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Mini Review

What is the Clue to Cure Hunter Syndrome (MPS II) and San Filippo A Syndrome (MPS IIIa) in Childhood?

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Abstract

Mucopolysaccharidoses (MPS) are classified as a group of lysosomal storage diseases. They are based on inherited disorders of the enzymatic breakdown of acidic mucopolysaccharides (glycosaminoglycans) by lysosomal hydrolases. The undegraded glycosaminoglycans are stored in the lysosomes. This eventually leads to disturbances in cellular metabolism and, in severe cases, cell death. Tissues of the skeletal system, central nervous system, visceral organs, skin, and endocardium are mainly affected. Four types of glycosaminoglycans are stored. Depending on the different distribution patterns and clinical criteria, different main forms of mucopolysaccharidoses can be distinguished, which are further divided into various subtypes. These subtypes either refer to different clinical manifestations of the same enzyme defect or different biochemical defects of a clinical manifestation. Almost all types have severe and mild attenuated forms. Classification is only possible through the clinical course and the speed at which the disease progresses. MPS II and MPS IIIa are the basis of this review focusing on curing aspects of these rare diseases in childhood.

Keywords: MPS-Hunter-San Filippo, Child, Genetics, Treatment

Introduction

MPS II is a rare, inherited lysosomal storage disorder that affects boys and is caused by a deficiency of the enzyme iduronate-2-sulfatase [1-16]. This enzyme deficiency leads to the accumulation of certain sugars in various organs, resulting in progressive damage [17-21]. MPS IIIa is an inherited metabolic disorder caused by an enzyme deficiency, leading to the accumulation of certain sugar molecules in the body and damaging the brain and other organs [22-36]. There is currently no cure, and treatment focuses on symptom management, ultimately leading to premature death. Both rare genetic diseases include treatment options, but curing means one-time gene therapy approaches to correct the genetic defect, which induces the enzyme defect in both diseases with severe phenotypic outcome [36-46].

Hunter Syndrome (MPS II)

Hunter syndrome, also known as mucopolysaccharidosis type II, is an X-linked recessive metabolic disorder [1-21,37-39,47-53]. It belongs to the mucopolysaccharidoses, a group of disorders in which the lysosomal breakdown of mucopolysaccharides is impaired. Due to its X-linked inheritance, the disease almost exclusively affects boys [1-21,37-39,47-53]. There is one case of Hunter syndrome per approximately 156,000 births. In Germany, this translates to about 4-5 new cases per year. The cause of Hunter syndrome is a defective gene on the X chromosome (Xq27.3-q28) that encodes for iduronate-2-sulfatase. The mutation disrupts the breakdown of dermatan and heparan sulfate [1-4]. The presentation ranges from severe forms with intellectual disability (formerly Type A) to very mild forms with minimal or no intellectual developmental delay (formerly Type B) [2,3]. The transitions between these forms are fluid. Specific to MPS type II are skin manifestations with pale, nodular, usually grouped thickenings ("peau d'orange"). Other symptoms include facial changes with thick eyebrows, flat, sunken nasal bridge, fleshy, broad lips, enlarged tongue and prognathism. Deep and hoarse voice and cardiac involvement up to heart failure is also found. Further symptoms are middle ear and inner ear hearing loss, optic atrophy, early-onset progressive joint

contractures and distended abdomen due to developing hepatosplenomegaly. Umbilical hernia and growth delay are also common features. Severely affected patients may develop tetra spasticity with swallowing and breathing difficulties after a phase of aggression and erethism, gross motor skill disturbances with gait instability and frequent falls.

Skeletal changes like dysostosis multiplex congenita are in some cases present. The diagnosis is made by the increased excretion of mucopolysaccharides, especially dermatan and heparan sulfate in the urine electrophoresis. Additionally, the defective enzyme is determined in leukocytes or fibroblasts. Molecular genetic analysis is possible, as well as prenatal diagnosis in amniotic cells or chorionic villi cells. There is no causal treatment available. The possibility of a stem cell transplant is possible in individual cases. Idursulfase (Elaprase) was the first enzyme replacement therapy approved in Europe in January 2007 [47,48]. Hunter syndrome is a genetic disease caused by a mutated gene. This gene carries the blueprint for the formation of an enzyme called iduronate-2-sulfatase (I2S or IDS). In the case of the disease, the IDS gene is altered, leading to the enzyme IDS not being produced correctly or at all, resulting in improper functioning. Over 300 different gene mutations have been identified that can be involved in the development of Hunter syndrome. The enzyme IDS is needed to break down Glycosaminoglycans (GAGs), a type of carbohydrate, in the body's catabolism process, which takes place in the lysosomes of cells. Lysosomes are cell organelles responsible for digesting various substances in the cells (20). IDS breaks down GAGs by removing a specific chemical group (sulfate) from the different forms of GAGs (dermatan sulfate and heparan sulfate) (20). In Hunter syndrome, this process is impaired or reduced due to the lack or deficiency of IDS, leading to the accumulation of GAGs in the body over time and causing the various symptoms of the disease. The IDS gene is located on the X chromosome, which is why Hunter syndrome is referred to as an X-linked recessive disorder. Recessive means that in a woman with two X chromosomes, Hunter syndrome will only manifest if both X chromosomes carry the defective gene. If only one of her X chromosomes is affected, she will not develop Hunter syndrome but will be a carrier and can pass on the faulty gene to her offspring. In men, who have only one X chromosome, inheriting an X chromosome with a defective IDS gene will result in the enzyme defect of Hunter syndrome. Men always inherit their second sex chromosome from their fathers, which is the Y chromosome. The likelihood of inheriting the defective gene depends on several factors. For example, if a mother is a carrier of the gene defect but is not affected by the disease herself, the probability of passing on the gene is 50%. Her offspring will receive 50% of her healthy X chromosome and 50% of her X chromosome with the defective gene, assuming the father is not affected by Hunter syndrome.

