A basic understanding of mucopolysaccharidosis: Incidence, clinical features, diagnosis, and management

Jing Zhou1,2,3,§, Jing Lin1,2,3,§, Wing Ting Leung1,2,3, Ling Wang1,2,3,*

1Laboratory for Reproductive Immunology, Hospital & Institute of Obstetrics and Gynecology, Shanghai Medical College, Fudan University, Shanghai, China; 2The Academy of Integrative Medicine of Fudan University, Shanghai, China; 3Shanghai Key Laboratory of Female Reproductive Endocrine-related Diseases, Shanghai, China.

1. 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 signaling (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 dysfunction (1). GAGs 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, etc. Symptoms of different types are usually similar especially MPS I and II, but may have distinguishable features such as severe neurological problems in MPS III and hydrops fetalis in MPS VII. These clinical features contribute to diagnosis, but early and precisely diagnosis in the asymptomatic stage is imperative for better outcomes. Novel approaches including urinary and blood GAG test, enzyme assay and gene test help to diagnose MPS and to determine its subtype. Hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) are conventional treatment for MPS, but are not effective at treating all MPS. Newer treatments, such as advanced ERT, gene therapy and substrate reduction therapy (SRT), improve therapeutic efficacy. In this review, we update information on the clinical manifestations, diagnosis, and treatment of the different forms of this disease in the hopes of stimulating further interest in MPS.

2. Epidemiology

As a rare set of conditions, MPS account for less than...
0.1% of all genetic diseases (1). The first reported case of MPS was described by Charles Hunter in 1917 (7). Two years later, MPS I was described by Hurler (8). MPS have a low incidence but have been reported throughout the world in various forms. Region and ethnic background may affect the phenotype of MPS. Analyzing the incidence of MPS and its types among people in different regions would help to better understand MPS.

In Asia, most patients with MPS have MPS II. In a study conducted from 1984 to 2012 in China, 506 patients with MPS were identified. MPS II accounted for nearly 50% of all cases of MPS, MPS I accounted for approximately 13.7%, MPS III accounted for 7.9%, MPS IV accounted for 24%, and MPS VI accounted for 2.6% (9,10). In South Korea, a total of 147 cases of MPS were reported between 1994 and 2013. MPS II was the most prevalent type of MPS (54.6%), followed by MPS III (18.4%), MPS I (15.3%), MPS IV (9.5%), and MPS VI (1.4%) (11). A study in Japan from 2003 to 2009 indicated that MPS II accounted for 58.1% of cases, while MPS I accounted for 16.2%, MPS III accounted for 11.1%, MPS IV accounted for 11.7%, and MPS VI accounted for 2.9% (12). A similar trend was also noted in the 1980s and 1990s in Japan.

MPS II is reported to have a relatively high incidence in some countries, but in Europe its incidence was lower than that of MPS I and MPS III. Data from Denmark and Norway from the 1970s to 2000s indicated that MPS I (30% in Denmark and 60% in Norway) was the most common type of MPS in both countries, followed by MPS IV (27% in Denmark and 24% in Norway) (13). In Germany, data on 474 patients with MPS from 1980-1995 indicated that the incidence of MPS III was 44%. The incidence of MPS I was 20%, that of MPS II was 18%, that of MPS IV was 11%, and that of MPS VI was 7%. A similar trend was noted in the Netherlands, where MPS I accounted for 25% of 331 cases of MPS, MPS II accounted for 15.5%, MPS III accounted for 47%, MPS IV accounted for 8%, and MPS VI accounted for 2% (14). Elsewhere in Europe, an Estonian study from 1985 to 2006 involving 15 cases of MPS reported no cases of MPS I and MPS VI (15). MPS II accounted for 53% of the 15 cases, MPS III accounted for 40%, and MPSIV accounted for 7%.

The incidence of MPS cannot be readily determined in the US. An American study from 1995-2005 indicated that MPS I accounted for 28.3% of cases, MPS II accounted for 24.2%, MPS III accounted for 31.7%, MPS IV accounted for 7.5%, and MPS VI accounted for 4.2% (12). In Canada, MPS I accounted for most (30%) of 20 cases from 1969-1996, followed by MPS IV (20%), MPS VI (15%), MPS III (15%), and MPS II (5%) (16).

The incidence of different types of MPS differs depending on the continent, indicating that MPS may be related to region and ethnic background. In Asia, MPS II was the most prevalent type of MPS. In Europe, MPS I and MPS III were slightly more prevalent than MPS II. Statistical studies of MPS in the US have not revealed which types are predominant, and further studies may need to be conducted to reveal trends in MPS. Some of the aforementioned data were from a specific area in a country, and different diagnostic methods were used. Given these limitations, a population-based and unified study of MPS needs to be conducted to help analyze its epidemiology and understand its pathology.

