

Patient Information

HUNTER SYNDROME



MUCOPOLYSACCHARIDOSIS II (MPS II):
UNDERSTANDING THIS SERIOUS GENETIC DISORDER

Contents

Hunter syndrome (MPS II)	1
Introduction and overview of symptoms	2
<i>Signs of Hunter syndrome</i>	
<i>Diagnosis of Hunter syndrome</i>	
<i>Genetics of Hunter syndrome</i>	
<i>Biochemistry of Hunter syndrome</i>	
Learning more about Hunter syndrome	7

Hunter syndrome (MPS II)

WHAT IS HUNTER SYNDROME?

Hunter syndrome, or mucopolysaccharidosis II (MPS II), is a serious genetic disorder that primarily affects males. It interferes with the body's ability to break down and recycle specific mucopolysaccharides (mew-ko-pol-ee-sak-ah-rides), also known as glycosaminoglycans (gli-ko-sah-mee-no-gli-cans) or GAG. Hunter syndrome is one of several related lysosomal storage diseases.

In Hunter syndrome, GAG build up in cells throughout the body due to a deficiency or absence of the enzyme iduronate-2-sulfatase (I2S). This buildup interferes with the way certain cells and organs in the body function and leads to a number of serious symptoms. As the buildup of GAG continues throughout the cells of the body, signs of Hunter syndrome become more visible. Physical manifestations for some people with Hunter syndrome include distinct facial features, a large head, and an enlarged abdomen. People with Hunter syndrome may also experience hearing loss, thickening of the heart valves leading to a decline in cardiac function, obstructive airway disease, sleep apnea, and enlargement of the liver and spleen. Range of motion and mobility may also be affected. In some cases of Hunter syndrome, central nervous system involvement leads to developmental delays and nervous system problems. Not all people with Hunter syndrome are affected by the disease in exactly the same way, and the rate of symptom progression varies widely. However, Hunter syndrome is always severe, progressive, and life-limiting.

If you or someone you know has Hunter syndrome, it is often helpful to get as much information as possible about the disease. This is particularly important in light of the ongoing research into a treatment for Hunter syndrome. Talk with your doctor about additional sources of information, including other healthcare professionals such as medical geneticists or genetic counselors, who can help you learn more about Hunter syndrome and how it may impact the lives of you and your family.

Introduction and overview of symptoms



SIGNS OF HUNTER SYNDROME

The symptoms of Hunter syndrome (MPS II) are generally not apparent at birth, but usually start to become noticeable after the first year of life. Often, the first symptoms of Hunter syndrome may include inguinal hernias, ear infections, runny noses, and colds. Since these symptoms are quite common among all infants, they are not likely to lead a doctor to make a diagnosis of Hunter syndrome right away. As the

buildup of GAG continues throughout the cells of the body, signs of Hunter syndrome become more visible. Physical manifestations of many children with Hunter syndrome include a distinctive coarseness in their facial features, including a prominent forehead, a nose with a flattened bridge, and an enlarged tongue. For this reason, unrelated children with Hunter syndrome often look alike. They may also have a large head as well as an enlarged abdomen. Many continue to have frequent infections of the ears and respiratory tract.

The continued storage of GAG in cells can lead to organs being affected in important ways. The thickening of the heart valves along with the walls of the heart can result in progressive decline in cardiac function. The walls of the airway may become thickened as well, leading to breathing problems while sleeping (obstructive airway disease). People with Hunter syndrome may also have limited lung capacity due to pulmonary involvement. As the liver and spleen grow larger with time, the belly may become distended, making hernias more noticeable. All major joints (including the wrists, elbows, shoulders, hips, and knees) may be affected by Hunter syndrome, leading to joint stiffness and limited motion. Progressive involvement of the finger and thumb joints results in decreased ability to pick up small objects. The effects on other joints, such as hips and knees, can make it increasingly difficult to walk normally. If carpal tunnel syndrome develops, a further decrease in hand function can occur. The bones themselves may be affected, resulting in short stature. In addition, pebbly, ivory-colored

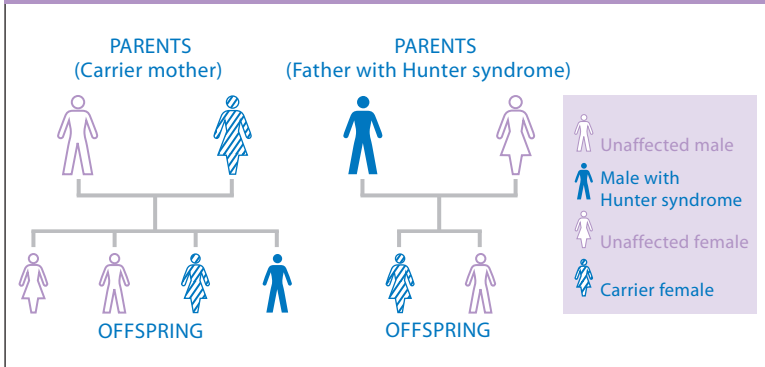
skin lesions may be found on the upper arms and legs and upper back of some people with Hunter syndrome. The presence or absence of the skin lesions is not helpful, however, in predicting clinical severity in Hunter syndrome. Finally, the storage of GAG in the brain can lead to delayed development with subsequent mental retardation. The rate and degree of progression may be different for each person with Hunter syndrome.

There is a broad range of severity in the symptoms of Hunter syndrome. It is important to note that though the term “mild” is used by physicians in comparing people with Hunter syndrome, the effects of even mild disease are quite serious. Two of the most significant areas of variability concern the degree of mental retardation and expected life span. Some people who have Hunter syndrome are not mentally retarded and live into their 20s or 30s; there are occasional reports of people who have lived into their 50s or 60s. The quality of life remains high in a large number of people, and many adults are actively employed. In contrast, others with Hunter syndrome develop severe mental impairment and have life expectancies of 15 years or less.

