Muscular Dystrophy New Zealand

Glycogen Storage Disease Type III also known as Cori or Forbe's Disease/Debrancher Enzyme Deficiency

What is GSDIII?

Glycogen Storage Disease type 3 is an inherited condition caused by a defect in a gene that controls the breakdown of a complex sugar called glycogen in the body's cells. Because the glycogen cannot break down the accumulated glycogen is structurally abnormal and impairs the function of certain organs and tissues, especially the liver and muscles. It is also called Cori Disease, Forbe's Disease or Debrancher Enzyme Deficiency.

The incidence of GSDIII in the United States is 1 in 100,000 individuals. This condition is seen more frequently in people of North African Jewish ancestry; in this population, 1 in 5,400 individuals are estimated to be affected.

Varieties and Features of GSDIII

Beginning in infancy, individuals with any type of GSDIII may have low blood sugar (hypoglycemia), excess amounts of fats in the blood (hyperlipidemia), and elevated blood levels of liver enzymes.

As they get older, children with this condition typically develop an enlarged liver (hepatomegaly). Liver size usually returns to normal during adolescence, but some affected individuals develop chronic liver disease (cirrhosis) and liver failure later in life. People with GSDIII often have slow growth because of their liver problems, which can lead to short stature. In a small percentage of people with GSDIII, noncancerous (benign) tumors called adenomas may form in the liver.

GSDIII is divided into types 3a, 3b, 3c, and 3d, which are distinguished by their pattern of signs and symptoms. GSD types 3a and 3c mainly affect the liver and muscles, and GSD types 3b and 3d typically affect only the liver.

• GSD 3a is the most common form and is present in about 85% of affected individuals affecting liver and muscles
• GSD 3b is the second most common form and presents with liver involvement only. This group makes up approximately 15% of all GSDIII.
• GSD types 3c and 3d are very rare, and their signs and symptoms are poorly defined. Only a small number of affected individuals have been suspected to have GSD types 3c and 3d.

Muscular Dystrophy New Zealand

Symptoms of GSDIII

The first signs and symptoms of GSDIII are usually poor muscle tone (hypotonia) and mild myopathy (weakness) in early childhood. The myopathy may become severe by early to midadulthood. These muscle problems can affect both heart (cardiac) muscle and the muscles that are used for movement (skeletal muscles). The level that the muscles are affected by the condition varies greatly among affected individuals.

Hypertrophic cardiomyopathy (HCM) is an inherited disease of your heart muscle, where the muscle wall of your heart becomes thickened.

Hypertrophic cardiomyopathy (see info box above) develops in the majority of those with GSD 3a, usually during childhood, but the seriousness of the presentation varies from asymptomatic in the majority (no symptoms even though present) to severe heart conditions and rarely heart failure.

Creatine Phosphokinase (CPK or PK) Testing

Creatine phosphokinase (CPK) is an enzyme found mainly in the heart, brain, and skeletal muscle. Enzymes are complex proteins that cause a specific chemical change in all parts of the body. For example, they can help break down the foods we eat so the body can use them. Blood clotting is another example of enzymes at work.
This is a simple blood test. Remember to tell your doctor about any medications you are taking. Drugs that can increase CPK measurements include amphotericin B, certain anesthetics, statins, fibrates, dexamethasone, alcohol, and cocaine.

When a muscle is damaged, CPK leaks into the bloodstream. Determining which specific form of CPK is high helps doctors determine which tissue has been damaged.
This test is used by doctors, in conjunction with other factors present, to detect muscular dystrophies including DMD, GSDIII, polymyositis and to help determine DMD carrier status. Factors that may affect test results include cardiac catheterization, intramuscular injections, trauma to muscles, recent surgery, and heavy exercise.

Genetics

Mutations in the AGL gene cause GSDIII. The AGL gene provides instructions for making the glycogen debranching enzyme. This enzyme is involved in the breakdown of glycogen, which is a major source of stored energy in the body. Between meals the body breaks down stores of energy, such as glycogen, to use for fuel.

