NEWER THERAPIES IN HURLER SYNDROME

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Abstract- **Hurler syndrome is an inherited and progressive multisystem disorder characterised with physical deformities and developmental anomalies. It is caused by the deficiency of lysosomal enzyme alpha-L-iduronidase, which results in intralysosomal accumulation of dermatan sulphate and heparin sulphate and in turn causes cell dysfunction and death in early child hood. It is also known as mucopolysaccharidosis type IH (MSP-IH) or lysosomal storage disease. This genetic disorder results in the build-up of large sugar molecules called glycosaminoglycans (GAGs) in lysosomes, as alpha-L iduronidase enzyme is responsible for breaking down GAGs. The deposition of GAG causes enlargement and thickening of various organs like heart, spleen, liver, muscles, connective tissues, joints, and the central nervous system causing severe functional impairment. 1919, Getrud Hurler, a German paediatrician introduced this hurler syndrome. He described that clinical symptoms of this disease like corneal clouding, skeletal abnormalities, and mental retardation are similar to disease called "Gargoylism" it had been described in 1917 by Charles A. Hunter. Hurler did not mention Hunter's paper. Because of the communications interruptions caused by World War I, it is likely that he was unaware of his study. Hurler syndrome now refers to MPS IH, while Hunter syndrome refers to MPS II. In 1962, a milder form of MPS I was identified by Scheie, leading to the designation of Scheie syndrome.[4]. Children with hurler syndrome are generally not born with signs but develop symptoms during the first year of life. Developmental delay may become apparent by the age of 1 to 2 years, with a maximum functional age of 2 to 4 years. The average age of mortality is 5 years, and nearly all patients die before 10 years of age.Gene therapy may provide a future alternative human treatment for mucopolysaccharidosis type disorder.**

AETIOLOGY:

The deficiency of alpha-L-iduronidase is caused mainly due to underlying IUDA mutations and a consequent residual degree of enzyme activity. And it is an inherited disorder.

INHERITANCE PATTERN:

If both partners are carriers of the same abnormal gene, they may pass on either their normal gene or their abnormal gene to their child. This occurs randomly. Each child of parents who both carry the same abnormal gene therefore has a 25% (1 in 4) chance of inheriting an abnormal gene from both parents and being affected by the condition. This also means that there is a 75% (3 in 4) chance that a child will not be affected by the condition. This chance remains the same in every pregnancy and is the same for boys or girls. There is also a 50% (2 in 4) chance that the child will inherit just one copy of the abnormal gene from a parent. If this happens, then they will be healthy carriers like their parents. Lastly, there is a 25% (1 in 4) chance that the child will inherit both normal copies of the gene. In this case the child will not have the condition, and will not be a carrier.
These possible outcomes occur randomly. The chance remains the same in every pregnancy and is the same for boys and girls.

EPIDEMIOLOGY:

The incidence is approximately 1 in 100,000 births. Male and female children are equally affected. All races and ethnicities are at risk of inheriting the disease. All of the mucopolysaccharidoses have a frequency of approximately one in every 25,000 births in the United States.

CLASSIFICATION:

This is broadly classified into three types

1. HURLER SYNDROME (MPS I H)
2. HURLER-SCHEIE SYNDROME (MPS IH-S)
3. SCHEIE SYNDROME (MPS IS)

HURLER SYNDROME (MPS IH):
This is the severe and most common form where patients die within the first year of their life.
Symptoms: shortly develop after birth and progress rapidly.

- Developmental delay
- Cognitive decline
- Characteristic coarse facial features
- Joint stiffness and contractures
- Short stature
- Cardiac diseases
- Hepatic diseases

HURLER-SCHEIE SYNDROME (MPS IH-S):
This is an intermediate phenotype, typically diagnosed at 2 to 6 years of age. Life expectancy extends into the late teens or early twenties. Death is usually due to respiratory failure.
Symptoms:

- Facial features are less than hurler syndrome
- Achilles tendon contractures lead to toe walking.
- Hepatosplenomegaly causing respiratory compromise
- Spondylolisthesis
- Kyphoscoliosis
- Meningitis cause compression of the spinal cord
- Paralysis
- Mild cognitive impairment

SCHEIE SYNDROME (MPS IS):
This is a rare and mild phenotype. Most patients die before the age of 25 to 30 years.
Symptoms:

- similar to that of hurler and hurler scheie syndromes but patients have normal intelligence.

Children with hurler syndrome are not usually born with signs but develop symptoms during the first year of life. The average age of mortality is 5 years, and nearly all patients die before 10 years of age.

CLINICAL MANIFESTATIONS:
GENERAL APPEARANCE:
Characteristic features include coarse facies, enlarged head with prominent frontal bones, widely placed eye sockets with protruding eyes, flat appearance of nasal bridge, enlarged lips, and wide open eyes, the neck is typically short and stiff

NEUROLOGICAL MANIFESTATIONS:
Progressive deterioration and loss of previously acquired skills before 2 years of age. Limited language skills because of developmental delay. GAGs get deposited in meninges and spinal cord resulting in obstruction of cerebrospinal cord thereby causing high pressure communicating hydrocephalus and convulsions. Atrophy and ventricular enlargement is also observed in the patients which may lead to sudden death.

