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HURLER SYNDROME: A MINI REVIEW

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Abstract:

Hurler syndrome is a lysosomal storage disorder also known as mucopolysaccharidosis type I. There are two other, less severe types of mucopolysaccharidosis type I, the Hurler - Scheie syndrome and the Scheie syndrome. Hurler syndrome is a rare autosomal recessive disorder with a prevalence of 1 in 200,000 and a life expectancy of less than 10 years. It is caused by a defective gene for the enzyme α-L iduronidase. The resulting enzyme deficiency leads to the progressive accumulation of glycosaminoglycans namely, dermatansulphate and heparan sulfate in multiple tissues in the body, causing abnormally thick mucus secretion in the respiratory and digestive tracts as well as abnormal enlargement, thickening, and malfunction of many tissues and organs. The symptoms include intellectual disability, characteristic musculoskeletal manifestations as well as cardiac disease and neurological impairments. Some of the symptoms appear during the first twelve months after birth and vary from patient to patient. However, the lack of a reliable prognostic biomarker makes it more difficult to make a treatment decision for newborns diagnosed through screening, making the timing of diagnosis and treatment initiation very important. Treatments found to improve life expectancy include Enzyme Replacement Therapy and Hematopoietic Stem Cell Transplantation. Several surgical procedures can also be performed to mitigate some of the symptoms of the syndrome. Today, gene therapy is considered a very promising method while transplantations of the bone marrow and the umbilicus are close to becoming crucial for Hurler's syndrome treatment.

Keywords: Hurler Syndrome,Mucopolysaccharidosis I, Lysosomal Storage Diseases,Glycosaminoglycans

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Introduction:

1. Definition

Hurler syndrome also known as mucopolysaccharidosis type I, is a rare, progressive inherited autosomal recessive storage disease (lysosomal storage disease), caused by a deficiency of alpha-L-iduronidase [1], which causes the progressive accumulation of glycosaminoglycans (GAG) within the lysosomes, leading to multiorgan dysfunction and damage [2].

Patients affected with MPS I cannot typically degrade the GAG, dermatan sulfate and heparan sulfate, which provides structural support in the body to the extracellular matrix and cartilaginous structures such as joints and heart valves[2].

Infants usually appear normal at birth, but sometimes may have different types of hernias (e.g. inguinal and umbilical hernias) [3].

The clinical disease diagnosis happens between 6 and 24 months of age during early child- hood which manifests with profound intellectual disability when the patient may exhibit coarse facial features, respiratory problems, enlarged liver, spleen poor growth, joint stiffness, and a prominent forehead [3].Without treatment,

survival beyond the early teen-aged years is rare. However, with treatments that are currently available, some children with Hurler syndrome have been able to live longer and more comfortable lives [13]. Life expectancy is estimated before the age of 10 years with prevalence in Europe estimated at 1/200,000. [4]

1.1 MPS 1 subtypes:

Due to variations among patients in the severity of the underlying IDUA mutations and consequent residual degree of enzyme activity MPS I differences are found with regard to disease presentation and course of disease. There are 7 sub-types of MPS disease and MPS I is the first subtype (the others are MPS II (Hunter syndrome), MPS III (Sanfilippo syndrome)) [5].

Based on the severity of symptoms, mucopolysaccharidosis type I (MPS 1) can be divided into three major clinical entities – Hurler syndrome, Hurler-Scheie syndrome, and Scheie syndrome, listed from most to least severe[6].

All of them are caused by the deficiency of alpha-L-iduronidase and distinction between them relies on the clinical criteria as well as the speed of progression of the symptoms.

Manifestations of each type of disease and the life expectancy is explained in the Table 1 below.

2. Causes of Hurler Syndrome

Hurler syndrome is strictly a genetic disorder caused by the hereditary deficiency of an enzyme, called alpha-L-iduronidase and it belongs to a group of lysosomal storage disorders. Lysosomes are microsomes within cells responsible to break down among others, certain fats [15] and are crucial for the breakdown of large sugar molecules referred as glycosaminoglycans (GAGs), which are responsible for mucous production in the surface of many tissue cells and contribute to the formation of the cartilage and joints. Glucosaminoglycans are located in most of the body's tissues and organs. Like most substances in the human organism, they are continually produced and broken down in order to maintain constant levels in the body[13].