THE DIAGNOSIS OF HUNTER SYNDROME

The visible signs and symptoms of Hunter syndrome (MPS II) in younger people are usually the first clues leading to a diagnosis. In general, the time of diagnosis usually occurs from about 2 to 4 years of age. Doctors may use laboratory tests to provide additional evidence that an MPS disorder is present, before making a definitive diagnosis by measuring the iduronate-2-sulfatase (I2S) enzyme activity. The most commonly used laboratory screening test for an MPS disorder is a urine test for GAG. It is important to note that the urine test for GAG can occasionally be normal and yet the child still may have an MPS disorder. A definitive diagnosis of Hunter syndrome is made by measuring I2S activity in serum, white blood cells, or fibroblasts from skin biopsy. In some people with Hunter syndrome, analysis of the I2S gene can determine clinical severity. Prenatal diagnosis is routinely available by measuring I2S enzymatic activity in amniotic fluid or in chorionic villus tissue.

HOW HUNTER SYNDROME IS PASSED ON



Hunter syndrome (MPS II) shows X-linked inheritance. On average, a carrier mother will pass on the abnormal I2S gene to 50% of her sons and 50% of her daughters. A father with Hunter syndrome will pass on the abnormal I2S gene to all of his daughters and none of his sons.

THE GENETICS OF HUNTER SYNDROME

Hunter syndrome (MPS II) affects a calculated estimate of at least 1 in 155,000 live births. Since Hunter syndrome is an inherited disorder (X-linked recessive) that primarily affects males, it is passed down from one generation to the next in a specific way. Nearly every cell in the human body has 46 chromosomes, with 23 derived from each parent. The I2S gene is located on the X chromosome. Females have two X chromosomes, one inherited from each parent, whereas males have one X chromosome that they inherit from their mother and one Y chromosome that they inherit from their father.

If a male has an abnormal copy of the I2S gene, he will develop Hunter syndrome. A male can obtain an abnormal copy of the I2S gene in one of two ways. His mother is often a carrier; i.e., she has one abnormal and one normal I2S gene, and she passes along the abnormal gene to him. However, during egg and sperm formation, a mutation can develop in the I2S gene on his X chromosome. In this second case, the mother is not a carrier and the risk of a spontaneous mutation occurring again in a future sibling is low but not zero. Females can carry one abnormal copy of the I2S gene and are usually not affected. Hunter syndrome has been reported to occur in females.

THE BIOCHEMISTRY OF HUNTER SYNDROME

The human body depends on a vast array of biochemical reactions to support critical functions, including the production of energy, growth and development, communication within the body, and protection from infection. Another critical function is the breakdown of large biomolecules, which is the underlying problem in Hunter syndrome (MPS II) and related storage disorders.

The biochemistry of Hunter syndrome is related to a problem in a part of the connective tissue of the body known as the extracellular matrix. This matrix is made up of a variety of sugars and proteins and helps to form the architectural framework of the body. The matrix surrounds the cells of the body in an organized meshwork and functions as the glue that holds the cells of the body together. One of the parts of the extracellular matrix is a complex molecule called a proteoglycan. Like many components of the body, proteoglycans need to be broken down and replaced. When the body breaks down proteoglycans, one of the resulting products is mucopolysaccharides, otherwise known as GAG. There are several types of GAG, each found in certain characteristic places in the body:

GAG	LOCATION IN BODY
Hyaluronic acid	Various connective tissues, skin, cartilage, synovial fluid
Chondroitin sulfate	Cartilage, cornea, bone, skin, arteries
Dermatan sulfate	Skin, blood vessels, heart, heart valves
Heparan sulfate	Lung, arteries, cell surfaces
Heparin	Lung, liver, certain immune system cells
Keratan sulfate	Cartilage, cornea, intervertebral disks

In Hunter syndrome, the problem concerns the breakdown of two GAG: dermatan sulfate and heparan sulfate. The first step in the breakdown of dermatan sulfate and heparan sulfate requires the lysosomal enzyme I2S. In people with Hunter syndrome, this enzyme is either partially or completely inactive. As a result, GAG build up in cells throughout the body, particularly in tissues that contain large amounts of dermatan sulfate and heparan sulfate. As this buildup continues, it interferes with the way certain cells and organs in the body function and leads to a number of serious symptoms. The rate of GAG buildup is not the same for all people with Hunter syndrome, resulting in a wide spectrum of medical problems.

Learning more about Hunter syndrome (MPS II)

This document is for informational purposes only.

To learn more, you may want to contact:

The National MPS Society (US)

PO Box 736

Bangor, ME 04402-0736

www.mpssociety.org

Society for Mucopolysaccharide Diseases (the MPS Society) (UK)

MPS House, Repton Place

White Lion Road

Amersham, Buckinghamshire, HP7 9LP

United Kingdom

www.mpssociety.co.uk

The Canadian Society for Mucopolysaccharide and Related Diseases

PO Box 30034

RPO Parkgate

North Vancouver, BC V7H 2Y8

Canada

www.mpssociety.ca

National Organization for Rare Disorders (NORD)

55 Kenosia Avenue

PO Box 1968

Danbury, CT 06813-1968

www.rarediseases.org

Genetic Alliance, Inc.

4301 Connecticut Avenue NW, Suite 404

Washington, DC 20008-2369

www.geneticalliance.org

Children Living with Inherited Metabolic Diseases (CLIMB)

CLIMB Building

176 Nantwich Road

Crewe, CW2 6BG

United Kingdom

www.climb.org.uk



Shire Human Genetic Therapies
700 Main Street · Cambridge, MA 02139
www.shire.com
www.HunterPatients.com