



Mucopolipidoses

U.S. DEPARTMENT OF HEALTH
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Mucopolysaccharidoses

What are the mucopolysaccharidoses?

The mucopolysaccharidoses (MPS) are a group of inherited metabolic diseases that affect the body's ability to carry out the normal turnover of various materials within cells. In MPS, abnormal amounts of carbohydrates and lipids (fatty materials such as oils) accumulate in cells. Because our cells are not able to handle such large amounts of these substances, damage to the cells occurs, causing symptoms that range from mild learning disabilities to severe intellectual disability and skeletal deformities. The onset of symptoms of MPS can be congenital (present at birth) or begin in early childhood or adolescence. Early symptoms can include vision problems and developmental delays. Over time, many children with MPS develop poor mental capacities, have difficulty reaching normal developmental milestones, and, in many cases, die prematurely of the disease.

What causes the mucopolysaccharidoses?

The MPS are classified as lysosomal storage diseases because they involve increased storage of substances in the lysosomes, which are specialized sac-like components within most cells. Lysosomes play a critical role in the metabolic function of our bodies. One of their primary roles is to work as a cellular recycling plant, where they pick up substances such as

carbohydrates and lipids and digest them down into smaller molecules that can be re-used. This process is possible because lysosomes contain enzymes, which are proteins that increase the rate of metabolic chemical reactions. Working continuously, lysosomal enzymes break down carbohydrates and lipids and assist in transferring their byproducts throughout the rest of the cell for energy production or excretion.

Individuals with ML are born with a genetic defect in which their bodies either do not produce enough of certain enzymes or, in some instances, produce ineffective forms of enzymes. Without functioning enzymes, lysosomes cannot break down carbohydrates and lipids and transport them into the lysosomes. The molecules then accumulate in the cells of various tissues in the body, leading to organ damage. In individuals with ML, the molecules accumulate in nerve, liver, and muscle tissue as well as in bone marrow, and this abnormal storage causes the various symptoms associated with ML. For example, excess storage of these molecules in nerve tissues can cause intellectual disability; accumulation in the tissues of the spleen and liver can cause poor functioning of these vital organs; and excess storage in the bone marrow can damage bones, leading to skeletal deformities.

The accumulation of carbohydrates and lipids in tissue can result from deficiency in many different individual enzymes. Lysosomes contain as many as 40 or 50 different enzymes, each responsible for a highly specialized function. Therefore, a deficiency in one particular enzyme causes symptoms that may be somewhat different from the symptoms caused by the deficiency of another type of enzyme.

There are four types of ML and each is classified according to the enzyme(s) or other protein that is deficient or mutated (altered). Symptoms can range from mild to severe.

The MLs are similar to another group of lysosomal storage diseases known as the mucopolysaccharidoses. While both conditions produce similar symptoms and are caused by the lack of enzymes necessary to break down and transport carbohydrates and lipids, the mucopolysaccharidoses result in an excess of sugars, known as mucopolysaccharides, in the urine. An excess of mucopolysaccharides is not seen in the urine of people with ML, so screening of the urine can help doctors distinguish between the two groups of disorders.

Since some of the mucopolysaccharidoses are similar in nature or cause to other disorders, the classification of the mucopolysaccharidoses may be evolving following future research.

What are the different types of mucopolysaccharidoses?

The four types of ML are sialidosis (sometimes referred to as ML I), and types II, III, and IV.

Mucopolysaccharidosis type I (ML I), also known as sialidosis, results from a deficiency in one of the digestive enzymes known as sialidase. The role of sialidase is to remove a particular form of sialic acid (a sugar-like molecule) from sugar-protein complexes (referred to as glycoproteins), which allows the cell to function properly. Because the enzyme is deficient, small molecules containing the sugar-like material accumulate in neurons, bone marrow, and immune system cells that defend the body against infection.

Mutations in the *NEU1* gene, which produces the enzyme NEU1, cause the disorder.

Symptoms of the infantile form of ML I are either present at birth or develop within the first year of life. In many infants with ML I, excessive swelling throughout the body is noted at birth. These infants are often born with coarse facial features, such as a flat nasal bridge, puffy eyelids, enlargement of the gums, and excessive tongue size (macroglossia). Many infants with ML I are also born with skeletal malformations such as hip dislocation. Infants often develop sudden involuntary muscle contractions or jerks (called myoclonus) and have red spots in their eyes (called cherry-red macules) that are seen on ophthalmologic exam. They are often unable to coordinate voluntary movement (called ataxia). Tremors, impaired vision, and seizures also occur in children with ML I. Tests reveal abnormal enlargement of the liver and spleen and extreme abdominal swelling. Infants with ML I generally lack muscle tone (hypotonia) and have intellectual disability that is either initially or progressively severe. Many individuals suffer from failure to thrive and from recurrent respiratory infections. Most infants with ML I die before the age of 1 year.

