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A Review on Mucopolysaccharidosis

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Abstract: *Mucopolysaccharidosis (MPS) refers to a group of rare genetic disorders caused by the deficiency of specific enzymes required to break down glycosaminoglycans (GAGs), which are long chains of sugar molecules. These disorders lead to the accumulation of GAGs in various tissues and organs, resulting in progressive damage and a range of symptoms.*

There are several types of MPS, including MPS I, II, III, IV, VI, and VII, each associated with different enzyme deficiencies and varying severity of symptoms. Common features of MPS include skeletal abnormalities, cardiovascular issues, respiratory problems, vision and hearing loss, and developmental delays.

Diagnosis typically involves clinical evaluation, biochemical tests to measure enzyme activity, and genetic testing to identify specific mutations. Treatment options vary depending on the type of MPS and may include enzyme replacement therapy, hematopoietic stem cell transplantation, and supportive care to manage symptoms.

Early diagnosis and intervention are crucial for improving the quality of life and outcomes for individuals affected by MPS. Ongoing research aims to develop new therapies and improve understanding of these complex disorders..

Keywords: Mucopolysaccharidosis

I. INTRODUCTION

Mucopolysaccharidoses (MPS) are a group of rare lysosomal storage diseases (LSD) caused by genetic defects. These genetic defects lead to a lack or deficiency of enzymes involved in degradation of glycosaminoglycans (GAGs), [1] which are long and unbranched polysaccharides functioning in processes such as cell adhesion and cellular signalling. [2] Undegraded GAGs are considered to be the primary and direct cause of MPS, and GAG storage can lead to secondary and tertiary effects in cells, such as autophagy, apoptosis, and mitochondrial dysfunctionGAGs can accumulate in the lysosomes of cells, resulting in the dysfunction of affected tissues and causing multi-organic and severe symptoms including coarse facial features, cognitive retardation, hepatosplenomegaly, hernias, kyphoscoliosis, corneal clouding. [3,4] Mucopolysaccharidoses (MPSs) are rare lysosomal storage disorders that are caused by abnormal accumulation of glycosaminoglycans (GAGs), which is due to defciency of enzymes involved in degradation of GAGs. As a rare set of conditions, MPS account for less than0.1% of all genetic diseases. [5] The first reported case of MPS was described by Charles Hunter in 1917. [6]

TYPES OF MUCOPOLYSACCHARIDOSIS

a) Type: I (Hurler syndrome)

Mucopolysaccharidoses (MPSs) are a subgroup of inherited lysosomal storage disorders caused by the deficiency of specific lysosomal enzymes on the glycosaminoglycans (GAG) catabolism pathway. The consequent storage of GAG in tissues leads to progressive multisystemic damage. [7] Mucopolysaccharidosis type I (MPS I) is an autosomal recessive disorder caused by alpha-L-iduronidase deficiency. This enzyme catalyzes the degradation of the GAG dermatan and heparan sulphate. Therefore, pathological accumulation of both GAGs occurs in patients with MPS I, with manifestations in multiple organs. This disorder has traditionally been divided into three syndromes, namely, Hurler syndrome (severe form), Hurler-Scheie syndrome (moderate form), and Scheie syndrome (mild form). However, phenotypes are present on a spectrum of severity, no biochemical differences have been identified, and clinical findings

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overlap. Currently, affected individuals are better divided into severe (Hurler) and attenuated (HurlerScheie, Scheie) forms as this distinction influences therapeutic options. [8]

b) TYPE:II(Hunter syndrome)

Mucopolysaccharidosis type II (MPS II, MIM # 309900), also known as Hunter syndrome, is a rare genetic disorder that is inherited as an X-linked trait, with an incidence rate ranging from 0.38 per 100,000 live newborns in Brazil to 1.09 per 100,000 live newborns in Portugal. European countries generally present a lower incidence than East Asian countries, where, in some of them, MPS II incidence accounts for about 50% of all mucopolysaccharidoses (MPSs).[9]MPS II belongs to the group of lysosomal storage disorders (LSDs) and is due to a deficit of the lysosomal enzyme iduronate 2-sulphatase, which catalyzes the hydrolysis of 2-sulphate groups of dermatan sulphate (DS) and heparan sulphate (HS). Therefore, its deficit causes the pathological accumulation of these two glycosaminoglycans (GAGs) and dysfunction of most organ-systems, including the brain, in the majority of patients, thus representing a severe clinical phenotype. [10]

c) TYPE: III (Sanfilippo syndrome)