Alpha-L-iduronidase is found in lysosomes, inside cells that digest and recycle differing kinds of molecules[7].Lysosomal storage diseases results once the molecule(s) accountable for breaking down a specific substance within the lysosomes is missing or it is defective[13]. As a result, glycosaminoglycans build up in abnormally large amounts throughout the body.

The build-up of glycosaminoglycans leads to abnormally thick mucus secretion within the metabolic process and biological process in the respiratory and digestive tracts. It also leads to abnormal enlargement, thickening, and malfunction of many tissues and organs. Body elements affected include the heart, spleen, liver, muscles, connective tissues, joints, and the central nervous system. Hence, the normal development and functioning of an extremely wide variety of organs is severely impaired [11].

Table 1: Types of MPS 1 Disease

TYPES OF MPS I DISEASE	CAUSES	SYMPTOMS	EPIDIMIOLOGY – LIFE EXPECTANCY
Hurler Syndrome (most severe MPS I phenotype)	Mutation in IDUA gene-deficiency leading in complete deficiency of alpha-L-iduronidase enzyme [3]	Early stage: not specific Later stage: skeletal dysplasia, umbilical or inguinal hernia, mental disabilities, hearing loss, cardiorespiratory failure (10th year of age) [14]	Estimated life expectancy at ten years old [4] Prevalence: 1/200.000 children in Europe [4]
Hurler-Scheie syndrome (intermediate form of MPS I phenotype)	Mutation in IDUA gene-deficiency leading in partial deficiency of alpha-L-iduronidase enzyme [7]	Early stage: not specific Later stage:short stature, corneal clouding, joint stiffening, umbilical hernia, dysostosis multiplex, hepatosplenomegaly, and little to no intellectual dysfunction. (Between 3 and 9 years of age) [14]	Estimated life expectancy at ten years old Prevalence:1/100.000 children in Europe [9]
Scheie syndrome (mildest form of MPS I phenotype-rarest form of lysosomal disease)	Mutation in IDUA gene-deficiency leading in partial deficiency of alpha-L-iduronidaseenzyme [8]	Symptoms occur after 5th year of age. [10] Progression and severity of disease is mild [10] Characterized by skeletal abnormalities, mild coarsening of the facial features, big mouth, thick libs, delay motor development (11), neurosensorial hearing loss, stiff joints, mild skeletal changes and carpal tunnel syndrome, Aortic valve disease[13]	Life expectancy: slightly affected Prevalence: 1/500.00 children in Europe [13]

Hurler syndrome is a genetic disorder, and there are not any specific environmental risk factors known to affect the progression or severity of the disease. It is an autosomal inheritance

disease which means two copies of an abnormal gene from both parents need to be present in order for the disease or trait to develop [12]. However, every parent nearly always has one of the traditional copy factor and thus is able to manufacture enough alpha-L-iduronidaseforglycosaminoglycansto continue be broken down normally. As a result, neither parent that carries a copy of the defective factor exhibits any of the disease symptoms [13].

3. Pathophysiological mechanisms of Hurler Syndrome

The principle enzyme that has been found to regulate Hurler Syndrome is alpha-L-iduronidase (IDUA) [17] which is involved in the degradation of GAGs, heparin sulphate (HS) and dermatansulphate (DS). HS and DS are found in free form in the extracellular matrix or as part of the structure of proteoglycans and they are involved in very important functions such as signal transduction[17], the structure of tissues and intercellular communication. Intralysosomal accumulation of HS and DS can trigger pathological processes which consequently lead to chronic and progressive cell dysfunction in cells, tissues and organs of many systems[18].

3.1 Storage of GAGs in the tissues

Deposition of large amounts of HS and DS in the organs of patients with MPS I seems to be responsible for the organs enlargement[19]. Tissues that have extensive intercellular compartment of which GAGs are a major constituent where found to be 30 to 77% more affected than others.Accumulation of high amounts of GAGs lead to neurological manifestations such as cerebral atrophy and ventriculomegaly by interfering in the signal pathways of the periventricular white matter[20].