Muscular Dystrophy New Zealand

Most AGL gene mutations lead to the production of a nonfunctional glycogen debranching enzyme. These mutations typically cause GSD types 3a and 3b. The mutations that cause GSD types 3c and 3d are thought to lead to the production of an enzyme with reduced function. All AGL gene mutations lead to storage of abnormal, partially broken down glycogen molecules within cells. A buildup of abnormal glycogen damages organs and tissues throughout the body, particularly the liver and muscles, leading to the signs and symptoms of GSDIII.
Inheritance of GSDIII This condition is inherited in an autosomal recessive pattern. We all have two copies of each chromosome except for the sex chromosomes. In recessive conditions both copies of the gene must be defective for the disease to develop fully. In this situation each parent is a carrier of one defective gene. And in each pregnancy they have a 25% chance of have a child affected with the condition.

Genetic counselling is available to families who have had a diagnosis of Cori Disease (GSDIII). This service provides information, helps families understand inheritance patterns and what this means in their family, as well as enabling people to make more informed family-planning decisions. You can access this via your GP, self-refer or an MDA Fieldworker can assist you. They can also assist with the diagnosis of at-risk siblings which allows for early dietary intervention to prevent hypoglycemia.

Diagnosis

An enlarged liver, low blood glucose with ketosis on fasting (energy coming primarily from ketones in the blood instead of glucose), and elevated serum concentrations of transaminases and CK are the hallmarks of GSD III.

The serum CK may not be elevated at the time of the diagnostic work-up, but the absence of lactic acidosis and markedly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations may provide clues to the diagnosis.

The debranching enzyme which is faulty in this condition is a single polypeptide with two active sites. Measuring the level of Debranching enzyme activity can be measured in muscle and liver biopsy specimens and compared to controls can assist diagnosis.

Measurement of fasting serum concentration of glucose after glucagon administration can be used to help determine the diagnosis, glucagon administration should cause the glucose concentration to rise following a fast of two hours or less.

Muscular Dystrophy New Zealand

Molecular genetic testing of AGL, the only gene in which mutations are known to cause GSD III, allows confirmation of the diagnosis.

In biochemistry, a transaminase or an aminotransferase is an enzyme that catalyzes a type of reaction between an amino acid and an α-keto acid. They are important in the synthesis of amino acids, which form proteins. In medicine, they are an important indicator of liver damage.

Liver biopsy is likely to show prominent distension of hepatocytes (70-85% of the liver is made up of these cells) by glycogen, the liver is also likely to display fibrosis. The extent of fibrosis in GSD III is typically greater than in the other forms of GSD, and will increase during the course of the disease potentially leading to cirrhosis.

If growth has been affected by the condition then catch-up growth may be observed with the establishment of good metabolic control.

Osteoporosis and osteopenia have been noted in GSD III as in other glycogen storage diseases and this thought to be due to a variety of factors.

Polycystic ovary disease may be seen in GSD III although fertility does not appear to be affected.

Management

• A high-protein diet and frequent feeds (every three to four hours) to maintain normal blood sugar levels is the mainstay of management in infancy. Fructose and galactose can be used and no special formulas are required.
• Toward the end of the first year of life, one to three daily doses of 1g/kg cornstarch can be used to avoid hypoglycemia.
• A protein intake of 3g/kg is recommended.
• Keep vaccinations up to date and consider including a hepatitis B vaccination.
• A medic Alert bracelet is recommended in case of hypoglycemia.
• Liver transplantation is reserved for those with severe hepatic cirrhosis, liver dysfunction, and/or hepatocellular carcinoma. Liver transplantation may adversely affect the symptoms of myopathy and cardiomyopathy.
• It is recommended to maintain metabolic control that blood or urine ketones upon awakening and blood glucose concentrations at 2 to 4 AM should be measured at least several times per month.
• Caution should be taken during periods of fasting e.g. surgery or while ill.