MPS III is categorized into four subtypes, MPSIIIA, IIIB, IIIC, and IIID, that are characterized by a lack of heparan-N-sulfatase (SGHS), α-Nacetylglucosaminidase (NAGLU), α-glucosaminidase acetyltransferase (HGSNAT), and N-acetylglucosamine 6-sulfatase (GNS), respectively. All of these lysosomal enzymes are involved in the degradation of HS, and any deficiency leads to HS storage. MPS IIIA and IIIB are more common than IIIC and IIID in clinical settings. Clinical features vary among the different subtypes. Progressive symptoms of central nervous system dysfunction including idiopathic developmental delay, cognitive decline, hyperactivity, and sleep disorder are prominent characteristics of MPS III. Somatic symptoms are also present in MPS III but are more subtle than in other types and are heterogeneous among patients .[11,12]

d) TYPE: IV (Morquio syndrome)

MPS IV is subdivided into MPS IVA and MPS IVB depending on a deficiency in N-acetylgalactosamine-6- sulfate sulfatase (GALNS) or β-galactosidase (GLB1). A deficiency in GALNS in MPS IVA impairs the degradation of chondroitin-6-sulfate (C6S) and keratan sulfate (KS), which contributes to severe clinical symptoms. A GLB1 deficiency in MPS IVB leads to a moderate phenotype with only accumulation of KS. Unlike the other types, MPS IV involves mild cognitive impairment but more obvious systemic skeletal dysplasia. MPS IV usually starts at the age of 1-3 with skeletal dysmorphia including growth retardation, a short neck, cervical spinal cord compression, odontoid hypoplasia, hypermobile joints, pectus carinatum, and an abnormal gait. [13,14]

e) TYPE: VI(Maroteaux-Lamy syndrome)

Mucopolysaccharidosis type VI (MPS VI), also known as Maroteaux–Lamy syndrome, is caused by the deficiency of enzyme N-acetylgalactosamine-4-sulfatase (ARSB). [15,16] This enzyme participates in the catabolism of glycosaminoglycans (GAGs), dermatan sulfate (DS), and chondroitin sulfate. In MPS VI, these partially degraded GAGs accumulate in several tissues of the organism. The gene that codifies ARSB has been mapped to chromosome 5q13–14 and has eight exons .[15,17,18]

f) TYPE: VII (Sly syndrome)

f3-Glucuronidase is a lysosomal enzyme expressed in most, if not all, mammalian tissues. Murine beta-glucuronidase has been studied extensively because it provides a useful system for understanding mammalian gene regulation .[19] In mouse kidney and liver the enzyme is also found in the microsomes in association with the accessory binding protein, egasyn. [20] The active enzyme is a tetrameric glycoprotein that degrades glycosaminoglycans by removing fl-glucuronosyl residues at the nonreducing end of oligosaccharides .[21]

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II. SIGNS AND SYMPTOMS OF MPS

The mucopolysaccharidoses share many clinical features but have varying degrees of severity. These features may not be apparent at birth but progress as storage of GAGs affects bone, skeletal structure, connective tissues, and organs. Neurological complications may include damage to neurons (which send and receive signals throughout the body) as well as pain and impaired motor function. This results from compression of nerves or nerve roots in the spinal cord or in the peripheral nervous system, the part of the nervous system that connects the brain and spinal cord to sensory organs such as the eyes and to other organs, muscles, and tissues throughout the body.

Depending on the mucopolysaccharidosis subtype, affected individuals may have normal intellect or have cognitive impairments, may experience developmental delay, or may have severe behavioral problems. Many individuals have hearing loss, either conductive (in which pressure behind the eardrum causes fluid from the lining of the middle ear to build up and eventually congeal), neurosensory (in which tiny hair cells in the inner ear are damaged), or both. Communicating hydrocephalus—in which the normal reabsorption of cerebrospinal fluid is blocked and causes increased pressure inside the head—is common in some of the mucopolysaccharidoses. Surgically inserting a shunt into the brain can drain fluid. The eye's cornea often becomes cloudy from intracellular storage, and glaucoma and degeneration of the retina also may affect the patient's vision.

