective.

At the University of California Davis MIND Institute, IDDRC director Dr. Leonard Abbeduto leads a research consortium that is developing standardized tests of expressive language (using words and language). Such tests will provide a way to measure responses to pharmacologic and behavioral interventions in people with intellectual disabilities, such as Down syndrome. Data collection will occur at 7 sites, including the IDDRCs at UC Davis, the University of Wisconsin-Madison, and the University of Washington. In a related project, Dr. David Hessler and other investigators at the MIND Institute are working with colleagues at the University of Denver and Rush University to adapt a set of computerized tests of overall cognitive function specifically for those with Down syndrome. The goal of these projects is to validate the reliability of these tests for use across the pediatric and early adult years. “These projects are benefitting from the services of our IDDRC. Moreover, the IDDRC will support the use of these measures by other investigators within the IDDRC network once they are validated,” Dr. Abbeduto noted.

Long-Term Outcomes for People with Down syndrome: The Problem of Dementia

Over the past 20 to 30 years, researchers have focused on the long-term outcomes of people with Down syndrome. Advances in managing congenital heart disease and other complications have dramatically increased life expectancy. In 1960, a person with Down syndrome was expected to live an average of only 10 years. By 2007, the majority of children with Down syndrome were surviving into adulthood. Experts note that life expectancy is continuing to

increase, and many people with Down syndrome are now living past middle age and becoming senior citizens.

The increase in life expectancy has prompted a focus on long-term characteristics of people with Down syndrome, one of the most worrisome being Alzheimer's disease. By the time they reach 35 to 40 years of age, almost all people with Down syndrome will likely develop brain changes associated with Alzheimer's disease, known as amyloid plaques. However, dementia rarely occurs until they are considerably older, and those changes do not occur in every person with Down syndrome. Nevertheless, the risk for dementia is high for adults with Down syndrome, which has prompted a search for blood or brain imaging markers (called "biomarkers") that will help detect cognitive decline early and eventually lead to therapies that prevent or reduce memory loss.

One example of this search for biomarkers comes from the IDDRC at Vanderbilt. Drs. Alexandra Keys and Elisabeth Dykens have examined event-related potential (ERP) markers of visual memory in both younger (19-25 years old) and older (35-40 years old) adults with Down syndrome. The researchers measured the subjects' response to unfamiliar scenes of cities or nature and found changes in the electrical signals that corresponded with the subjects' learning differences. This study underscores the usefulness of electrical brain signals as early markers of cognitive decline in Down syndrome. Dr. Dykens commented that their findings hold promise not only for aging individuals with Down syndrome, but also for other groups that have difficulty providing a behavioral or verbal response.

Two other IDDRCs are playing major roles in large, multi-site projects to identify biomarkers of Alzheimer's disease in adults with Down syndrome. The research teams behind these projects have several long-term goals, which include discovering why adults with Down syndrome are more likely to develop Alzheimer's disease, determining which factors affect who will develop dementia, recognizing early clinical symptoms, and learning how to support clinical trials aimed at slowing or preventing dementia progression.

The IDDRC at the Waisman Center of the University of Wisconsin is supporting the research of Drs. Bradley Christian and Sigan Hartley, who are using MRI (magnetic resonance imaging) and PET (positron emission tomography) to study early signs of Alzheimer's disease in the brains of adults with Down syndrome. Their research has shown that adults with Down syndrome often have amyloid plaques, or protein deposits in the brain, despite showing no signs of dementia. This pre-dementia marker appears several decades earlier in people with Down syndrome than it does in the general population. A new project will involve approximately 200 adults with Down syndrome and those without the condition and will characterize the progression of Alzheimer's disease by studying a set of clinical, cognitive, neuroimaging, genetic, and biochemical markers. This project is an international, multi-center effort that includes investigators at the University of Pittsburgh, the Banner Institute in Arizona, and Cambridge University in the United Kingdom.

Using many of the same methods, the IDDRC at the Kennedy Krieger Institute and Johns Hopkins University is supporting a second multi-site collaboration involving Columbia

University, New York State; the University of California, Irvine; Massachusetts General Hospital; and the University of North Texas Health Science Center. Drs. Wayne Silverman (Kennedy-Krieger/Hopkins), Nicole Schupf (Columbia), and Ira Lott (U.C. Irvine) are the lead investigators, and their teams plan to follow an additional group of approximately 200 to 300 older adults with Down syndrome to document their cognitive abilities as they age.

An IDDRC-supported collaboration between investigations at the Children’s Hospital of Philadelphia, the University of Pennsylvania (CHOP/Penn), and the Children’s National Medical Center (CNMC) seeks to understand whether the onset of dementia in people with Down syndrome is related to their overall metabolic status. As children with Down syndrome age, they accumulate more body fat than those without Down syndrome. This form of body fat is closely linked to heart disease and could be a risk for obesity-related conditions such as diabetes and heart and vascular disease. Led by Drs. Andrea Kelly and Babette Zemel (CHOP/Penn) and Dr. Sheela Magge (CNMC), the team is investigating the relationship between body composition and cognitive abilities by collecting information such as measures of bone density, blood lipids (fats) and hormones, glucose tolerance, and cardiac function. Their preliminary findings suggest that children and adolescents with Down syndrome do have a lipid profile associated with atherosclerosis (narrow and hardened arteries), even though they have less body fat. The researchers seek to understand the biologic basis for this contradiction and will explore whether one or more genes on chromosome 21 might cause a potentially dangerous lipid profile in blood or if people with Down syndrome have a defect in their mitochondria, cell components that regulate how energy is made and used.

Conclusion

Collaborations among the IDDRC Network have significantly advanced our understanding of Down syndrome. IDDRC-supported research has allowed us to progress from Dr. Down’s relatively simple, 19th Century description of physical findings to a rich understanding of Down syndrome’s impact on brain development, acquisition of language, and the aging process. The collaborative efforts of the 15 IDDRCs and their research partners have helped us to appreciate how Down syndrome manifests itself across cultures and in different environments. Most importantly, this information promises to help improve developmental outcomes and provide families and communities with the tools they need to support people with trisomy 21.

Dr. Down likely would be astounded to learn how much has been discovered in the 150 years since he first described this syndrome. He undoubtedly would endorse the proposition that only additional investigation will yield the knowledge necessary to prevent and even reverse the consequences of being born with an extra copy of chromosome 21.