GENETIC AND METABOLIC TESTING OF CHILDREN WITH GLOBAL DEVELOPMENTAL DELAY

This fact sheet is provided to help you understand which genetic and metabolic tests can help in finding the cause of global developmental delay (GDD) in children. Many of these children also have intellectual disability (ID), or serious problems with thinking ability. ID was formerly known as mental retardation.

Neurologists from the American Academy of Neurology (AAN) and Child Neurology Society (CNS) are doctors who identify and treat diseases of the brain and nervous system. The following evidence-based information is provided by experts who carefully reviewed all available scientific studies on genetic and metabolic tests for diagnosing GDD.

A 2003 AAN and CNS guideline studied the evidence for testing to diagnose GDD in children. This fact sheet summarizes the AAN's 2011 evidence report that updates that guideline. The 2011 evidence report is titled "Genetic and Metabolic Testing in Children with Global Developmental Delay." Visit *www.aan.com/guidelines* to read the complete report, which explains how the studies were rated.

Many tests are available that look for the underlying cause of GDD or ID. Improvements in genetic testing greatly increase the rate at which a specific cause of GDD or ID is found. Choosing the right test is important, and so is a careful medical exam. By carefully examining the child and understanding the child's history, clinicians can determine what testing is needed.

Finding the cause of GDD can help families care for affected children. It can also give families information to understand better their chances of having another child with GDD.

What is GDD?

GDD is a condition that involves serious delays in two or more areas of development in children under age 6. Many areas of development can be affected. These include vision, hearing, speech, and body coordination (motor skills). Thinking ability and social and emotional development also may be affected.

About one percent to three percent of children have GDD. Many of these children also have ID. In this evidence report, mild ID is defined as having an IQ of 50 to 70 points. Moderate ID is defined as having an IQ under 50 points.

If a child shows signs of delay in any developmental areas, he or she should be examined by a doctor for possible problems.

What causes GDD?

GDD has several causes, most of which develop before birth. These include genetic disorders and disorders of metabolism. Another cause is fetal alcohol syndrome. This is damage to the fetus from alcohol the pregnant woman consumes. In some cases GDD develops soon after birth. This typically happens because of serious medical problems related to a premature (early) birth. This evidence report focuses on GDD caused by genetic and metabolic disorders.

Genetic disorders involve problems caused by changes or errors in a person's genes. Genes are parts of the cells in the body that hold genetic information. This information tells the body's cells how to function. Genes are located on chromosomes, or material within the cells. Genetic information is passed down from parents to children through the 23 chromosomes. Through reproduction, both parents give a copy of their chromosomes to the child. Changes or errors in genes can lead to many types of medical conditions.

Common genetic disorders are Down syndrome and fragile X syndrome. Both conditions lead to ID. Down syndrome results from an extra copy of the 21st chromosome. In fragile X syndrome, the disorder is passed on through changes in a gene on the mother's X chromosome.

Other types of disorders affect a person's metabolism. Metabolism is the body's process of changing food into chemicals that give the body energy. To do this, the body uses special proteins called enzymes. Information in individual genes can affect how well these enzymes can function. Disorders of metabolism happen when the genes that make these enzymes are damaged.

I think my child has GDD. Which tests are best to make a diagnosis?

Many tests are available for diagnosing GDD. Changes in technology have improved the accuracy of these tests. GDD can affect children in many ways. Thus, it is important to choose the right test(s) for the situation.

Often doctors start with genetic screening tests that examine the content and structure of chromosomes. Examples of

these tests are microarray, karyotype, and subtelomeric fluorescence in situ hybridization, or StFISH. Experts believe microarray testing is the first choice of genetic testing when the cause of GDD is unknown.

Microarray testing looks for extra or missing pieces of chromosomes. It can detect some well-known disorders and some that are less well understood. Studies have shown that microarray testing detects some types of genetic problems more often than do other tests. Studies show that microarrays give positive results in about 7.8 percent of children tested. This rate is higher than the rates of positive results from other genetic tests used to find the cause of GDD. Some studies also show that microarray gives abnormal results at a higher rate (in 10.6 percent) in children with problems in addition to GDD. These include unusual facial features, birth defects, or neurologic symptoms.

Genetic tests other than microarry may also provide information. Karyotype testing can also give results that point to a specific diagnosis. Some studies show that karyotype testing gives positive results in about 4 percent of children with GDD. This rate is lower than the rate of positive results from microarray. However, a karyotype can detect the genetic changes responsible for some causes of GDD, such as Down syndrome. Experts say that karyotype testing should be the first test done in some cases. These include children who show signs of a specific disorder, have a family history of genetic disorders, or have a parent who has had two or more miscarriages. A karyotype may also be the second test performed in some cases. This is because it is the only test that can detect when chromosomes are rearranged. Having this information may be important for genetic counseling.