Physical symptoms generally include coarse or rough facial features (including a flat nasal bridge, thick lips, and enlarged mouth and tongue), short stature with disproportionately short trunk (dwarfism), dysplasia (abnormal bone size and/or shape) and other skeletal irregularities, thickened skin, enlarged organs such as liver (hepatomegaly) or spleen (splenomegaly), hernias, and excessive body hair growth. Short and often claw-like hands, progressive joint stiffness, and carpal tunnel syndrome can restrict hand mobility and function. Recurring respiratory infections are common, as are obstructive airway disease and obstructive sleep apnea. Many affected individuals also have heart disease, often involving enlarged or diseased heart valves.

Another lysosomal storage disease often confused with the mucopolysaccharidoses is mucolipidosis. In this disorder, excessive amounts of fatty materials known as lipids (another principal component of living cells) are stored, in addition to sugars. Persons with mucolipidosis may share some of the clinical features associated with the mucopolysaccharidoses (certain facial features, bony structure abnormalities, and damage to the brain), and increased amounts of the enzymes needed to break down the lipids are found in the blood. [23]

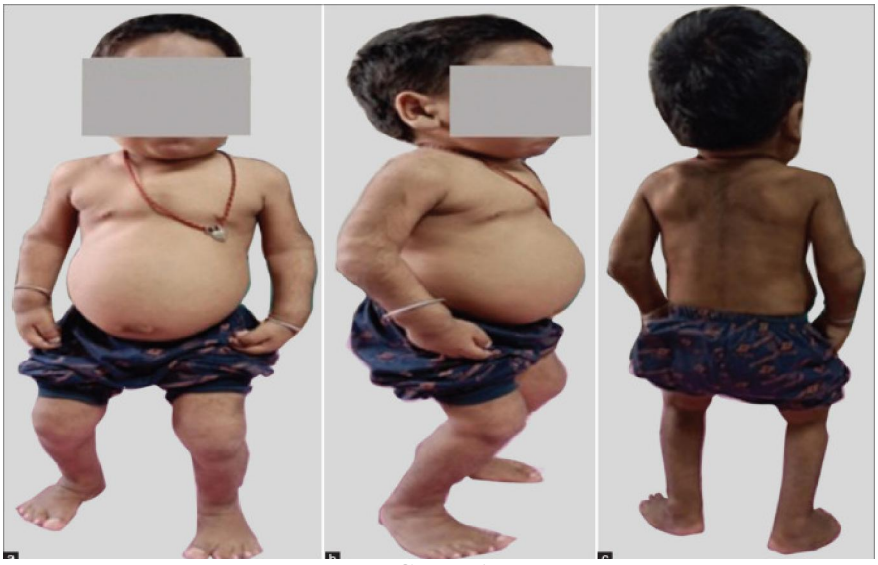

FIGURE:1

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III. DIAGNOSIS OF MPS:

3.1) Introduction:

The mucopolysaccharidoses (MPSs) comprises 11 lysosomal diseases in which there is a deficiency in a specific step of the degradation of glycosaminoglycans (GAGs). This deficiency leads to storage of GAGs in tissues and to a range of clinical consequences, which may include CNS impairment, depending on the specific MPS type. [24,25]

3.2) Clinical Suspicion and High-Risk Groups

Where no newborn screening program is available, physicians face the challenge of recognizing an MPS patient in the early stages of the disease, before irreversible damage has developed. In many cases, patients with MPSs and other LDs (lysosomal disorders) may present specific signs that are highly suggestive of the diagnosis. [26]

The low diagnostic yields of those studies that focused on single manifestations may be explained by the rarity of MPS as compared to other causes of intellectual disability and osteoarticular problems. Considering the rarity of MPS and the nonspecific nature of isolated manifestations, investigating patients with a combination of manifestations is also a reasonable approach. For instance, in a study from Malaysia, high-risk patients were selected based on having at least two of a list of eight signs and symptoms related to MPS. [27]

3.3) Biomarkers

Biomarkers are analytes that can be measured and used to indicate a pathological or physiological process, thus they allow discrimination within disease vs. non-pathological events. If well-chosen, a biomarker can be helpful for diagnosis, prognosis, and they might also be useful to monitor therapeutic efficacy. [28,29,30]