3. Clinical features

MPS are differentiated biochemically by their associated enzyme deficiency and can be classified into 7 types, designated MPS I to MPS IX (excluding MPS V and MPS VIII), and some types are further categorized into subtypes. In total, MPS are classified into 11 types and subtypes. The clinical symptoms of MPS differ depending on the specific enzyme deficiency, but major clinical features are mainly neurological symptoms, facial dysmorphism, cardiac and valvular diseases, skeletal dysfunction, respiratory problems, and ocular disorders (Table 1).

3.1. MPS I (Hurler syndrome)

Patients with MPS I have a deficiency of α-L-iduronidase (IDUA), an enzyme involved in the degradation of heparan sulphate (HS) and dermatan sulphate (DS). The accumulation of these GAGs in lysosomes triggers a cascade of cellular events and ultimately leads to organ dysfunction. MPS I is classified into three subtypes: Hurler syndrome (IH), Hurler/Scheie syndrome (IH/S), and Scheie syndrome (IS). Clinical differences between the three syndromes are not easily identified, and this is especially true for IH/S and IS. Clinically, MPS I is a continuum of phenotypes from severe (IH) to intermediate (IH/S) and milder (IS).

MPS I is a life-threatening disease that results in a severe disease burden and premature death. Striking clinical features are neurodegeneration, respiratory deterioration, cardiac diseases, and skeletal and joint disorders. Other common symptoms include ocular problems, organomegaly, deforming facies, and hearing and visual deficits (17). In severe cases, GAG storage usually involves the brain and bone, causing progressive neurological disease (cognitive disorders, dyslexia, therm anesthesia, etc.) and skeletal diseases (kyphoscoliosis, dysostosis multiplex, etc.) (18). The symptoms of IH may start in the first year of life with severe and multisystem symptoms. Without effective treatment, patients with IH may die in the first decade of life. Patients with milder symptoms can reach adulthood but also suffer multisystem syndromes.

3. MPS III (Sanfilippo syndrome)

MPS III is categorized into four subtypes, MPS

Table 1. Classification of mucopolysaccharidosis (MPS)

<table>
<thead>
<tr>
<th>Items</th>
<th>Subtypes</th>
<th>Deficient enzyme</th>
<th>Mutation of Gene</th>
<th>Locus</th>
<th>GAGs</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I</td>
<td>Hurler Syndrome</td>
<td>α-L-iduronidase</td>
<td>IDUA</td>
<td>4p16.3</td>
<td>HS, DS</td>
<td>Severe. Skeletal deformation, coarse facial features, hepatosplenomegaly, cardiac diseases, respiratory diseases, cognitive retardation, ocular disorders</td>
</tr>
<tr>
<td>MPS II</td>
<td>Schie Syndrome</td>
<td>α-L-iduronidase</td>
<td>IDUA</td>
<td>4p16.3</td>
<td>HS, DS</td>
<td>Intermediate.</td>
</tr>
<tr>
<td>MPS III</td>
<td>MPS III A</td>
<td>heparan-N-sulfatase</td>
<td>SGSH</td>
<td>17q25.3</td>
<td>HS</td>
<td>Cognitive retardation, behavioral problems</td>
</tr>
<tr>
<td>MPS III B</td>
<td>α-N-acetylgalactosaminidase</td>
<td>IDUA</td>
<td>17q21.2</td>
<td>HS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPS III C</td>
<td>α-glucosaminidase N-acetyltransferase</td>
<td>HGSNAT</td>
<td>8p11.21-p11.1</td>
<td>HS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPS III D</td>
<td>N-acetylgalactosamin-6-sulfatase</td>
<td>GNS</td>
<td>12q14.3</td>
<td>HS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPS IV A</td>
<td>N-acetylgalactosamine-6-sulfate sulfatase</td>
<td>GALNS</td>
<td>16q24.3</td>
<td>KS, C6S</td>
<td>Skeletal deformation, corneal clouding.</td>
<td></td>
</tr>
<tr>
<td>MPS IV B</td>
<td>β-galactosidase</td>
<td>GLB1</td>
<td>3p22.3</td>
<td>KS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPS VI</td>
<td>N-acetylgalactosamine-4-sulfatase</td>
<td>ARSB</td>
<td>5q13-14</td>
<td>DS, C4S</td>
<td>Skeletal deformation, coarse facial features, may have normal intelligence</td>
<td></td>
</tr>
<tr>
<td>MPS VII</td>
<td>β-glucuronidase</td>
<td>GUSB</td>
<td>7q11.21</td>
<td>DS, HS, C4S, C6S</td>
<td>Hydrops fetalis</td>
<td></td>
</tr>
<tr>
<td>MPS IX</td>
<td>Hyaluronidase 1</td>
<td>HYAL1</td>
<td>3p21.3</td>
<td>HA</td>
<td>Periarticular masses, mild short stature</td>
<td></td>
</tr>
</tbody>
</table>