Hydrocephalus is often associated with high amounts of GAGs storage as a result of inadequate reabsorption of the cerebrospinal fluid in the arachnoid granulations due to thickening of the meninges. The aforementioned mechanism increases intracranial pressure which is associated with intellectual disability[20].

Vision and hearing abilities of patients with Hurler syndrome are often affected by accumulation of high amounts of GAGs in the iris, cornea and sclera[21]and in the spiral ganglion and vestibular – cochlear nerve[22] respectively.

3.2 Effects on gangliosides metabolism

Gangliosides accumulation can also contribute in the pathophysiology of Hurler Syndrome especially in the CNS dysfunction[23]. Studies have demonstrated that gangliosides GM2 and GM3 are the dominant gangliosides accumulated in MPS I patients [24] along with non-esterified cholesterol which is responsible for their storage [25]. GAGs can directly influence the enzymes responsible for their degradation since HS molecules can bind selectively to different hydrolases (such as neuraminidase)and reduce their activity towards their natural substrates. [26] The above mechanism alters the metabolism of gangliosides.

3.3 Inflammatory Response

Castaneda et al. [27] in their study found that in lysosomal storage diseases (LSDs), activation of immune effectors can cause inflammatory response in the brain. During disease or trauma, under normal circumstances, the micronglia in the brain activate an inflammatory response. Microglia exhibit a self-limiting feature namely, remain active until disease or trauma are resolved [28]. However, in LSDs the immune response never ceases yet it progressively increases [29]. Inflammatory response can be triggered through activation of TLR4 receptor [18]. TLR4 activation requires a lipopolysaccharide (LPS) to bind with. After activation, pro-inflammatory cytokines are released and cause an innate immune response. HS accumulation in the extracelluar fluid can activate this receptor as it resembles the LPS [30]. This has been proven by the study of Simonaro et al. [31], who found in animal models with accumulation of HS increased expression of genes involved in TLR4 receptor.

3.4 Oxidative stress

Accumulation of GAGs in MPS 1 increases the possibilities of lysosomes to be in an oxidative imbalance [32]. Oxidative stress can be a result of an inflammatory response because during activation of microglia neurotoxic substances maybe released [18]. The study of Simonaro et al. [33] demonstrated that in MPS I animals there was an increased expression of cytochrome b558 which is part of the NADPH oxidase complex, that regulates the oxidative burst of phagocytes.

3.5 Lysosomal membrane permeabilisation:Ion homeostasis& apoptosis

Studies with MPS 1 animals found that there is lower concentration of H^+ and a higher concentration of Ca^{2+} in the lysosomes as well as an increase in the release of cysteine-proteases from the lysosomes to the cytoplasm and increase cell death apoptosis[34]. When the lysosomal membrane is permeable and there is ionic imbalance autophagosomes could no longer

bind to the lysosomes for autophagy to take place; therefore is leading to dysregulation

This homeostatic alteration might impair the endocytic pathway and deregulate autophagy in cells. In addition, in lysosomal membrane permeabilisation, cysteine proteases (ie. Cathepsins) are released to the cytosol which may trigger apoptosis [35].

3.6 Altered cell signalling pathways

HS are also important for cell signalling and distribution of growth factors, cytokines and morphogens, by stabilizing receptors to their ligand [36]. The overall work of HS is determined by their post translational modification such as O-sulfation [37].

Fibroblast growth factors (FGF) are involved in tissue morphogenesis and neurogenesis. FGF receptors have two cell- surface receptors namely, a high affinity FGF receptor (FGFRs) and a low affinity FGF receptor composed of HS proteoglycans (HSPGs) [38]. The aforementioned complex is disturbed in MPS I patients [39], leading to neurodegeneration and increased rate of cell apoptosis[40].

Bone Morphogenic Proteins (BMPs) are group of growth factors that regulate proliferation, differentiation and apoptosis in neural and skeletal tissues [41].BMPs are believed to be regulated by HS, threrefore accumulation of HS proteoglycans may impair this pathway [42].