3.4) Enzyme Assays

In several cases, the biochemical investigation of an MPS started with the analyses of glycosaminoglycans (GAG) in urine before the enzyme assay; this is performed because the GAGstorage is due to a primary defect in the enzymatic activity. This analysis in urine can then drive more robust specific enzyme assays, saving time and costs. The GAG monitoring also offers the advantage of treatment monitoring. For post-natal evaluations, the sample types that are most used are the dried blood spots (DBS), plasma, leukocytes, and fibroblasts, while, for the pre-natal investigations, chorionic villi and amniotic fluid are most used. In the post-natal period, the gold standard is the quantification of enzymes in leukocytes or fibroblasts, and the results for DBS require confirmation .[31,32]

3.5) Molecular Genetics Analyses

Although enzyme activity assay is considered the gold standard for the diagnosis of MPS disorders, molecular genetic testing is recommended and, whenever possible, diagnostic conclusions should be made taking the clinical, biochemical, and molecular genetics results into consideration. [33]

3.6) Newborn Screenin

Newborn screening is extremely powerful for conditions that are not too rare and whose patients are usually asymptomatic at birth. MPSs are progressive, debilitating, and often life-threatening conditions. The correct diagnosis for these conditions usually takes several years, in what is known as the “MPS odyssey”, and treatment is already approved for several of the MPS subtypes. Thus, NBS for MPS is tremendously important once early diagnosis leads to early intervention, which could make a significant difference in the patient’s outcomes and prevent debilitating manifestations. [34]

3.7) Diagnostic Work-Up

We propose that for every patient with suspected MPS, samples of urine (typically 15–20 mL) and of EDTA blood (typically 8 mL, or two purple cap tubes) are obtained. Urine should be kept frozen until processed. The blood should be kept in the fridge (4–8 ◦C until shipped to the laboratory, which should occur as soon as possible). When the blood arrives at the diagnostic laboratory, leukocytes should be isolated, plasma should be obtained and DBS should be prepared. The leukocyte pellet and the plasma should be kept frozen, and the DBS should be allowed to dry at least for

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4 h and then it should be kept in the freezer (–20 ◦C) in an individual plastic bag, preferably with desiccant. If the sample will not be able to arrive at the diagnostic lab in 3–4 days, plasma and DBS should be obtained after collection (plasma should be kept in the freezer and DBS in the fridge, until shipment to the diagnostic laboratory).

The diagnostic lab could start the investigation by measuring urinary GAGs and identifying the GAG species present in the urine. If GAGs are increased and/or GAG pattern is abnormal, blood samples should be retrieved from the fridge or freezer and processed for the measurement of the activity of specific MPS enzymes, according to the GAG results and clinical suspicion, which usually leads to the diagnosis of the specific MPS type and enables specific therapy to be introduced whenever available. Thereafter, DNA could be obtained from the blood (leukocytes or DBS) and the specific gene sequenced. With the mutations identified, the family could benefit from phenotype prediction, carrier identification, genetic counseling, and prenatal diagnosis. A summary of the proposed diagnostic flow-chart is presented in Figure 2