GAGs: glycosaminoglycans, HS: heparan sulfate, DS: dermatan sulfate, KS: keratan sulfate, C4S: chondroitin-4-sulfate, C6S: chondroitin-6-sulfate, HA: hyaluronic acid

Patients with IS have a more attenuated disease burden and longer lifespan than those with IH/S (19).

3.2. MPS II (Hunter syndrome)

MPS II, or Hunter syndrome, is characterized by a deficiency of a lysosomal enzyme, iduronate-2-sulfatase (IDS), that results in the deposition of HS and DS in lysosomes (20). MPS II is the only type of MPS that is X-linked recessive while the other types are autosomal recessive diseases. MPS II primarily affects males, though a small number of females are affected because of autosomal X-chromosomal translocation and nonrandom X-chromosome inactivation (21). MPS II can be subdivided into two types according to its phenotype, MPS IIA (severe) and MPS IIB (moderate).

MPS IIA has a higher incidence than MPS IIB. Its clinical features are similar to those of MPS I, including short stature, coarse face, inguinal and umbilical hernias, thickening of tissues, valvular disease, and hepatosplenomegaly (22). Patients with the severe form, similar to MPS I-IH, rapidly present with symptoms and tend to die in the first decade of life. Patients with the moderate form, similar to MPS I-IH/S and IS, have a longer life span and slower progression of somatic deterioration. Usually, patients have an average of life span of one or two decades, and only patients with milder forms can survive into adulthood. Neurological degeneration varies between the severe and mild forms. Patients with MPS IIA present with progressive central nervous symptoms such as a cognitive disorder, hyperactivity, and aggressiveness (23), while those with MPS IIB may have normal neural development.

3.3. MPS III (Sanfilippo syndrome)
IIIA, IIIB, IIC, and IID, that are characterized by a lack of heparan-N-sulfatase (SGHS), α-N-acetylgalcosaminidase (NAGLU), α-glucosaminidase acetyltransferase (HGSNAT), and N-acetylgalcosamine 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 IIC and IID 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 (24,25).

The development of MPS III consists of three phases after a pre-symptomatic phase with normal development (26). The first phase starts at 1-3 years of age (may occur later in patients with mild phenotypes) with slowing or halted cognitive deterioration. Speech deterioration is usually noticeable and accompanied by behavioral problems. Physical development may be normal in the first stage (27).

The second phase is characterized by progressive cognitive decline, sleep disturbance, and obvious behavioral problems. Behavioral problems including aggressive behavior result from hyperactivity, anxious behavior, and autistic-like behavior. This phase occurs at the age of 3-4, while patients with the mild phenotype may have a gradual progression and longer survival.

The third phase usually starts in the teenage years and involves a decline in motor function and lack of behavioral problems due to a loss of locomotion. During this stage, severe dementia, spasticity, and swallowing difficulties start to manifest and may eventually result in patients becoming bedridden or entering a vegetative state (28).

3.4. MPS IV (Morquio syndrome)

MPS IV is subdivided into MPS IVA and MPS IVB depending on a deficiency in N-acetylgalcosamine-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 dysmophia including growth retardation, a short neck, cervical spinal cord compression, odontoid hypoplasia, hypermobile joints, pectus carinatum, and an abnormal gait (29,30). Other common features are corneal clouding, hearing loss, respiratory obstruction, and sleep apnea (31,32).

3.5. MPS VI (Maroteaux-Lamy syndrome)

MPS VI is characterized by a deficiency of N-acetylgalactosamine-4-sulfatase that results in the storage of DS and chondroitin-4-sulfate (C4S). The accumulation of GAGs in organs and tissues also leads to multisystem clinical symptoms and progressive deterioration with age. Clinical features, the age of onset, and the rate of progression vary among patients with MPS VI but are generally distributed into slowly and rapidly progressing phenotypes (33).