RESPIRATORY AND PULMONARY MANIFESTATIONS:
Patients develop pulmonary infections and sinus. Soft tissue thickening in the nose, pharynx, tonsils and adenoids along with abnormalities in tracheal cartilage causes progressive airway obstruction and sleep apnea.in some patients, sleep apnea is unrecognised and can cause significant hypoxemia at night, leading to complications like pulmonary hypertension and cor pulmonale. Initially, respiratory symptoms are more pronounced in the upper airways, but as the disease progresses, tracheobronchial manifestations can emerge, which in severe cases are frequently the cause of death.

CARDIAC MANIFESTATIONS:
These include cardiomyopathy, endocardial fibroelastosis, valvular regurgitation and heart failure. GAG deposition within the blood vessels causes diffuse narrowing of the coronary arteries. Most hurler syndrome patients die from heart failure before the age group

of 10. Occlusion of abdominal aorta and renal arteries and associated systemic hypertension are also seen. Valve abnormalities, coronary artery diseases, and other vascular changes are observed.

GASTROINTESTINAL MANIFESTATIONS:
Difficulty in swallowing is caused due to GAGs deposition in the muscle tissue of the tongue, which results in macroglossia which might impair speech. Inguinal hernia, umbilical hernia, and hepatosplenomegaly are notes where inguinal and umbilical hernias develop within several months of life as first clinical symptoms.

MUSCULOSKELETAL MANIFESTATIONS:
Patients stop growing in height by the age of 2 years. They may not reach a height of greater than 4 feet. Skeletal abnormalities become more clinically obvious by 10 to 14 months. An enlarged head size is due to craniosynostosis and hyperostosis of the skull is usually seen. The patient may experience debilitating spine and hip deformities, abnormal bone and cartilage development (particularly hand and spine), carpal tunnel syndrome and joint stiffness which limit mobility and are painful. Gibbus deformity (dorsal kyphosis) is common in these patients. Cervical myelopathy is seen due to congenital vertebral anomalies and atlantoaxial subluxation. Patients usually develop typical skeletal abnormalities, known as dysostosis multiplex. The other abnormalities include flattened vertebral bodies, odontoid hypoplasia at cervical vertebrae, oar- shaped ribs, short and thickened clavicles, bullet shaped phalanges, and J-shaped Sella turcica. These individuals often suffer from low bone mineral density which is treated by hematopoietic cell transplantation. These musculoskeletal deficiencies occur due to accumulation of partly digested GAG in the ECM and the loss of function of GAGs.

OCULAR MANIFESTATIONS:
Ocular manifestations occur due to deposition of GAG in the majority of ocular tissues. Corneal clouding occurs due to structural alteration of the corneal stroma and derangement of collagen fibrils which leads to blindness. Retinal degeneration and optic nerve compression occur within the first year of life. Ocular hypertension (glaucoma), refractive errors, optic nerve swelling, retinopathy and ocular motility abnormalities are also noted.

HEARING MANIFESTATIONS:
Hearing manifestations occur due to build up of GAGs in the tubes of middle ear which prevent them from draining properly which may lead to recurrent ear infections. The major concern is about conductive and sensorineural hearing loss.

COGNITIVE MANIFESTATIONS:
Symptoms of cognitive impairment begin around 6-9 months of age and progress to a decline thereafter. Manifestations of CNS involved in cognitive impairment are poor attention, poor adaptive skills and poor speech or language function.

INTEGUMENTARY MANIFESTATIONS:
Hair is abundant and coarser than normal children. Mongolian spots (bluish birth marks) are commonly seen.

DIAGNOSIS:
The evaluation is mainly done on the basis of detecting increased urinary excretion of heparan and dermatan sulphate and is confirmed by demonstration of enzymatic deficiency in leukocytes or fibroblasts. As the first clinical manifestations are not specific, early detection is not easy. Positive family history is often noted and genetic testing is also possible.

LABORATORY FINDINGS:
Enzyme activity assays based on cultured fibroblasts, leukocytes, plasma and serum are confirmatory and are considered the golden standards. Closely related mucopolysaccharidosis type 1 subtypes can be distinguished by suing an enzyme assay or DNA analysis. To establish a specific diagnosis along with symptom severity the age of onset should also be considered.

GENE SEQUENCING:
It can be done to identify the mutations in families at risk to offer genetic counselling and carrier testing in order to allow more informed family planning.

ANTENATAL DIAGNOSIS:
It is possible by the measurement of enzymatic activity in cultivated chorionic villus or amniocytes and by genetic testing if the disease-causing mutation is known.

Other tests that may be done depending on symptoms include:

- ECG
- X-ray of the spine

TREATMENT:

Most therapies for Hurler syndrome are directed towards treatment of complications and are not specific for an underlying abnormality.

