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Mini Review

Hurler Disease (MPS I) in Childhood: Treat or Cure?

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Abstract

Hurler syndrome is the most severe form of the rare metabolic disorder mucopolysaccharidosis type 1, caused by an enzyme deficiency that prevents the breakdown of certain sugars, leading to the accumulation of dermatansulfate and heparansulfate in tissues. The gene defect is located at chromosome 4p16.3 gene locus. The incidence is 1:145.000 respectively. It is a monogenetic disease with an autosomal recessive trait.

The gene defect leads to an enzyme defect of the enzyme alpha-L-iduronidase (IDUA) with the result of extensive accumulation of glycosaminoglycanes in different cell tissues. There are 3 different forms of Hurler disease. Morbus Hurler shows an serious involvement of the CNS, Morbus Hurler-Scheie an attenuated form with an incidence of 1:280000, and Morbus Scheie, which is found in 1:500000 newborns, shows only a moderate form of the disease. Typical symptoms include coarse facial features, skeletal changes, enlarged organs with heptoslenomegaly, heart and breathing problems, and intellectual disabilities due to central nervous system involvement. Early diagnosis and specialized therapies such as stem cell transplantation are important, but the prognosis is of ten limited due to the severity of the condition. The challenge treating the diease in childhood is delivering sufficient enzymes to the brain to ameliorate the cognitive brain development by accumulation of GAG in the brain cells. Recent research is focusing on next generation enzyme replacement therapies with crossing the blood-brain-barrier, HSCT, targeting nonsense mutations at mRNA level through nonsense suppression and mRNA editing suppressor t`RNA`s, in vivo and ex vivo gene transfers,

Introduction

In Europe, the prevalence of the Hurler subtype of MPS1 is estimated at 1/200,000. The main features of Hurler syndrome are skeletal deformities and delayed motor and intellectual development. Patients typically present in the first year of life with changes in the musculoskeletal system: short stature, dysostosis multiplex, thoracolumbar kyphosis, progressive coarsening of facial features, large head, frontal bossing, flat nasal bridge with broad nasal tip and anteverted nares, full cheeks, widened lips, cardiomyopathy with valve abnormalities, sensorineural hearing loss, enlarged tonsils and adenoids, nasal discharge. Developmental delay becomes apparent between 12 and 24 months, especially in the area of speech, followed by progressive cognitive and sensory decline. Hydrocephalus may develop in some patients by age 2. By age 3, diffuse corneal changes progress to corneal opacification. Organomegaly, hernias, and hirsutism are additional symptoms. Hurler syndrome is caused by mutations in the IDUA gene, leading to complete loss of alpha-L-iduronidase activity and lysosomal storage of Dermatan Sulfate (DS) and Heparan Sulfate (HS). Hurler syndrome is inherited in an autosomal recessive manner. Early diagnosis is challenging as the initial clinical signs are nonspecific. However, early diagnosis is crucial for initiating treatment as soon as possible. Laboratory diagnosis involves detecting increased

excretion of HS and DS in urine using the DMB test and GAG electrophoresis, as well as demonstrating enzyme deficiency in leukocytes or fibroblasts. Molecular testing is available. Differential diagnoses include the milder form of mucopolysaccharidosis type 1, Hurler-Scheie syndrome, although this form is associated with only mild cognitive impairment. Differential diagnoses also include mucopolysaccharidosis type 6 and type 2, and mucolipidosis type 2. Prenatal diagnosis is possible enzymatically or molecularly. Genetic counseling should be offered to affected families. Management is multidisciplinary. Hematopoietic Stem Cell Transplantation (HSCT) is the treatment of choice for patients with Hurler syndrome under 2.5 years (and selected patients over this age) as it can prolong survival, preserve neurocognition, and improve some somatic features. HSCT should be performed early in the disease course before developmental decline begins. Enzyme Replacement Therapy (ERT) with laronidase is recommended for all Hurler patients and is a lifelong therapy that alleviates non-neurological symptoms. Early ERT has been shown to delay or even prevent the development of some clinical features of the disease. Additional management of Hurler syndrome is largely supportive and includes surgical interventions (e.g., adenotonsillectomy, hernia repair, ventriculoperitoneal shunt, heart valve replacement, carpal tunnel release, spinal decompression), physical therapy, occupational therapy, speech therapy, respiratory support (e.g., continuous positive airway pressure with oxygen supplementation), hearing aids, and medications for pain and gastrointestinal disturbances. Patients often succumb to the disease in the first decade due to respiratory and cardiac complications, but ERT and HSCT can improve life expectancy. The timing of diagnosis and initiation of treatment is a crucial factor for the success of HSCT and laronidase.

