

The Fundamental Aspects of Hurler Syndrome

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Abstract: Hurler syndrome is a genetic condition characterized by an alpha-L-iduronidase (IUDA) enzyme deficiency. A severe physiological deformity is caused by the lysosomal storage disorder, which damages one or more acid hydrolases of glycosaminoglycan. While there are currently available therapies, including hematopoietic stem cell transplantation, enzyme replacement therapy, and gene therapy, children with Hurler syndrome initially appear normal at birth and developing the typical clinical manifestations including coarse facies, growth retardation, photophobia and visual impairment, crystalline keratopathy, retinal degeneration, and optic nerve swelling. Therefore, I have attempted to emphasise all the hurler syndrome's essentials in this article.

Keywords: Hurler syndrome, glycosaminoglycan, ERT, HSCT

Introduction

Hurler Syndrome-

Hurler syndrome (Mucopolysaccharidosis Type I) is additionally referred to as gargoylism due to the related everted lip and protruding tongue. Hurler syndrome was first characterized by German paediatrician Gertrud Hurler in 1919. It is one of the 11 mucopolysaccharidosis disorders. In 1962, Scheie syndrome was recognised as a milder form of MPS I. MPS Type I (Hurler, Schieie, and Hurler-Scheie Syndrome; MPS IH, IS, IHS) is a rare autosomal recessive lysosomal storage disease caused by a loss-of-function variant of the IDUA gene, which encodes the enzyme -L-iduronidase (IDUA) and is mapped to chromosome 4p16.3 resulting degradation of glycosaminoglycans i.e. heparan and dermatan sulfate. The lysosomal enzyme is mandatory for the breakdown of certain complex carbohydrates term as glycosaminoglycans (GAGs). If the enzyme is not present in an adequate amount, the normal breakdown of GAGs is incomplete or blocked. The cell is then enable to excrete the carbohydrate residues that have accumulated in its lysosomes. This accumulation disrupts the cells' normal functioning and gives rise to the clinical manifestations of the disease.

Etiology

Hurler syndrome is caused by a deficiency of the enzyme alpha - L - iduronidase (IUDA), which is present on chromosome 4p16.3. extends 19 kb and includes 14 exons.

Epidemiology

The incidence of Hurler syndrome is approximately 1 in 100000 births. Male and female children are equally affected.

-Carriers of MPS I (Hurler syndrome) have one gene that is normal and one that has a mutation; they do not have Hurler's syndrome, and there are no known health issues associated with being a carrier. However, carriers can be recognized by genetic testing and by the decreased activity of the enzyme in their bodies. Less than 1% of the population or about 1 in 150 people, carry Hurler's disease. A kid born to two heterozygous [carrier] parents has a one in four probability of contracting the disease and a one in two chance of becoming a carrier. The severity of the illness makes it crucial to be aware of your carrier status. For carriers, genetic counselling is suggested. Every time, the earlier

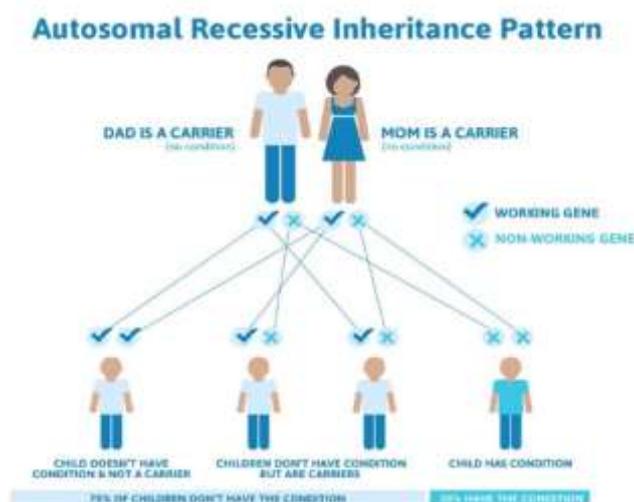


Fig no.1 Autosomal Recessive

Clinical manifestation : Hurler syndrome is caused by a lack of a lysosomal enzyme, which leads to a buildup of glycosaminoglycan in the body, causing enlargement and thickening of various organs such as the spleen, heart, muscles, liver, connective tissues, joints and the central nervous system causing severe functional impairment.

1.Hurler Syndrome (MPS I H):

Appear normal at birth and develop the characteristic coarse facies over the first year of life. significant growth retardation, mental retardation, hepatosplenomegaly, hearing loss and death occurs at first decade of life.

2.Scheie Syndrome (MPS IS):

Has milder systemic manifestation normal life expectancy, lack of growth and mental retardation.

-photophobia and visual impairment.