4. Symptoms-clinical description

Mucopolysaccharidosis type I (MPS I) is a rare lysosomal storage disorder caused by the absence activity of enzyme α-L-iduronidase. Lysosomes break down unwanted materials in each cell into simple wastes [17].The absence of a specific lysosomal enzyme causes an accumulation of waste products in most of the body cells. Such as waste products are glycosaminoglycans (GAG). This accumulation of glycosaminoglycans (specific group/subcategory of glycosaminoglycans is areglycosaminoglycans) leads in gradual cellular damage and finally leads to destruction of many systems of the human organism and this affecting the life expectancy as it reduce it[10].

MPS I it has been divided into three clinical phenotypes. The most severe one which is typically appear the first twelve months of child life is Hurler syndrome and unfortunately leads to death the first decade of their life if they do not treat them correct. The other two phenotypes which are known as Scheie syndrome and Hurler–Scheie syndrome, appears later on their patients life symptoms, they live longer and they do not have any problem with their central nervous system[50].The symptoms of each of these three types of lysosomal storage disorder depend on which cells and tissues use the specific enzyme and if there is any amount of working enzyme there.

Children with Hurler syndrome may appear normal at birth but at the first year of their life they reveal some symptoms of the disease. It is important to mention that symptoms vary between patients. Abnormalities which are connected with the facial features can be detected at the first six months of their life. Large head with full cheeks and thick lips which makes it difficult for them to keep their jaws close. All of them they will present musculoskeletal deformities where sometimes may not be clinically obvious until twelve months. Such abnormalities may be dysostosis multiplex (chondrodystrophic muscular changes) which results in limited mobility and short stature. That means that they are below the typical height and patients may not reach a height of 4 feet. Hand involvement is also common in the patients and include curved finger and decreased wrist motion. These abnormalities can result in loss of hand function [53].

Patients additionally present thoracic-lumbar kyphosis. Moreover, they have a valvular abnormality which denotes damage to one or more of the four heart valves and cardiomyopathy abnormalities which is disease of the heart muscle. As the time pass they will present a gradual hearing loss and a vision loss [21]. During the first and second year of their life it is observed a delay in their speech, hearing problems and gradually sensorial and cognitive decay. Hydrocephaly can also be presented but when the child becomes three years old, thus it cannot be detected through fetal ultrasound scanning. Additionally, eye problems can be shown at the age of three, such as corneal clouding. Unfortunately, they will also present frequent respiratory infections and chronic diarrhea. Hurler syndrome patients can die within a decade if they are not diagnosed with the disease and treated.

Epidemiology:

To study the epidemiology of the disease data were collected from Switzerland between 1975 and 2008, Japan between 1982 and 2009 and USA between 1995 and 2005 and then they were compared with data from other countries. The term birth prevalence is calculated by the number of the disease cases during a period divided by the total number of live births during

the same period and expressed as cases per 100,000 live births. Additionally, the term incidence rate at birth is equivalent to birth prevalence. Data included year of birth of the patients, geographic location, the type of the disease and the year of death[43].

The incidence and prevalence in the USA was found to be 34 / 100000 live births and 50 / 1000000 respectively. In Japan tests and studies were performed at Gifu University, screening of urinary GAG across the country and uronic acid quantitative test was carried out. The birth prevalence of MPS I was 0.23 per 100,000 live births.

In Switzerland patient's data were collected either by molecular analysis or/and by measurement of reduced enzyme activity in fibroblasts or leukocytes. Using only Japans method was not satisfactory for the final diagnosis but was performed anyway in all cases [44]. The pre-diagnostic interval relied on diagnosis and the age of patients when the symptoms were presented. The average age was 8 months for Hurler syndrome when the symptoms were presented and 15 months when they diagnosed. Birth prevalence of MPS I was 0.19 per 100,000 live births.

Data from other countries used to compare the results. Generally, diagnosis was made by urinary GAG and/or enzyme assay in leukocytes, serum, and/or fibroblasts.In Saudi Arabia data were collected from 1983 to 2008 and the birth prevalence of MPS I was 3.62 per 100,000 live births. In Taiwan data were collected from 1984 to 2004 and the birth prevalence was 0.11 per 100,000 live births. Data from lot of countries were collected and the result was that MPS disorders are distributed worldwide. Nevertheless, there are regional differences in their distribution. Hurler Syndrome is caused by mutations in the gene encoding IDUA, which is located on chromosome 4p16.3 [45,46].Studies shown that the incidence is higher in most European countries point out that mutations found in Caucasians are more common than those found in the Asians [44].