Former and Present Therapy Options for Mucopolysacharidosis Type 1

Until the age of about 2.5 years, bone marrow or Hematopoietic Stem Cell Transplantation (HSCT) is the treatment of choice for patients with M. Hurler. Through the transplantation of bone marrow from a suitable donor, the patient receives blood cells that can produce the enzyme alpha-L-iduronidase. These cells release some of the produced, intact enzyme into the environment, which can be taken up by other body cells and transported into their lysosomes. This allows the stored glycosaminoglycans to be broken down. However, transplantation can only positively influence cognitive development and life expectancy. HSCT cannot cure the disease. In patients with M. Hurler, enzyme replacement therapy is often used before or after bone marrow or hematopoietic stem cell transplantation. In this therapy, the defective enzyme is replaced by a biotechnologically produced form of the human enzyme, allowing the pathological storage of glycosaminoglycans to be broken down again. However, due to the blood-brain barrier, the enzyme replacement therapy does not reach the Central Nervous System (CNS), so this therapy cannot directly affect the cognitive and motor symptoms of M. Hurler. This can currently only be achieved through early stem cell transplantation. Before HSCT, enzyme replacement therapy can improve the overall condition of patients. Additionally, enzyme replacement therapy can support the transplantation and alleviate symptoms, as MPS I cannot be cured by HSCT. For M. Hurler patients who are diagnosed later than 2.5 years and for whom bone marrow or stem cell transplantation is no longer an option, enzyme replacement therapy is available to treat the non-neurological manifestations of the disease.

4. Future Perspectives to treat and cure MPS 1

The future prospects for Hurler syndrome are improving due to therapy-specific advances, with gene therapy and Enzyme Replacement Therapy (ERT) as well as early hematopoietic Stem Cell Transplants (HSCT) being the main pillars that increase life expectancy and alleviate symptoms, even though a complete cure is still pending; the key lies in early diagnosis to protect brain and skeletal development, which are currently the biggest challenges. Enzyme Replacement Therapy (ERT): By providing the missing substance through recombinant enzymes, non-neurological symptoms are improved and quality of life is increased, but it does not cross the blood-brain barrier. Hematopoietic Stem Cell Transplantation (HSCT): In younger patients (under 2.5 years), it can preserve neurocognitive development, extend life expectancy, and is the most effective method so far, although it carries risks and requires a donor search. Treats specific complaints such as heart or breathing problems and improves daily life. Gene therapy aims to directly correct the gene defect and has the potential to address the root cause of the disease, enabling more comprehensive treatments.

Substrate Reduction Therapy (SRT): Aims to reduce the production of harmful substances. The combination of ERT with gene therapy or SRT is being researched to increase effectiveness and also reach the brain. The biggest challenge is the CNS involvement, therefore overcoming the blood-brain barrier remains the biggest hurdle for ERT. Newborn screening detection is crucial for therapy success, especially for neuroprotection. In conclusion, with innovative approaches such as gene therapy and improved stem cell transplantation procedures, there is increasing hope to better control the life-threatening aspects of Hurler syndrome and improve quality of life, even though the path to a complete cure is not yet complete [1-65].

Discussion

In patients with MPS I, an enzyme called Alpha-Iduronidase is not produced in sufficient amounts or not at all due to a genetic mutation. There are three forms of the disease: the most severe form, Hurler syndrome (MPS I H), the attenuated form, Scheie syndrome (MPS I S), and a form that cannot be clearly classified as severe or mild, Hurler-Scheie syndrome (MPS I HS). The severity of the disease can only be assessed through long-term observation of the patient. Each patient has their own individual

form of the disease in terms of severity, progression, and organ involvement. The symptoms and complications mentioned below do not apply equally to all patients and can be mitigated through the use of therapies. Many MPS I patients, especially those with Hurler syndrome, have a very typical appearance. They have a large head, broad nose, full to puffy lips, enlarged tongue, short neck, thick, coarse hair, and overall increased body hair. However, the appearance can also be completely unremarkable, especially in milder forms of the disease. Another characteristic feature is the protruding abdomen, usually due to an enlarged liver and spleen. However, the function of these organs is typically not impaired. Growth is often slowed in affected individuals. In Scheie syndrome, intellectual development is not affected, while in Hurler syndrome, it is severely delayed. Patients with Hurler-Scheie syndrome may have normal intelligence, but some may experience learning difficulties. The heart can be significantly affected, leading to heart failure (the heart valve does not close properly), heart stenosis (narrowing of the heart valve opening), and cardiomyopathy (thickening of the heart sac, making it harder to pump). This can cause patients to feel tired and fatigued, have difficulty breathing under exertion, chest pain, paleness, sudden sweating, and high blood pressure. Regular heart examinations are important, and some patients may require stabilizing or blood pressure-lowering medications. Defective heart valves can be replaced surgically with artificial replacements, preferably in a clinic experienced in treating MPS. In individuals with Hurler syndrome, special attention must be paid to the respiratory system. Recurrent respiratory infections, sleep apnea syndrome, and restrictive and obstructive lung diseases are particularly problematic. Sleep apnea syndrome, characterized by prolonged pauses in breathing during sleep, can be treated by removing enlarged tonsils and adenoids and using a CPAP breathing mask. The stiffness of the chest can also hinder lung expansion and restrict breathing (restrictive lung disease). Breathing is further complicated by changes in the lung structure and airways (obstructive lung disease). Removal of tonsils and adenoids and regular breathing exercises are often recommended in these cases.

In conclusion, with innovative approaches such as gene therapy with AAV-vector gene-or enzyme delivery systems or CRISP/Cas9 therapy and improved stem cell transplantation procedures, there is increasing hope to better control the life-threatening aspects of Hurler syndrome and improve the quality of life, even though the path to a complete cure is not yet complete.

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Conflict of Interest

None.

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