-crystalline keratopathy.

-retinal degeneration.

-optic nerve swelling.

The attenuated form of MPS I is characterized by Subnormal intelligence. Most patient die before the age of 25 to 30 year.

3.Hurler-Scheie Syndrome (MPS I H-S):

Appear normal at birth. Coarsening of the facial feature occurs within the first 2 years.

-progressive skeletal dysplasia.

-linear growth stop by age 3 years

-hearing loss occurs.

-Death caused by cardiorespiratory failure, usually occurs within the 10 years of life.

-onset of progressive severity of psychomotor development usually between 3-to-10-year age.

The intermediate form of MPS I is characterized by normal or near normal intelligence but more severe physical symptoms.

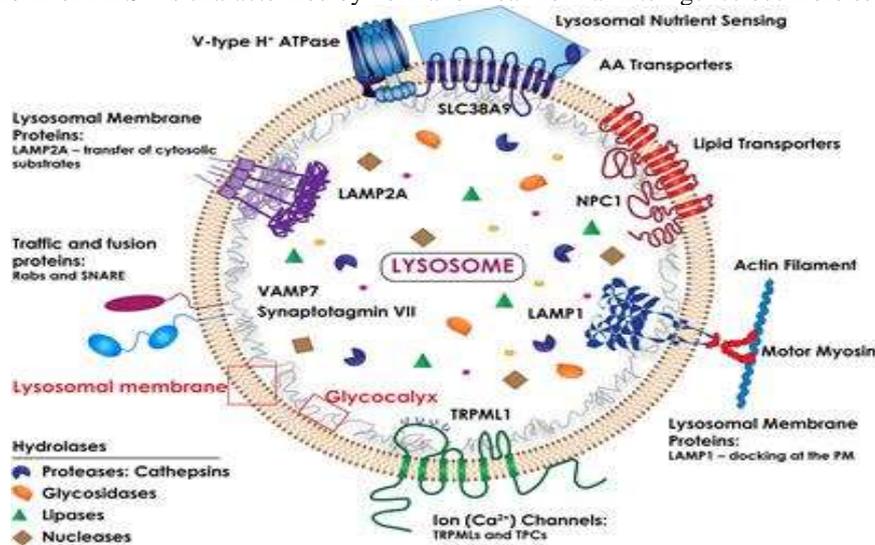


Fig no.2 Pathological MPS I cascade

Representative pathological MPSI cascade. could be responsible for lysosome rupture with subsequent release of proteases, cathepsins and toxic products inside the cytoplasm. This could potentially result in mitochondrial oxidative stress, ROS formation, impaired cell function and eventually, apoptosis.

Diagnosis

The first clinical signs are not specific, so it is difficult to diagnose early, but it is especially important to allow early treatment to begin based on -

1.Detection of increased urinary excretion of heparan and dermatan sulfate by 1,9-dimethylmethylene blue test (DMB).

2.Prenatal diagnosis- measurement of enzyme activity in cultivated chorionic villus or amniocytes can be used.

3.Glycosaminoglycan electrophoresis.

4.Mass spectrometry.

5.Enzyme assay or DNA analysis-

Enzymatic deficiency is based on cultured fibroblasts, leukocytes, plasma and serum.

Treatment

1.Enzyme Replacement Therapy

-Recombinant human alpha-L-iduronidase (Aldurazyme) is given as a weekly intravenous injection.

-ERT does not cross the blood-brain barrier and therefore does not treat the central nervous system (CNS) effects of the disease.

-The majority of patients produce anti-IDUA antibodies, which could reduce ERT's effectiveness.

2.Hematopoietic Stem Cell Transplant (HSCT)

-It is most effective treatment in which progressive replacement of enzyme deficient hematopoietic cells with donor -derived enzyme competent cell. Donor -derived hematopoietic cell constitute a stable endogenous source of enzyme released into systemic

circulation and locally in the tissue form tissue – resident myeloid cell replaced after transplantation. It can prevent mental deterioration if performed early enough (before age 2)

3. New Therapies

-The gene therapy in animal models which include the delivery of iduronidase enzyme gene by using viral vectors i.e. lentivirus vector which expressing IUDA. Hurler syndrome is now routinely treated using gene therapy.

Conclusion

Hurler syndrome is a hereditary illness that causes physiological deformity in children. By the time MPS IH/S Hurler/Scheie is diagnosed at age 6.5, death usually occurs before age 10. This illness can be diagnosed based on a clinical examination and a measurement of the level of urine GAG. Enzyme replacement therapy and hematopoietic stem cell transplant are available as treatments. For Hurler syndrome, gene therapy has recently become widely used.

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