The conclusion of these studies was that the overall birth prevalence varies depending on the country and region or ethnic background.

Prognosis – life quality

Patients are often diagnosed during the first decade of their life. There is a high mortality due to cardiac and respiratory complications. Symptoms vary and thusit is difficult to decide on the appropriate treatment. When someone is diagnosed early and be appropriately treated, especially in those cases (MPS I, II and VI) that can be treated by enzyme replacement therapy (ERT) and/or those that haematopoietic stem cell transplantation (HSCT) is available[51,52].

In 1981 University of Minnesota performed the first allogeneic blood and marrow transplant (BMT) for a child with Hurler syndrome. The therapy was based on the principle of metabolic cross-correction provided by normal leukocytes. Blood and marrow transplant was the first try to stabilize the disease and increase the patient life.

Enzyme replacement therapy (ERT) and Haematopoietic Stem Cell Transplantation (HSCT)

can improve life expectancy [47]. Therefore, the timing of diagnosis and treatment initiation is very important for the success of both treatments. In 2003 in the United States and in Europe, Enzyme replacement therapy with laronidase was approved for all phenotypes of MPS I disease, in 2005 was approved in Brazil and 2006 in Japan. Studies showed that survival was worse when comparing ERT vs HCT, and untreated patients vs ERT.

A panel of specialists for metabolic disorders and for bone marrow transplant physicians participated in a process to develop statements on MPS I treatment. Fifteen cases were used to discus and decide the treatment. Their decisions after their meeting were that treatment for patients that they diagnosed before the age of 2.5 is Haematopoietic Stem Cell Transplantation [48].Additionally, all Hurler syndrome patients, even those who have not been transplanted or those who graft has failed, may benefit from Enzyme replacement therapy.

Even though hematopoietic cell transplantation has been performed for more than thirty years, and allows affected individuals to live longer, studies of patients on the long-term outcome with Hurler syndrome after hematopoietic cell transplantation (HCT) are lacking. A study carried out in order to identify predictors of the long-term outcome of patients after successful hematopoietic cell transplantation [49].A lot of factors have been suggested to influence the prognosis, but these studies gave us the ability to draw useful conclusions [50]. 217 patients with an average follow-up age of nine years were included in this study. Primary endpoints were growth and neurodevelopmental outcomes. Secondary endpoints included cardiac, neurologic, respiratory, orthopedic, ophthalmologic, endocrinologic and audiologic outcomes.

Awareness – education

Diagnostic tests for MPS I cannot predict if a child will develop Hurler syndrome with central nervous system problems, or the phenotypes - Hurler–Scheie and Scheie syndromes – which do not have or they have minimal problem with the central nervous system. The treatment is different for the Hurler syndrome and the two phenotypes, thus, the lack of a reliable prognostic biomarker makes it more difficult to take a treatment decision for newborns diagnosed through screening [51].

Studies were carried out in 55 patients. Their medical history was obtained including parents interview. All patients underwent daily neurodevelopmental and physical evaluations. Almost all patients showed symptoms such as difficulty latching, respiratory symptoms and otitis media during the first six months of their life. Two to four months later other symptoms appeared like cardiac disease, kyphosis, joint restrictions and corneal clouding. Two months later language delays were observed.

The newborn screening for this syndrome may take years. This will lead patients to continue to be diagnosed with the disorder. So, increased awareness for the initial symptoms of this disease is important for the early identification and treatment of the patients. The nonspecific nature of the newborns symptoms probably conduce to diagnostic delays. Pediatricians must be aware that the occurrence of these symptoms in connection with other characteristic signs like corneal clouding, hepatomegaly and kyphosis warrants direct evaluation for a MPS disorder. More research is needed to give us clues for the early clinical symptoms of MPS I so doctors will be able to predict phenotype and treatment outcomes.