For StFISH testing, some studies show that test results will be positive in 3.5 percent of children tested. When children show signs of having severe GDD, some studies suggest that StFISH will give positive results more often (in about 7.5 percent of children tested). In milder GDD cases, some studies suggest positive results will occur less often (in 0.5 percent).

Can testing specific genes or sets of genes help with GDD diagnosis?

Testing of specific genes or sets of genes can be helpful in determining a genetic cause of GDD. Often GDD stems from changes or errors in genes known as X-linked. These are located on the X chromosome. This is one of the two chromosomes that determine a person's sex. Females have two X chromosomes, and males have one X chromosome and one Y chromosome. Females often carry abnormal genes on the X chromosome. Yet these females often are unaffected by the abnormal gene. They may be protected by having a normal copy of the gene on their second X chromosomes. Males, who have only one X chromosome, are more likely to show signs of a disorder caused by an abnormal gene on the X chromosome.

Experts believe problems with these genes may account for up to 10 percent of all genetic causes of GDD. Researchers have looked at the X chromosomes of families with multiple males affected by GDD, ID, or other neurologic problems not explained by previous genetic testing. One study found that 42 percent of the affected males tested positive for X-linked problems when their families showed GDD was passed on through the X chromosome. This study also found that 17 percent of affected males tested positive when their family information showed possible, but less certain, X-linked GDD.

Researchers have also studied whether individual genes are linked to GDD. Some studies suggest that testing for lengthening of the *FMR1* gene gives positive results for fragile X syndrome in about 2 percent of children with mild GDD. Researchers also studied the *MeCP2* gene. This gene is abnormal in most children with Rett syndrome. This is a developmental disorder that mainly affects girls. Some studies show testing of this gene gives positive results in 1.5 percent of girls with moderate or severe GDD. In males with GDD or ID, positive results show up in less than 0.5 percent.

GDD and ID also can result from disorders of metabolism. These disorders happen when the genes that make metabolic enzymes are abnormal. In these cases, the enzyme is absent or unable to function properly. In one group of disorders, known as inborn errors of metabolism (IEM), some studies suggest screening tests give positive results in about 1.8 percent to 5 percent of children tested. In another group of disorders, known as congenital disorders of glycosylation, studies suggest that screening tests give positive results in about 1.4 percent of children tested. In other conditions, such as creatine synthesis and transport disorders, some studies suggest about 2.8 percent of children tested will test positive.

Some experts suggest that some children may be more prone than others to having IEM. These are children whose parents have had other children with similar problems or children who have died of unclear causes (either before or after birth). Children with IEM can have a range of health problems. These include problems with two or more internal organs, risk of early death, dietary problems, and hearing loss. Other signs also can be present, such as seizures or unusual body odors. If an IEM is suspected, it is important to consider metabolic testing. Some IEM symptoms can improve with treatment.

My child has GDD. Is testing for the cause of GDD the best thing to do?

Having the right choice of test to diagnose the cause of GDD is important. Because of improved technologies, the available tests are much better at detecting the cause of GDD than tests available just a short time ago. However, a positive test result alone is not enough to make a clear diagnosis. Other factors are also important to consider. For example, physical

signs of the disease, such as unusual facial features, birth defects, or neurologic symptoms, might give clues. A family history of GDD or an abnormal genetic test result in a family member might also point to a problem.

For some children, genetic and metabolic testing may not be the best option. It is important for family members or caregivers to discuss testing options with their child's doctor.

Having a specific diagnosis of the cause of GDD rarely leads to a specific therapy that will improve a child's functioning. However, the diagnosis can be very helpful in other ways. The family may be better able to manage related health and behavior problems that may arise. The child's loved ones may feel relieved to know what may be causing the child's medical problems. This can lead to positive action such as getting involved in support and research networks. Further costly and sometimes painful medical testing and exams may no longer be needed. Genetic screening and counseling may help the parents to understand their chances of having another child with GDD in the future.

It is important that families and caregivers of children with GDD or ID discuss the available options with their child's doctor. Getting the best possible information from the appropriate tests and medical exams may help to understand the cause and what steps to take next.

Visit *www.aan.com/guidelines* to read the complete report "Genetic and Metabolic Testing in Children with Global Developmental Delay," which explains how the studies were rated.

CHILD NEUROLOGY SOCIETY

Copies of this summary and additional companion tools are available at *www.aan.com* or through AAN Member Services at (800) 879-1960.

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1080 Montreal Avenue • St. Paul, MN 55116
www.aan.com • (651) 695-1940