- **Enzyme replacement therapy:** Recombinant human alpha L- iduronidase (Aldurazyme) is given as a weekly intravenous injection. Better outcomes can be achieved if it is given before severe complications. It is used for patients with the Hurler and Hurler-Scheie forms of mucopolysaccharidosis type 1 and moderate-to-severe symptoms in patients with Scheie form.
- **Hematopoietic stem cell transplant:** Hematopoietic stem cell transplant or bone marrow transplant or blood stem cell transplant, is the progressive replacement of enzyme-deficient hematopoietic cells with donor-derived enzyme competent cells. It is the ideal treatment for patients who are under 2 years of age and in selected patients over this age limit as it can prolong survival. Hematopoietic stem cell transplant decreases hepatosplenomegaly, airway obstruction, CSF pressures and increases joint mobility, cardiac function, and improves or stabilises hearing (mostly in young patients). Hematopoietic stem cell transplant is more effective at preventing disease progression than reversing the established disease.
- **Additional management** of Hurler syndrome is supportive and includes surgical interventions like adenotonsillectomy; hernia repair; ventriculoperitoneal shunt; cardiac valve replacement; carpal tunnel release; spinal decompression; physical, occupational, and speech therapies; respiratory support such as continuous positive pressure ventilation with oxygen supplementation (CPAP); hearing aids; and medications for pain and gastrointestinal disturbances. Corneal transplants can be done for vision problems; however, surgery in patients with Hurler syndrome often presents with complications related to anaesthetic procedures.

- Specialised surgical care can reduce hydrocephalus, and corneal transplantation may help some patients.

- Valve replacement for cardiovascular disease has been accomplished and tracheostomy has been performed to improve breathing in some cases.

- Spinal fusion can help prevent further progression of curvature in the cervical spine, and carpal tunnel release has helped some patients.

LIFE EXPECTANCY:
The life expectancy is highly variable with MPS I. The life expectancy is related to the severity of the disease. For example, individuals with the mildest form of MPS I (MPS IS) may have a reasonably normal lifespan, while those with intermediate (MPS IH/S) usually live to teen age or early adulthood. Those with severe MPS I (MPS IH or Hurler syndrome) rarely live longer than 10 years.

DIETARY NEEDS:
Changes to the diet will not prevent disease progression, but limiting milk, sugar, and dairy products has helped some individuals experiencing excessive mucus. It is important to discuss dietary needs of the child with the parents to learn if there are restrictions. If there isn't a special diet required for an individual with an MPS, a well-balanced diet is important. If the child is experiencing sleep apnea or obstructive airway disorder, surgery to remove tonsils and adenoids may be done to improve breathing. Sleep studies can assess airway status and the possible need for nighttime oxygen. Surgery may also be done to correct hernias, help drain excessive cerebrospinal fluid from the brain, and free nerves and nerve roots compressed by skeletal and other abnormalities. Mobility problems, hearing loss and vision difficulties are the major medical complications in MPS that may need the special attention of school personnel in program planning. It is important to discuss the nature of the student's condition and implications for school activities. The child's physicians will determine the student's permitted activity levels.

PREVENTION:
Experts recommend genetic counselling and testing for couples with a family history of MPS I who are considering having children. Prenatal testing is available.

NEWER THERAPIES:
Research is ongoing with gene therapy in animal models, which includes the delivery of iduronidase enzyme gene by using viral vectors. It demonstrated correction of disease in the liver, spleen, and brain effects to a certain extent. Gene therapy may provide a future alternative human treatment for mucopolysaccharidosis type disorder.

Hurler syndrome (mucopolysaccharidosis type I) is caused by absent α-L-iduronidase (IDUA) expression due to autosomal recessively inherited mutations in the IDUA gene, leading to accumulation of glycosaminoglycans (GAGs). Enzyme replacement therapy with iduronidase reduces somatic symptoms but the enzyme does not cross the blood–brain barrier. Until now, definitive treatment has been allogeneic haematopoietic cell transplantation, which requires an HLA-matched donor and immunosuppression. An Italian group now reports eight patients, mean age 1.9 (standard deviation 0.5) years, with Hurler syndrome who lacked a donor, had an IQ >70 and were treated with autologous haematopoietic stem and progenitor cell gene therapy.1 The researchers used a lentivirus vector expressing IDUA, with a strong promoter resulting in supraphysiological IDUA levels, greater than those seen with allogeneic haematopoietic cell transplantation. At follow-up after a median of 2.1 years, high IDUA levels persisted, including being detectable in the CSF associated with local clearance of GAGs, and urinary GAG excretion fell to normal in four of five patients evaluated. Magnetic resonance imaging of the brain and spine was stable or improved. The patients' cognitive ability was stable, motor development continued, joint stiffness reduced and growth was normal. While these results are encouraging, an accompanying editorial stressed limitations including short term follow-up and the need for immunosuppression to allow the gene-corrected product to be delivered to the patient's marrow.

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