MPS2 patients appear healthy at birth, with the first symptoms appearing between 18 months and 4 years of age. Macrocephaly develops in infancy, and children initially grow normally or at an above-average rate. Early symptoms include frequent respiratory infections (especially otitis media), umbilical and inguinal hernias, persistent diarrhea, hepatosplenomegaly, and skin changes resembling an orange peel (on the shoulders, back, and thighs). A distinctive facial appearance with thickened lips and nostrils, and an enlarged and protruding tongue slowly develops and may become visible between the ages of 2 and 4 years, in milder cases even later. The course varies from a severe form (MPS2, severe form) with early psychomotor regression to a milder form (MPS2, attenuated form) that occurs without cognitive impairment. MPS2 is caused by a deficiency of iduronate-2-sulfatase (I2S), leading to lysosomal accumulation of two specific mucopolysaccharides, Dermatan Sulfate (DS) and Heparan Sulfate (HS). The causative gene (IDS) has been mapped to the Xq28 chromosomal region. Approximately 320 different mutations have been described so far.

The diagnosis is based on clinical signs and elevated DS and HS levels in urine, and is confirmed by demonstrating the enzyme deficiency in serum, leukocytes, or fibroblasts, or in dried blood smears. To exclude multiple sulfatase deficiency, the activity of another sulfatase must also be determined. Genetic tests involve searching for exon or complete gene deletions, point mutations in the IDS gene and its promoter region, and recombination's with the adjacent IDS2 pseudogene. Differential diagnoses include mucopolysaccharidosis type 1,6,7, sialidosis type 2, mucolipidosis type 2 and 3, and multiple sulfatase deficiency. Prenatal diagnosis through measurement of IDS activity or mutation analysis in chorionic villi or amniocytes is only performed in male fetuses. It is an X-linked recessive disorder. However, not only hemizygous boys are affected, 12 affected girls have been described. Most of them were heterozygotes with skewed X-inactivation and preferential expression of the mutated allele. All patients should consider weekly intravenous Enzyme Replacement Therapy (ERT), which has been shown to alleviate somatic symptoms. A cranial shunt should be performed to address cases of hydrocephalus. Hernia repair, tonsillectomy and adenoidectomy (to clear the upper airways), and in some cases positive pressure ventilation or tracheostomy may be necessary. Over time, heart valve or hip joint replacement and carpal tunnel release may be required. Patients need regular echocardiographic examinations, respiratory function must be assessed, a complete radiological examination to identify dysostosis multiplex, cranial and cervical MRI with or without lumbar puncture to assess cerebrospinal fluid pressure, hearing tests, eye examinations, and nerve conduction velocity tests are necessary. The prognosis varies greatly. In the severe form (60-80% of cases), life expectancy is greatly shortened, and death usually occurs before the age of 25, often due to cardiorespiratory complications. In the attenuated form, patients can survive into adulthood, sometimes even beyond 60 years, and intellectual deficits are usually not present in these cases.

San Filippo Syndrome (MPS IIIa)

On the other hand, Sanfilippo syndrome is a rare inherited metabolic disorder [22-24,54,55]. The syndrome was subsequently named after the lead author. It belongs to the group of mucopolysaccharidoses, a group of disorders involving the breakdown of long-chain sugar molecules called glycosaminoglycans [25-36,40-46,56-79]. Sanfilippo syndrome is referred to as Type III of the mucopolysaccharidoses, which is further divided into four sub-