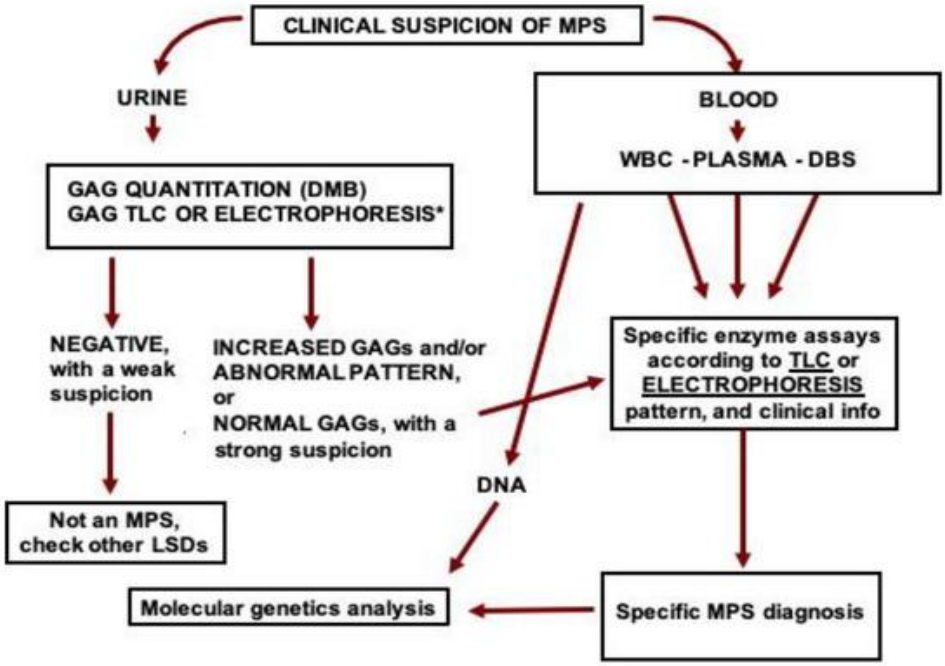

FIGURE NO.2

IV. TREATMENT OF MPS

4.1 TYPE:I (Hurler syndrome)

Mucopolysaccharidosis type I (MPS I) is a lysosomal disease, caused by a deficiency of the enzyme alpha-L-iduronidase (IDUA). Currently approved treatments consist of enzyme replacement therapy (ERT) and/or hematopoietic stem cell transplantation (HSCT). While these treatments significantly improve disease manifestations and prolong life, a considerable burden of disease remains. Both treatments may at best prevent the development or worsening of abnormal function and somatic complications but cannot revert already existing symptoms. Therefore, treatment must commence as early as possible for maximum effect and diagnostic delay-due to the nonspecific nature of early symptoms-limits treatment success.

a) Standard Therapies for MPS I

1. Allogeneic HSCT
2.Mortality Rates and Conditioning Regimens
3. Effectiveness of HSCT
4.Enzyme Replacement Therapy (ERT

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b) Impact of HSCT and ERT on Tissue-Specific Disease Manifestations

1. Ocular Manifestations
2. Respiratory System
3. Hearing Loss
4. Skeletal Manifestations
5. Joint Mobility
6. Cardiac Function
7. Cognitive Function

c) Experimental Therapies

1. Substrate Reduction
2. Accelerated GAG Degradation
3. Anti-Inflammatory Therapy
4. Intracerebroventricular and Intrathecal Delivery ERT
5. In Utero ERT Treatment
6. Shuttling of Enzyme Across the BBB

d) Molecular Therapies

1. Nonsense Suppression and mRNA Engineering
2. Ex Vivo Gene Transfer
3. In Vivo Gene Transfer. [35]

4.2 TYPE:II (Hunter syndrome)

a) Anti-inflammatory therapy

Several treatments are available that target the consequences of IDS deficiency without correcting the enzyme deficiency directly. Osteoarthritis is very common in MPS II patients. It results from the accumulated GAGs in bone, cartilage, the extracellular matrix (ECM) and inducing proinflammatory factors that stimulate cartilage degradation.[36]Suppression of metabolic inflammation with anti-inflammatory agents can help patients manage this discomfort, thereby improving their quality of life .[37]

b) ERT (conventional and intrathecal)

Conventional ERT for MPS II is administered by weekly intravenous (IV) infusions of recombinant IDS. A review of the efficacy of IV-ERT on patients, who were given at least one year of ERT, were between the ages of 2–24 years old, and were classified as severely affected showed that 50 out of 66 patients experienced at least one type of somatic improvement including reduction in the frequency of respiratory infections, a reduction in the coarseness of facial features, and/or an improved range of motion in joints. [38]

c) Hematopoietic stem cell transplantation

The efficacy of HSCT on visceral organs is well documented. These effects can include normalization of hepatosplenomegaly, improvement of the thickening of the aortic valve and an increase in elasticity of the joints allowing for increased independence and mobility for the patient. HSCT has shown better improvement in the quality of life measured by activity of daily living (ADL) when compared to conventional ERT .[39,40,41,42]

d) Gene Therapy

Since MPS II is caused by a genetic defect in only one gene, the IDS gene, gene therapy is an emerging treatment that could potentially offer a permanent solution for patients. Gene therapy aims to deliver the defective gene to host cells by a specific vector; *ex vivo,* IV, IT, or intracisternal injections. Since treatment of CNS manifestations remains unsolved for current treatment, many strategies of gene therapy are currently being investigated on the use of CNS-targeted vectors to decrease CNS manifestations of the disease. [43,44]

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e) Substrate reduction therapy

Recent studies suggest that Genistein modulates cell cycle in addition to modifying GAG metabolism. Its effect on cell proliferation was similar in fibroblasts from MPS II patients and healthy individuals, although the MPS II fibroblasts had significantly higher proportion of cells in G0/G1. [45]

f) Surgical interventions, palliative care

The two currently approved treatments for MPS II (ERT and HSCT) have limited efficacy. Therefore, MPS II patients need supportive treatment to manage symptoms. It is necessary for each patient to have a team of specialists who can treat the different symptoms, particularly in regards to the CNS and skeletal manifestations. A comprehensive assessment of the patient's condition should be completed at least once a year. Continuous follow-up of disease progression should improve both physical and psychological well-being of the patient and the patient's caregiver.

