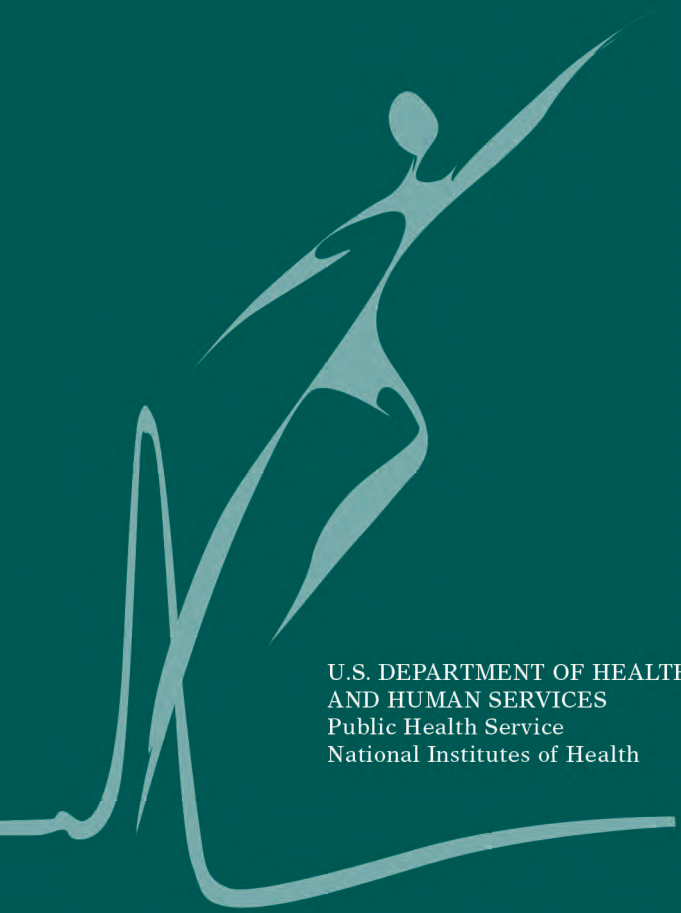
The Mucolipidoses



U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

The Mucolipidoses

What are the mucolipidoses?

The mucolipidoses (ML) 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 ML, abnormal amounts of carbohydrates or fatty materials (lipids) 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 mental retardation and skeletal deformities. Symptoms of ML 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 ML develop poor mental capacities, have difficulty reaching normal developmental milestones, and, in many cases, eventually die of the disease.

What causes the mucolipidoses?

The MLs 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 pick up substances

such as carbohydrates and lipids and break them down into smaller molecules so that they can be used again in the metabolic process. This process is possible because lysosomes contain enzymes, which are proteins that help the body's chemistry work better and faster. Working continuously, enzymes break down carbohydrates and lipids and assist in the transfer of their byproducts throughout the rest of the cell for the production of energy or excretion.

Patients with ML are born with a genetic defect in which their bodies either do not produce enough enzymes or, in some instances, produce ineffective forms of enzymes. Without functioning enzymes, which are proteins, lysosomes cannot break down carbohydrates and lipids and transport them to their normal destination. The molecules then accumulate in the cells of various tissues in the body, leading to swelling and damage of organs. In patients 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 mental retardation, 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 is not the result of just one deficient enzyme. Lysosomes contain as many as 40 or 50 different enzymes, each responsible for a

highly specialized function. Therefore, a deficiency in one particular enzyme or activator protein 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. Mucopolysaccharides are not seen in urine of patients with ML, therefore screening of the urine can help doctors distinguish between the two groups of disorders.

What are the different types of mucolipidoses?

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

Mucolipidosis type I (ML I) or 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 chains

containing the sugar-like material accumulate in neurons, bone marrow, and various cells that defend the body against infection.

Symptoms 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 (called myoclonus) and have red spots in their eyes (called cherry-red macules). 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 mental retardation that is either initially or progressively severe. Many patients 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 sialidosis — sialidosis type 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 are often the initial symptoms. Patients usually develop seizures and progressive deterioration of coordinated muscular and mental activities.

Mucolipidosis types II and III (ML II and ML III) result from a deficiency of the enzyme N-acetylglucosamine-1-phosphotransferase. Just as luggage in an airport is tagged to direct it to the correct destination, enzymes are often "tagged." In ML II and ML III, the deficient enzyme is supposed to tag other enzymes (activator proteins) so that they can initiate certain metabolic processes in the cell. Because the activator proteins are not properly tagged, they escape into spaces outside the cell and therefore cannot do their usual work of breaking down substances 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 their lack of growth, develop short-trunk dwarfism (underdeveloped trunk). These young patients are often plagued by recurrent respiratory tract infections, including pneumonia, otis 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 child is 3–5 years of age. One of the milder forms of the MLs, ML III (sometimes referred to as pseudo-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.