The slowly progressing phenotypes develop slowly and have attenuated symptoms but require surgical intervention and may result in a severe morbidity (34). Bones and joints are commonly affected, and skeletal malformation is also a noticeable feature in MPS VI. Relevant skeletal diseases include dysostosis multiplex, scoliosis, joint stiffness, joint contractures, pectus carinatum, and spinal cord compression. Other somatic features are coarse facies, an enlarged tongue, teeth abnormalities, hirsutism, corneal clouding, umbilical hernia, and hepatomegaly (35,36). Patients with MPS VI usually have a low quality of life and die before the second decade of life because of cardiac and valvular diseases, pulmonary infection, or restrictive lung diseases (37,38). Mental retardation used to be considered unrelated to MPS VI, but central nervous pathological manifestation including communicating hydrocephalus, cerebral atrophy, and a low IQ have been found in patients with MPS VI (39,40).

3.6. MPS VII (Sly syndrome)

MPS VII is a rare type of MPS. The pathology of MPS VII is a lack of the β-D-glucuronidase enzyme that causes an accumulation of DS, HS, C4S, and C6S in tissues. MPS VII has a phenotypic heterogeneity and multiple systematic clinical features including a short stature, coarse facial features, corneal clouding, hydrocephalus, skeletal deformation, and cardiac diseases, resembling MPS I and II. However, hydrops fetalis, an abnormal accumulation of body fluids in several tissues, is a distinguishing feature of MPS VII (41). The time of onset ranges from infancy to childhood, but few patients survive into adulthood. Most fetuses with hydrops fetalis are stillborn or die shortly after birth. Others may begin to display clinical symptoms during early childhood and have a short life expectancy (41,42). Heart disease and airway obstruction are major causes of death in people with MPS VII (42).

3.7. MPS IX (Natowicz syndrome)

MPS IX is an extremely rare type of MPS caused by
a deficiency in the lysosomal enzyme hyaluronidase, resulting in the accumulation of hyaluronan. Hyaluronan is a high-molecular-weight polymer that modulates cell proliferation, migration, and differentiation, that regulates extracellular water and protein homeostasis, that is involved in cartilage composition, and that acts as a lubricant in joints (43-45). The first patient with MPS IX was described in 1996 with perarticual soft-tissue masses and nodular hyperplasia, a short stature, and acetabular erosions (46). In 2011, Imundo et al. described 3 siblings of Middle Eastern descent presenting with a phenotype limited to the joints that was evident as juvenile idiopathic arthritis (47). Skeletal and joint manifestations are common in MPS IX in accordance with the biological function of hyaluronan. Other symptoms may include a short stature, cysts, frequent ear infections, and a cleft palate (12).

### 4. Diagnosis

MPS is an inherited progressive LSD with early onset ranging from the fetal period to adolescence. Patients with MPS often have a low quality of life and short life expectancy and require timely treatment. However, the diagnosis of MPS is usually delayed until irreversible clinical features manifest (48). Thus, reliable and presymptomatic diagnosis is imperative to improving outcomes for patients with MPS.

Careful attention should be paid to the medical history of patients and their families because MPS are autosomal recessive inherited diseases except for MPS II, which is linked to a recessive X chromosome. Close attention to the same clinical symptoms in other family members could help to diagnose MPS. Clinical signs are important evidence for diagnosing MPS and distinguishing MPS phenotypes (Table 2). The age of onset, a chronological order of symptoms, the rate of progression, and complications are essential information leading to a diagnosis (49).

Radiographic findings including X-rays and computed tomography (CT) and magnetic resonance imaging (MRI) are frequently used diagnostic methods. Kyphosis often appears as the first sign of MPS, and of MPS IVA in particular (50). It can be detected in the lumbar vertebral bodies on X-rays (32). Patients, and especially those with MPS I, II, or III, often have central nervous symptoms that may be evident on brain CT or MRI. Sight, hearing, the oral cavity, and the respiratory system also need to be examined to assess somatic symptoms (3,21).

A definitive diagnosis relies on molecular tests, such as identification of the type of GAG, and genetic testing should be performed. Due to deficiencies in specific lysosomal enzymes, GAGs accumulate in various tissues and are partially eliminated in urine. Determining the type of GAG in urine can help to distinguish the enzyme that is deficient. However, diagnosis of MPS is often delayed since the majority of patients appear normal in the early stages and since their total GAG levels in urine may be normal and thus yield a false negative (51). Therefore, newborn screening and sensitive new biochemical markers for MPS are needed to diagnose MPS in a timely and precise manner. The genotype is correlated with the phenotype and can be used to predict the incidence and type of MPS. An enzyme assay and genetic testing of prenatal samples can be accomplished by testing chorionic villi, amniocytes, etc. Enzymes can also be determined in fibroblasts, leukocytes, and plasma. If there are initial suspicions based on medical history and clinical features, then screening and subsequent confirmatory studies need to be conducted to diagnose MPS and determine its subtype.