Other diseases that result from a deficiency in the sialidase enzyme are categorized in a broader group known as *sialidoses*. Because ML I is classified as a sialidosis, it is sometimes referred to as sialidosis type II.

A rarer form of ML I occurs in children and adolescents and is often referred to as the juvenile form of the disorder. Children usually begin to show symptoms during the

second decade of life, and myoclonus and cherry-red macules in the retina are often the initial symptoms. Affected individuals usually develop seizures and progressive deterioration of coordinated muscular and mental activities.

Mucopolipidosis types II and III (ML II and ML III) result from a deficiency of the enzyme N-acetylglucosamine-1-phosphotransferase, caused by a mutation in the *GNPTAB* gene. Just as luggage in an airport is tagged to direct it to the correct destination, enzymes are often “tagged” for transit to specific sites within cells. In ML II and ML III, the deficient enzyme is supposed to tag other enzymes so that they can initiate certain metabolic processes in the cell. Because the enzymes are not properly tagged, they escape into spaces outside the cell and therefore cannot do their usual work of breaking down large molecules inside the cells.

ML II is also referred to as inclusion-cell (I-cell) disease because waste products, thought to include carbohydrates, lipids, and proteins, accumulate into masses known as inclusion bodies. When tissues are examined under a microscope, the detection of inclusion bodies often provides a diagnosis of the disease.

ML II is a particularly severe form of ML that resembles one of the mucopolysaccharidoses called Hurler syndrome. Some physical signs, such as abnormal skeletal development, coarse facial features, and restricted joint movement, may be present at birth. Children with ML II usually have enlargement of certain organs, such as the liver or spleen, and sometimes even the heart valves. Affected children often fail to grow and develop in the first months of life. Delays in

the development of their motor skills are usually more pronounced than delays in their cognitive (mental processing) skills. Children with ML II eventually develop a clouding on the cornea of their eyes and, because of impaired growth, develop short-trunk dwarfism (underdeveloped trunk). These children are often plagued by recurrent respiratory tract infections, including pneumonia, otitis media (middle ear infections), and bronchitis. Children with ML II generally die before their seventh year of life, often as a result of congestive heart failure or recurrent respiratory tract infections.

In contrast, symptoms of ML III are often not noticed until the affected child is 3-5 years of age. One of the milder forms of the MLs, ML III (sometimes referred to as pseudo-Hurler, or false Hurler, polydystrophy) also results from a deficiency or defect of the enzyme *N*-acetylglucosamine-1-phosphotransferase that is characteristic of ML II. However, ML III produces less severe symptoms and progresses more slowly, probably because the deficient enzyme retains some of its activity, resulting in a smaller accumulation of carbohydrates, lipids, and proteins in the inclusion bodies.

People with ML III are generally of normal intelligence or have only mild intellectual disability. These individuals usually develop skeletal abnormalities, coarse facial features, short height, and corneal clouding. Some individuals with ML III survive until their fourth or fifth decade of life.

Mucopolipidosis type IV (ML IV) is caused by mutations in gene *MCOLN1*, which provides instructions for making the protein mucolipin-1

(also called TrpML1, which is believed to be involved in the movement of molecules such as calcium across cell membranes). The gene contains instructions for TRPML1, an ion channel protein that acts like a pore. When open, the protein allows charged molecules to flow in and out of the cell, which affects the conduct of cellular electrical activity. Most people with ML IV have developmental delays of movement and coordination, clouding of the cornea of the eye, strabismus (the eyes are improperly aligned, which affects vision), and severely reduced vision. Typically, individuals have an unsteady gait and cannot walk independently. Individuals with ML IV have occasionally been misdiagnosed as having cerebral palsy. Speech is usually severely impaired. However, some people with ML IV are more mildly affected and can walk and have better speech. In rare instances, individuals with ML IV may have only the eye abnormalities and visual impairment with no associated neurological problems or mental impairment. People with ML IV have dramatically reduced stomach acid secretion. This alteration results in an increase of a hormone called *gastrin* in the blood which can help diagnose ML IV.

How are the mucopolysaccharidoses inherited?

