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Mucopolysaccharidosis Type I (MPS-I)

(Hurler Syndrome, Hurler/Scheie Syndrome, Scheie Syndrome)

Background

Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders that are characterized by a deficiency in the enzymes needed to metabolize glycosaminoglycans (GAGs). Mucopolysaccharidosis Type I (MPS I) is a lysosomal storage disorder defined by alpha-L-iduronidase (IDUA) deficiency. This leads to the progressive accumulation of specific GAGs in cellular and organ tissue thus compromising their function. GAGs, formerly called mucopolysaccharides, are an important part of the extra cellular matrix, joint fluid and connective tissue. The GAGs associated with MPS I are dermatan sulfate and heparin sulfate. The overall incidence of MPS I is 1 in 100,000. It is the most common of the MPS disorders. The Irish Republic has a higher incidence (1 in 26,000) with a carrier frequency of 1 in 81. Irish Travelers population has the highest incidence (1 in 371) with 1 in 10 believed to be carriers.

Clinical

MPS I is a heterogeneous disease. It was previously defined separately as Hurler Syndrome, Hurler/Scheie Syndrome or Scheie Syndrome but there were no established guidelines for classification. It was found that all three of these syndromes shared the same deficiency and were merely describing the severity of phenotypes. Now, MPS I is described as a more (Hurler) or less (Scheie) severe form of the disease. The clinical manifestations are progressive and multi-systemic. The most severe forms include progressive, debilitating symptoms that begin within the first year of life and include mental retardation. The life span is usually less than 10 years of age. Less severe forms have similar but less pronounced manifestations of the disease with normal intellect and life span.

Neurological manifestations are usually evident by 18 months of age, especially in severe forms of the disease. There is marked developmental delay and mental retardation in the most severe form, apparent by 12-24 months of age. Maximum abilities are achieved by four years of age then will plateau for some years then slowly decline as the accumulation of GAGs interrupts organ function. There is often hydrocephalus, spinal cord compression and carpal tunnel syndrome.

Gastrointestinal complications are usually the first clinical signs and include inguinal or umbilical hernias and progressive hepatomegaly, though without organ dysfunction. Patients with MPS I can experience episodes of diarrhea or loose stools alternating with constipation.

Musculoskeletal symptoms are outwardly seen as coarse facial features: macrocephaly, bulging frontal bones, enlarged lips with an open mouth at three years of age, protruding eyes due to narrow sockets, depressed nasal bridge and broad nasal tip. These symptoms are usually evident between 3-6 months of age and become more pronounced over time. Phalanges are malformed, creating claw-shaped hands. Severe forms exhibit gibbus and dorsolumbar kyphosis between 10-14 months of age. Joint stiffness begins at two years of age and progresses to the point that range of motion is severely limited. Growth is also inhibited, mostly seen in the trunk versus the limbs. Height (length) usually ceases around two years of age. By age 3, the patient's height is in the 3rd percentile, with overall height rarely exceeding 4 feet.

Respiratory features include chronic rhinitis and rhinorrhea without infections. Sleep apnea has been reported due to obstructed upper airways. Patients exhibit macroglossia, and enlarged tonsils and adenoids. There is decreased lung volume due to a small thorax and hepatosplenomegaly that restrict the diaphragm. A major cause of mortality is respiratory insufficiency.

A common ocular finding is corneal clouding within the first year that can lead to loss of vision. Hearing loss is often reported. Cardiovascular disease is characteristic of later stages of MPS I as GAG storage in cardiac tissue leads to thickening of the mitral and aortic valves and can cause regurgitation and stenosis.

Testing

Diagnosis is made through enzyme assay. The specific enzyme deficiency defines the particular type of MPS. Elevated levels of dermatan sulfate and heparan sulfate can be found in the urine of patients with MPS I. Lymphocytes in blood smears are assessed for abnormal cytoplasm. Assay analysis of cultured fibroblasts and leukocytes can measure alpha-L- iduronidase levels. Prenatal testing of amniotic cells and CVS is available.

Treatment

Enzyme replacement therapy (ERT) is available for the treatment of MPS I. Laronidase (Aldurazyme) has shown to improve pulmonary function and the ability to walk. It also delays the development of chronic symptoms. ERT works to increase the catabolism of GAGs as evidenced by the decrease in storage of them in organs. Some cases have benefited from bone marrow transplant but it is not widely used. The progressive nature of the disease requires regular monitoring of clinical manifestations and symptom management. A multidisciplinary medical team of specialists is needed for treatment and care due to the multisystem involvement. This team should include a metabolic geneticist who specializes in lysosomal storage disorders.

Inheritance

MPS I follows an autosomal recessive inheritance pattern; affected patients have two copies of a disease gene (or mutation). People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child affected with the disorder. The IDUA gene that encodes for alpha-L-iduronidase is found on chromosome 4p16.3. Fifteen different mutations that cause premature stop codons in IDUA gene have been found.

As with all genetic diseases, genetic counseling is appropriate to help families understand recurrence risks and ensure that they receive proper evaluation and care.

References

Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly W, Valle D, eds. The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. McGraw-Hill. Chapter 136.