Specialists must address the orthopedic problems that affect the patient. Orthopedic problems affect patients of both phenotypes and can dramatically reduce the patient's independence and quality of life. Many of these secondary problems result from the inflammatory responses previously described. The hip joints are particularly susceptible to erosive dysplasia which can render a patient wheelchair bound because walking causes severe pain. The characteristic "claw hand" deformity often seen in patients results from the metaphyseal deformities and thickened joint capsules with inflammation causing carpal tunnel syndrome. These symptoms should be managed with steroids, physical therapy, and surgical release of the transverse carpal ligament if symptoms continue to worsen.

Cardiac problems must be managed by regular consultation with a cardiac specialist. Patients with MPS II often require valve replacement due to valve regurgitation or stenosis. [46]

4.3 TYPE:III(Sanfilippo syndrome)

There is currently no approval treatment for mucopolysaccharidosis type III.There are the number of therapies in development including :

a. Gene therapy

b. Enzyme replacement therapy.

C. Substrate reduction therapy. [47]

4.4 TYPEIV(Morquio syndrome)

a) ERT

This long-term study demonstrated that a global reduction in spirometry variables and improvement post adenotonsillectomy, while the overall results being a reduction in pulmonary function, suggesting that non-invasive ventilation and adenotonsillectomy should be more effective in the patients with ERT, either improving lung function or attenuating aggravation of symptoms. We have experienced tracheal reconstitution surgery in MPS IVA patients treated with ERT since 2015 (See the "Management of tracheal obstruction" chapter) and showed that the accumulation of storage material was observed in surgical remnants of trachea from these patients. After this tracheal surgery, the obstructive airway was resolved, and their pulmonary function and activity of daily living were markedly improved. Overall, these studies showed that conventional ERT for MPS IVA has little impact on airway obstruction in spite of long-term treatment. [48]

b) HSCT

The first successful case report of HSCT in MPS IVA was published in 2014 .Chinen et al. reported a male patient with MPS IVA who underwent allogeneic bone marrow transplantation (BMT) at age 15 years 8 months. At 5 years post-HSCT, the recipient GALNS activity in lymphocytes had matched the level measured in the donor, accompanied by several clinical improvements such as pulmonary function and increased bone mineral density (BMD). Although his height was not changed at 106 cm, pulmonary function was well-stabilized during 9 years post-BMT. BMD in the lumbar vertebrae (L2-L4) was also increased by 50% at one year post-BM In 2016, Yabe et al. reported allogeneic HSCT cases in 4 patients with MPS IVA, including a patient in the case study reported by Chinen et al. [49,50]

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V. CONCLUSION

MPS was first described in 1917; since then, thousands of cases have been reported worldwide. Although MPS are rare inherited diseases of LSD, their high mortality and expensive treatment make them a major medical and social problem. Due to their severe and progressive symptoms, MPS require intensive care for patients and keen awareness among physicians. Recognizing the onset and characteristic features of different subtypes of MPS will facilitate early diagnosis. However, symptoms of different subtypes are often similar and not easily differentiated. Greater emphasis is placed on treating severe and mild forms of MPS. Common clinical features such as a short stature and mental retardation often lead to misdiagnosis. Early diagnosis is imperative to preserve organic functions and improve quality of life. This review has concisely summarized the characteristic features of different MPS and described diagnostic methods as well as therapeutic options. HSCT and ERT are widely used in clinical practice but are ineffective in some patients with MPS because of unsolved challenges. Novel treatments including intrathecal ERT, gene therapy, and combined therapy have emerged to compensate for the disadvantages of conventional therapies. Guidelines for management of MPS should be drafted in light of the type of MPS, clinical development, disease stage, medical history, and socioeconomic status of the patient in order to standardize the diagnosis and treatment of MPS.

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