The mucopolysaccharidoses are inherited in an autosomal recessive manner, that is, they occur only when a child inherits two copies of the defective gene, one from each parent. When both parents carry the defective gene for a given type of ML, each of their children faces a one in four chance of developing the disease. At the same time, each child also faces a one in two

chance of inheriting only one copy of the defective gene. People who have only one defective gene are known as carriers. These individuals do not develop the disease but they can pass the defective gene to their own children. Because the defective genes involved in certain forms of ML are known, tests can identify people who are carriers in some instances.

How are the mucopolipidoses diagnosed?

The diagnosis of ML is based on clinical symptoms, a complete medical history, and certain laboratory tests. Diagnosis of ML I, II, and III can be confirmed by a blood test that measures enzyme activity in the person's white blood cells. Activity levels that are lower than normal indicate specific enzyme deficiencies.

Another way to confirm the diagnosis is through skin biopsy. A small sample of skin is taken from the person and grown in a cell culture. The activity of a particular enzyme in the cultured skin cells is then measured.

ML IV is suspected when cells that are easily obtained by swabbing the inside surface of the eyelid and corner of the eye (conjunctival swabbing) are found to have numerous inclusion bodies. In addition, measurement of the level of gastrin in the blood, which is significantly increased in individuals with ML IV, helps to confirm the diagnosis.

Identifying mutations in the *MCOLN1* gene aids in the accurate diagnosis of individuals with ML IV, as well as prenatal (before birth) diagnosis and the screening of carriers of the disease.

Prenatal diagnosis for ML is accomplished using a procedure known as chorionic villus sampling, or CVS. It is usually done around the 8th or 10th week of pregnancy and involves removing and testing a very small sample of the placenta. For ML types I, II, and III, placental cells called amniocytes are grown in culture and then tested to measure enzyme activity levels. For ML IV, no culture is required. DNA is obtained directly from the amniocytes and analyzed to find if mutations consistent with ML IV have occurred in the DNA. This technique is called genotyping.

Genetic testing for ML IV is available at specialized laboratories. Genetic counselors can help explain how the MLs are inherited and the effect of these diseases on people and their families. Counselors can also help adults who might have a defective gene make informed decisions about plans to have children. Psychological counseling and support groups for people with genetic diseases may also help individuals and their families cope with ML.

Are there any treatments?

No cure or specific therapies for ML currently exists. Therapies are generally geared toward treating symptoms and providing supportive care. For individuals with corneal clouding, surgery to remove the thin layer over the eye has been shown to reduce the cloudiness in the eye. However, this improvement may be only temporary. Physical therapy and learning new ways to perform activities of daily living (occupational therapy) may help children with motor delays. Children with language delays may benefit from speech therapy.

Care also should be taken to maintain the overall health of individuals with ML. For example, children at risk for failure to thrive (growth failure) may need nutritional supplements, especially iron for those with ML IV. Bacterial respiratory infections should be treated immediately and fully with antibiotics.

What research is being done?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. The NINDS is a component of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world.

Scientists have identified the genes responsible for all four types of ML, including the discovery of the *MCOLN1* gene by NINDS scientists and others. Knowing the genetic causes for these diseases has helped scientists to better understand underlying causes and identify targets for developing treatments. For example, investigators at NINDS and other research institutions are conducting studies to determine the effects of ML genetic mutations using the worm *Caenorhabditis elegans*, the fruit fly *Drosophila*, and the zebrafish. Studying disease mechanisms in these models may allow scientists to develop treatments for people with an ML disorder.

Clinical trials involving the mucopolysaccharidoses that are being supported by NINDS and other NIH Institutes include a natural history of individuals with Mucopolysaccharidosis IV, to better understand the disease and identify potential outcomes (<http://clinicaltrials.gov/show/NCT01067742>); and longitudinal studies of the glycoproteinoses (such as ML1), to better understand disease progression, assess current therapies, and identify potential treatments (<http://clinicaltrials.gov/show/NCT01891422>).

Through these and other research efforts, scientists are optimistic that they will one day discover treatments or even prevention strategies for the MLs.

More information on research on the mucopolysaccharidoses supported by NINDS or other NIH Institutes is available through the NIH RePORTER (<http://projectreporter.nih.gov>), a searchable database of current and previously funded research, as well as research results such as publications and patents.

Where can I go for more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN

P.O. Box 5801

Bethesda, MD 20892

800-352-9424

www.ninds.nih.gov

Additional information on the mucopolidoses is available from:

Genetic Alliance

4301 Connecticut Avenue, N.W.

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National Library of Medicine

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