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

Mucolipidosis type IV (ML IV) is caused by harmful alterations of a protein in the cell that is believed to be involved in the movement of molecules such as calcium across cell membranes. Many cells throughout the body are filled with granules. Most patients with ML IV have delay of movement development and coordination, clouding of the cornea of the eye, and severely reduced vision. Patients usually have an unsteady gait and do not walk independently. ML IV patients have occasionally been misdiagnosed as having cerebral palsy. Speech is usually severely impaired. ML IV patients have a dramatic reduction of secretion of acid by the stomach. This alteration results in an increase of a protein called *gastrin* in the blood.

How are the mucolipidoses inherited?

The mucolipidoses 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 a defective gene, each of their children faces a one in four chance of developing one of the MLs. 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 on 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 common are the mucolipidoses?

The four forms of ML are rare and little information is available on how often they occur in the United States. ML IV is more common among Jewish children of Eastern European descent (Ashkenazi Jews), but children of different ancestries also appear to be affected. Although the MLs are classified as rare diseases, more than one person can be affected in families that carry the defective genes.

How are the mucolipidoses 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 patient'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 patient 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 conjunctival swabbing are found to have numerous inclusions. In addition, measurement of the level of gastrin in the blood, which is significantly increased in ML IV patients, helps to confirm the diagnosis.

Scientists have identified the genes responsible for all four types of MLs. In 2000, scientists at NINDS laboratories and other research institutions identified the gene responsible for ML IV. This gene, *MCOLN1*, makes the protein mucolipin-1. Due to mutations in the gene, mucolipin-1 is missing or dysfunctional in people with ML IV. This important genetic finding allows for the accurate diagnosis of patients 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 patients and their families. Counselors can also help adults who might have a defective gene decide whether or not they wish to have children. Psychological counseling and support groups for people with genetic diseases may also help patients and their families cope with ML.

Are there any treatments?

No cure for ML currently exists. Therapies are generally geared toward treating symptoms and providing supportive care to the child. 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 is only temporary. Physical and 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 patients with ML. For example, children at risk for failure to thrive (growth failure) may need nutritional supplements, especially iron and vitamin B12 for patients with ML IV. Respiratory infections should be treated immediately and fully with antibiotics.

What research is being done?

The National Institute of Neurological Disorders and Stroke (NINDS), a component of the National Institutes of Health (NIH), is the federal agency with primary responsibility for conducting and funding research on disorders of the brain and nervous system, including the MLs.

Discovery of the ML genes is enabling NINDS researchers to study the genes' function and will facilitate studies on drugs that may lead to effective treatments. In addition, investigators at grantee institutions are conducting studies on an animal model, *Caenorhabditis elegans*, which is frequently used to determine the effects of genetic mutations. Other grantees are using the fruit fly model, *Drosophila*, to

study a mutation in the ML IV gene. And one of the research teams involved in the discovery of the ML IV gene is conducting further genetic studies to explore the normal and abnormal functions of the ML IV gene.

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

Where can I find more information?

For more information on the MLs, you may wish to contact:

Association for Neuro-Metabolic Disorders
5223 Brookfield Lane
Sylvania, Ohio 43560-1809
(419) 885-1497

Mucolipidosis IV Foundation
719 East 17th Street
Brooklyn, New York 11230
(718) 434-5067
www.ml4.org

National MPS Society, Inc.
PO Box 736
Bangor, Maine 04402-0736
(207) 947-1445
www.mpssociety.org

National Organization for Rare Disorders
P.O. Box 1968
55 Kenosia Avenue
Danbury, Connecticut 06813-1968
(203) 744-0100
(800) 999-6673
www.rarediseases.org

National Tay-Sachs and Allied Diseases Association
2001 Beacon Street, Suite 204
Brighton, Massachusetts 02135
(617) 277-4463
(800) 906-8723
www.ntsad.org

For information on genetic counseling and testing contact:

Genetic Alliance
4301 Connecticut Avenue, N.W., Suite 404
Washington, DC 20008-2369
(800) 336-4363
www.geneticalliance.org

National Society of Genetic Counselors (NSGC)
233 Canterbury Drive
Wallingford, Pennsylvania 19086-6617
(610) 872-7608
www.nsgc.org

For information on other 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, Maryland 20824
(800) 352-9424
www.ninds.nih.gov

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