In the school teachers must be very careful as the children will need a special attention. Because of the hearing loss, the mobility and the vision problems, they will need different education supports than the other kids. It is very important to have realistic expectations from these children as some of the disease conditions are progressive. These children will have musculoskeletal support from their teacher, physical therapy, speech therapy, a specific treatment to avoid scoliosis related complications and a vision therapy. If it is necessary they will also have a nursing support.

For the vision problem a good solution is to seat the child close to the board and teacher must use a larger font. For the hearing problem a class with no noise would be preferable and hearing aids could be a very good approach. They may need extra time to go from one class to another, desks and seats must be adapt to their needs to keep the comfortable as they have skeletal differences from the other children. The first worry must be the safety so they must do something with the heavy doors and the doorknobs which are high. Additionally, they must use safe tools to reach the blackboard as stools or extenders.

Teachers must make sure that children will be socially interacting with other students and communicate each other. Encourage them to use a regular bathroom with adaptations so they will be more independent. This will give them the opportunity to control their lives and take their own choices for life [51].

Genetic counselling

As mentioned before, Hurler syndrome is inherited as an autosomal recessive disease. It is well-known that this kind of diseases can somehow be prevented by genetic counseling. This is a process that offers important information and advice to couples that have a positive family history of the disease. In other words, future parents are able to assure whether they are carrying the mutated gene that causes the disorders, or not. Genetic counseling plays a vital role in these circumstances, as it is not only able to estimate the risk of the disease affecting the descendant but also its healthcare provider can give psychological support to help families adapt to their condition or the risk of the disease. [14]

Diagnostic Methods

Diagnosis of MPS I is achieved in many ways, even though early diagnosis is not that easy, since clinical manifestations are not specific. Firstly, it is provided by urine tests, as scientists can find excess mucopolysaccharides secreted in the urine, as well as detect increased urinary excretion of heparan and dermatan sulfate. Secondly, laboratory cell and fluid cultures can be performed so as to point out any enzymatic deficiency in either leukocytes or fibroblasts, a testing method called enzyme assay.

Moreover, a typical prenatal diagnosis also includes amniocentesis and chorionic villus sampling that can verify if a fetus is a carrier of the copy of the defective alpha-L-iduronidase (IDUA) gene or is already affected with the disorder [54]. Furthermore, ECGs and spine X-Rays can provide clues about the disease. At this point, it should be mentioned that in order to correlate Hurler's syndrome with other diseases or conditions that have similar signs and symptoms, one should perform a so-called differential diagnosis. In reality, this type of

diagnosis includes the milder for of MPS I, the aforementioned Hurler-Scheie syndrome. It also includes both MPS types 2 and 6, as well as the mucolypidosis type 2.

Treatment

Unfortunately, concerning the treatment of mucopolysaccharidosis type 1, there is currently no cure, regardless the numerous experiments and clinical trials performed. However, several ways were discovered in order to ameliorate the patient's situation, which can be characterized as multidisciplinary, since it encompasses both curative and palliative elements. The treatment for patients under 2.5 years of age, performed before the beginning of developmental deterioration, is hemopoietic stem cell transplantation (HSCT), which can prolong survival, preserve neurocognition and fix some somatic features [55].

Generally, enzyme replacement (ERT) is considered to e the most common treatment. The replacement is made using the iduronidase enzyme, achieving significant improvement in pulmonary function, walking ability, as well as alleviation of other non-neurological symptoms of the disease, like excess carbohydrates that are improperly stored in some organs [56]. This enzyme is a glycoprotein found in the cells' lysosomes and its main function is to catalyze the hydrolysis of unsulfated alpha-L-iduronosidic linkages in dermatan sulfate. It is sold as aldurazyme, a drug that has been approved for sale by the U.S. Food and Drug Administration, back in April 2003, and was the first approved treatment for tackling Hurler's syndrome. Although this method and the abilities of this drug seem really promising, unfortunately, taking into account the fact that laronidase cannot pass through the barrier between the blood and the brain and typically reach the central nervous system, the neurodegeneration caused by the disease cannot stop. Surgical approach is also made in the effort of treating MPS I. More specifically, surgical corrections and interventions may be essential for patients that have hand or feet deformities along with joint contractures.