types (A-D). Affected children are typically normal at birth, but their intellectual development is delayed between the ages of two to four years. Skills that have been learned may regress. The children exhibit extremely restless behavior. By the second decade of life, behavioral disturbances take a backseat and are replaced by increasing spastic paralysis. Unlike other mucopolysaccharidoses, this syndrome primarily affects the brain, with other organs being less affected. Patients are usually of normal stature and have minimal skeletal abnormalities. Treatments were previously only symptomatic, as there was no causal therapy available. With genetic methods, successful treatments have been achieved in early childhood. Sanfilippo syndrome is caused by an autosomal recessive defect in four different enzymes (Types A-D) that are responsible for breaking down the glycosaminoglycan heparan sulfate. At birth, children with Sanfilippo syndrome appear normal. Due to the rarity of the disease, there are limited studies on the progression of symptoms. In severe cases, children may begin to lag behind in their development between the ages of two to four years. They exhibit noticeably restless, hyperactive, and possibly aggressive, destructive behavior. During this phase, affected individuals experience pronounced sleep disturbances. They speak less and gradually lose their ability to understand speech. Later, increasing signs of paralysis develop. Eventually, affected individuals lose their ability to walk due to spastic paralysis. Swallowing difficulties arise, leading to feeding challenges. Epilepsy may also occur as a result of progressive brain dysfunction. A study from 2010 concluded that nearly 80% of affected individuals have a milder course of the disease, with only slight decline in intellectual abilities. These children can generally reach adulthood with minimal restrictions. In comparison to neurological symptoms, manifestations in other organs are less pronounced in Sanfilippo syndrome compared to other mucopolysaccharidoses: body length reaches almost normal proportions, facial features become coarser only with significant brain function deterioration. The hair is notably thick and brittle, and eyebrows may grow together in the middle. The course of the disease is highly variable, with the majority of affected individuals dying in the second or third decade of life, depending on the severity. When Sanfilippo syndrome is suspected, a urine test to determine glycosaminoglycans levels can be conducted. However, GAG excretion may only be marginally or mildly elevated in Sanfilippo syndrome. For a more definitive diagnosis, electrophoresis can be used to detect increased excretion of heparan sulfate. If suspicion persists, enzyme activity levels in white blood cells or fibroblasts can be measured to confirm the diagnosis. Since Sanfilippo syndrome is an inherited disorder, a causal treatment was not available for a long time. An approved enzyme replacement therapy, like those available for other types of mucopolysaccharidoses, does not exist for Type III. Symptoms such as hyperactivity and sleep disturbances can be treated with medication. However, each child may respond differently to various medications, and their effectiveness may diminish over time, requiring individualized treatment for each patient. Protective measures may be necessary in the home environment for children with pronounced hyperactive and aggressive behavior to prevent self-injury. Swallowing difficulties may require a transition to a pureed diet or even feeding through a gastric tube. Increasing joint stiffness may occur with the loss of mobility, which can be prevented with physical therapy. In some mucopolysaccharidoses, foreign bone marrow transplantation can mitigate the course of the disease, especially if done before skeletal changes occur. This approach is generally not recommended for Sanfilippo syndrome, but there are reports of reduced disabilities after bone marrow transplantation in some cases.

Discussion

In patients with MPS II, an enzyme called iduronate-2-sulfatase may not be produced in sufficient amounts or at all due to a genetic mutation [1-6]. Long-term, MPS II or Hunter syndrome can present with varying degrees of severity, with transitions between milder and more severe forms [5]. Typically, the respiratory system, skeleton and joints, as well as the heart, are affected, and in severe cases, the central nervous system may also be involved. This more severe form is referred to as the neuropathic form, while if the nervous system is not affected, it is called a non-neuropathic form. Ultimately, only long-term observation of the patient allows for an assessment of the severity. Each patient has their own individual form of the disease in terms of severity, progression, and organ involvement. The disease symptoms and complications mentioned below do not apply equally to all patients and can be mitigated through the use of therapies. Sanfilippo syndrome is a rare metabolic disorder caused by the deficiency of a specific enzyme. This enzyme is responsible for breaking down sugar molecules, which accumulate and damage nerve cells in its absence. Gene therapies are being clinically tested in humans in both diseases. Enzyme replacement therapies and stem-cell gene therapies were introduced especially in MPS II [47,48,50-52].

Stem cells are taken from the bone marrow of a child with the disease and genetically corrected in the laboratory using a gene vector. Somatic gene corrections with the CRISPR/Cas method are expected to be more precise and effective. Researchers are working on using modified adenoviruses or other viruses as carriers for the corrected gene. A promising method is intracerebral administration of gene therapy in both diseases, where the vector containing the genetic information is injected directly into the brain tissue [36,37,42-44,46,58]. This method is similar to the treatment successfully used for other neurological disorders. Initial studies show that early gene therapy can enable largely normal cognitive development, but the therapy should start before the second year of life. Many gene therapies for Sanfilippo syndrome (MPS IIIa) are still in the clinical trial phase and are not approved for widespread use. Currently, the treatment of Sanfilippo syndrome is limited to symptom management and palliative measures. Enzyme replacement therapies will be updated by more effectiveness in brain tissues in both diseases, but this means long-term treatment but no curing of the disease. In both diseases, MPS II and III, the future of research will be the one-time gene therapy approach to correct the genetic defect, which induces the enzymatic defects in both diseases. Recent research efforts are promising to achieve this goal in the next few years.

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Conflict of Interest

None.

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