### 5. Treatment

Once a diagnosis of MPS is confirmed, specific treatment should be provided in a timely manner.

---

**Table 2. Recognition of mucopolysaccharidosis (MPS)**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>MPS I</th>
<th>MPS II</th>
<th>MPS III</th>
<th>MPS IV</th>
<th>MPS VI</th>
<th>MPS VII</th>
<th>MPS IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse facial features</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Cognitive retardation</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Valve disease</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Inguinal and umbilical hernias</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Corneal clouding</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Short stature</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Joints stiffness</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Teeth abnormalities</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Enlarged tongue</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

+: positive; -: negative; +/-: normal or positive; +/-: negative but suspicious in some cases.
Management of MPS means slowing disease progression and improving quality of life. Palliative treatment, surgery, and disease-specific treatments are the main options for patients with MPS. Palliative treatment and surgery are intended to mitigate symptoms to reduce suffering. At present, disease-specific treatments for MPS include HSCT and ERT.

HSCT is based on the assumption that transplanted cells from bone marrow, peripheral blood or umbilical cord blood can penetrate to various tissues and organs and then produce enough of an enzyme to alleviate symptoms (1). Since the donor cells continuously secrete enzymes in the body, HSCT is considered to be a permanent treatment. Clinical trials have demonstrated the efficacy of HSCT for MPS I, II, IV, VI, and VII but not for MPS III (41,52-55). However, the main limitation of HSCT are the rarity of matching donors and transplant rejection.

ERT directly introduces a functional enzyme into the body to decrease or normalize GAG levels. Like with HSCT, clinical trials of ERT have noted positive results with MPS I, II, IV, VI, and VII (56-60). Both HSCT and ERT have proven unsatisfactory in patients with MPS III because MPS III is a special type of MPS that mainly involves central nervous diseases (25). Adverse effects of ERT have been reported, and anti-ERT antibodies are observed in most patients (61). Moreover, its efficacy is reduced by its low level of blood-brain barrier penetration and inefficient delivery to avascular tissues (6). Advanced forms of ERT including intracerebroventricular and intrathecal administration have been explored. Normal GAG storage and neurological improvement were noted in a murine model of MPS with intracerebroventricular administration (62). However, indications and the risk of site-specific injections are unsolved challenges, and clinical efficacy is uncertain. Therefore, novel approaches such as gene therapy and substrate reduction therapy (SRT) are important therapeutic options for MPS to improve outcomes.

Gene therapy refers to introducing a therapeutic gene into a patient's cells. This novel therapy is permanent and does not require a matching donor like HSCT or have blood-brain barrier restrictions like ERT. Gene therapy can be in vivo or ex vivo. In vivo gene therapy directly delivers gene products into the body via systematic or in situ administration (63). Ex vivo gene therapy involves modifying a patient's stem cells externally and then infusing them back into the body. Thus, an immune response to a vector or gene products could occur. Although clinical trials are already underway, gene therapy is still in development since its long-term effects are not known (64).

SRT seeks to reduce an excess of a substrate, thus slowing GAG synthesis, instead of increasing GAG degradation. Generally, small molecules that inhibit substrate synthesis are administrated orally. These facilitate SRT and penetrate the blood-brain barrier. Genistein, a soy-derived isoflavone, was first identified as a potential drug for SRT; it acts as a tyrosine kinase inhibitor and alleviates neurological manifestations (65). However, a sequent clinical trial of SRT failed to find any significant neurological benefit as a result of a decline in urinary GAGs (66). Therefore, novel inhibitors of GAG synthesis need to be identified as therapeutic targets. A point worth noting is that the combination of HSCT and ERT has proved to be associated with better outcomes (67), indicating that the management of MPS requires combined and multidisciplinary treatment.

6. 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.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grant nos. 31571196 and 30801502 to Ling Wang), the 2018 Program to Guide Medicine ("Yixue Yindao") of the Shanghai Municipal Science and Technology Commission (grant no.18401902200 to Ling Wang), the 2015 Program to Guide Medicine ("Yixue Yindao") of the Shanghai Municipal Science and Technology Commission (grant no. 15401932200 to Ling Wang), the Shanghai
References


Received January 31, 2020; Revised February 7, 2020; Accepted February 10, 2020.

These authors contributed equally to this work.

Address correspondence to: Ling Wang, Obstetrics & Gynecology Hospital of Fudan University, 419 Fangxie Road, Shanghai 200011, China. E-mail: Dr.wangling@fudan.edu.cn

Released online in J-STAGE as advance publication February 16, 2020.