Typical surgery procedures for Hurler's syndrome patients include denotonsillectomy, hernia repair, ventriculoperitoneal shunt, cardiac valve replacement, carpal tunnel release, spinal decompression. Furthermore, physical, speech, hearing and ventilatory support is often administered to MPS I patients [57]. Transplantation attempts are also made in surgery for the MPS type 1 disease. Precisely, bone marrow transplantation (BMT), umbilical cord blood transplantation (UCBT) and corneal transplantation were performed so as to mitigate several symptoms of the syndrome. However, taking into consideration that the white blood cells of the donor's immune system (the graft) recognize the recipient (the host) as foreign (graft versus host disease) as a severe complication, uncertainty on these specific procedures as fundamental treatment for this disease, arises [58]. Recapitulating, no one can dispute the fact that these patients need continuous monitoring, as MPS I is a constantly progressive disease, as well as the contribution and the medical support of many specialists.

Clinical Trials

As the aforementioned paragraph indicated, in fact, there is no cure for Hurler's syndrome. Scientists and clinicians are continuously trying to find the best solution to every medical and genetic problem though experimentation, clinical trials and research. Concerning MPS type 1, a great deal of interest and attention is shown towards gene therapy [59].

Iduronidase was administered to animals in the laboratory with the aid of retrovirus, adenovirus, adeno-associated virus and plasmid vectors. The animals that had MPS I were treated, with scientists seeing improvements in neurological and physical aspects of the disease. However, a severe complication came to surface, which was the development of liver tumors, without any relevant explanation. Surely, if scientists deal with this problem, gene therapy is a really auspicious method for the MPS I treatment.

Transplantations of the bone marrow and the umbilicus are close of becoming crucial methods for Hurler's syndrome treatment [58]. In fact, Dr. Rena Falk and Dr. William Wilcox, at the Cedars-Sinai Medical Center and the Children's Hospital at Los Angeles, are investigating the use of in utero bone marrow transplantation. Practically, in this procedure, they extract and isolate bone marrow from the pregnant woman between the 18th to 25th weeks of pregnancy. The bone marrow cells are processed while hematopoietic cells are singled out [60]. Professor Arndt Rolfs is currently attempting to develop a biomarker used for early diagnosis of Hurler's disease, from the blood, especially from the plasma. Its name is considered to be BioHurler. After its discovery, the goal of the study is to assure and test the biomarker's long-term stability, effectiveness and specificity, in other words its robustness [61]. Moreover, Paul Orchard and his team, in University of Minnesota, are investigating whether a possible stem cell transplantation will aid in the effort of treating MPS I.

More specifically, the goal of this clinical trial is to determine the engraftment of hematopoietic stem cells from the donor and also the safety of this procedure [62]. Finally, a quite interesting laboratory attempt for the treatment of Hurler's disease is an experiment which was held in Brazil, by the scientific collaborators Schuh RS, Poletto É, Pasqualim G, Tavares AMV, Meyer FS, Gonzalez EA, Giugliani R, Matte U, Teixeira HF, Baldo G., who used cationic liposomes carrying the CRISPR/Cas9 plasmid and a donor vector for both in vitro and in vivo MPS I gene editing. Then, this potential treatment was compared to the one with the usage of naked plasmids [63].

All these examples constitute the most famous and relatable attempts to find a final treatment for mucopolysaccharidosis type I and aid patients to alleviate their symptoms. Clinicians and scientists are confident that through continuous efforts and trials, the pathway which will eventually lead to the treatment of the disease will be found.

Conclusion:

A better future for patients suffering from Hurler syndrome and other phenotypes of mucopolysaccharidoses depends on an earlier detection and treatment of the disease. A better understanding and management of Hurler syndrome's complex manifestations may contribute to a better prognosis. As for the treatment, an increasingly promising method is the Gene Therapy, however, certain obstacles need to be overcome first to standarize it as a relible method for treatment of Hurler syndrome. Finally, Haematopoietic Stem Cell Transplantation along with Enzyme Replacement Treatment represent the two other possible methods with the potential to become a difinitive treatment of this severe, multisystemic disease.

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