Muscular Dystrophy New Zealand

It is also recommended that the following be checked annually:
• measurement of height and weight
• liver ultrasound examinations
• laboratory studies (LFTs, CK, lipid profile)
• echocardiogram
• A bone density determination is recommended after growth is complete

During pregnancy increased monitoring and support is suggested because of the increased glucose needs during the course of a pregnancy and maintaining a normal blood sugar as well as avoiding low blood sugar levels and ketosis is important.

If you require surgery make sure your condition is disclosed as there is a need to undertake special precautions to avoid hypoglycemia and determine the appropriate anesthetic.

Agents/circumstances to avoid: High simple sugar intake, steroid-based drugs, growth hormone replacement. Use with caution: hormonal contraceptives and statins for control of hyperlipidemia.

Support

The MDA Fieldworkers are available for support. They have in-depth knowledge of a range of neuromuscular conditions, and will have a better understanding of your needs and challenges. Have a chat over the phone or they can come to you for a kanohi ki te kanohi/face-to-face visit. They may have some real practical suggestions that have worked for others to offer as well. This service is offered free of charge to MDA members and is funded through donations and grants. Contact your local MDA Branch to be put in contact with your fieldworker.

The MDA Support Network allows people with similar circumstances or challenges to come together to share their experiences and provide each other with emotional and moral support in addition to practical advice and information. By bringing together people with common experiences, support networks can provide an invaluable addition to medical care. The MDA of New Zealand Support Network currently has over 700 members throughout New Zealand who want to be in touch with others livings with neuromuscular conditions. Please see the MDA website www.mda.org.nz for contact details and more information that you might find relevant for you and your whanau.

Muscular Dystrophy New Zealand

There is no reason why individuals with GSDIII should be disadvantaged in terms of receiving full education. For more information, request the Education Pack available from the MDA.

Disability should not hinder employment possibilities. Any individual has the right to equal pay and equal rights for employment. For more information contact the Employment Relations infoline on 0800 800 863 or visit www.ers.dol.govt.nz.

The government promotes equal employment opportunities in private sector and can be contacted on (09) 525 3023 or visit www.eeotrust.org.nz

Workbridge provides a professional employment service for people with all types of disabilities and administers support funding on behalf of Work and Income. Contact on 0508 858 858 or visit www.workbridge.co.nz More Information

Muscular Dystrophy Association can be contacted for further information, assistance, advice, support and referrals, on 0800 800 337 or by e-mail at info@mda.org.nz.

The Muscular Dystrophy Association Website also contains information on services available within NZ, our quarterly magazine, contacts, membership details, news and links to other sites - www.mda.org.nz

Further Resources

www.nzord.org.nz – the New Zealand Organisation for Rare Disorders website provides information on a number of rare disorders, a directory of support groups, practical advice, health and disability resources, research information, news and issues.

www.agsdus.org – The Association for Glycogen Storage Disease - AGSD - was established in 1979 in order to create an organization which would be a focus for parents of and individuals with glycogen storage disease (GSD) to communicate, share their successes and concerns, share useful findings, provide support, create an awareness of this condition for the public, and to stimulate research in the various forms of glycogen storage diseases.

Muscular Dystrophy New Zealand

www.agsd.org.uk - The AGSD-UK provides support and help for individuals and families affected by Glycogen Storage Disease (GSD). It does this by putting people in contact, providing information, issuing Newsletters and holding Conferences and Workshops. Find out more about us and what we do by exploring the menus above or using the site map.

Sourced from

https://ghr.nlm.nih.gov/condition/glycogen-storage-disease-type-iii
http://www.ncbi.nlm.nih.gov/books/NBK26372/
https://www.bhf.org.uk/heart-health/conditions/cardiomyopathy/hypertrophic-cardiomyopathy
https://en.wikipedia.org/wiki/Ketosis
https://en.wikipedia.org/wiki/Transaminase
https://en.wikipedia.org/wiki/Hepatocyte