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Presentation and Treatments for Mucopolysaccharidosis Type II (MPS II; Hunter Syndrome)

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Abstract

Introduction—Mucopolysaccharidosis Type II (MPS II; Hunter syndrome) is an X- linked lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase (IDS). IDS deficiency leads to primary accumulation of dermatan sulfate (DS) and heparan sulfate (HS). MPS II is both multi-systemic and progressive. Phenotypes are classified as either attenuated or severe (based on absence or presence of central nervous system impairment, respectively).

Areas covered—Current treatments available are intravenous enzyme replacement therapy (ERT), hematopoietic stem cell transplantation (HSCT), anti-inflammatory treatment, and palliative care with symptomatic surgeries. Clinical trials are being conducted for intrathecal ERT and gene therapy is under pre-clinical investigation. Treatment approaches differ based on age, clinical severity, prognosis, availability and feasibility of therapy, and health insurance.

This review provides a historical account of MPS II treatment as well as treatment development with insights into benefits and/or limitations of each specific treatment.

Expert opinion—Conventional ERT and HSCT coupled with surgical intervention and palliative therapy are currently the treatment options available to MPS II patients. Intrathecal ERT and gene therapy are currently under investigation as future therapies. These investigative treatments are critical to address the limitations in treatment of the central nervous system (CNS).

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Declaration of Interest

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Keywords

MPS II; enzyme replacement therapy; hematopoietic stem cell transplantation; gene therapy; anti-inflammatory therapy

1. Overview

1.1. Historical aspect

Mucopolysaccharidosis Type II (MPS II; Hunter Syndrome) was first described in 1917 by Dr. Charles Hunter who examined two brothers (8 and 10 years old) with short stature, large heads, umbilical hernias, and joint stiffness [1]. The younger brother experienced central nervous system involvement (CNS) while the older brother did not. Both cases died at ages 11 and 16, respectively, due to respiratory and cardiovascular complications [1].

In 1952, clinical features associated with a general accumulation of mucopolysaccharides or glycosaminoglycans (GAGs), including defects of collagenous tissues- cartilage, tendons fasciae and heart valves, were recorded [2]. In 1962, Teller et al. reported an elevation of GAGs in the urine of MPS children, and found that differentiation of MPS types was possible based on accumulation of different GAG subclasses [3]. In 1970, cross-correctional studies elucidated differences in enzyme deficiencies between MPS II and MPS I (Hurler) syndromes, though both MPS I and MPS II lead to accumulation of dermatan sulfate (DS) and heparan sulfate (HS) [4]. In 1973, Bach et al. identified sulfoiduronate sulfatase as the deficient enzyme in MPS II, causing the accumulation of dermatan DS and HS [5], and from 1982 to 1991, the first ten hematopoietic stem cell transplantations (HSCT) were conducted on MPS II patients [7]. The cDNA of IDS was cloned in 1990 [8], and the first clinical trial of enzyme replacement therapy (ERT) for patients with MPS II was conducted in 2001 [9]. Phase III clinical trials for ERT in MPS II patients were completed in 2006 after which it gained approval for patient treatment [10].

1.2. Biochemical aspect

MPS II is an X-linked disorder caused by the deficiency of iduronate-2-sulfatase (IDS) due to mutations in the *IDS* gene (Xq28) [11, 12]. Typically, males are affected, however, females can be affected [11–19], due to skewed X-chromosome inactivation [19, 20] or chromosomal rearrangement [17,18].

1.3. Clinical phenotype

MPS II is a progressive disease involving multiple systems and presenting with a wide spectrum of clinical symptoms. The primary accumulation of DS and HS leads to impairment of several processes including cell trafficking, endocytosis, autophagy, ion homeostasis, and nutrient sensing [21]. DS accumulation results in enhanced cytotoxicity via nitric oxide (NO) release [22] and induction of the inflammatory response [23].

Accumulation of HS results in accumulation of secondary molecules such as gangliosides (GM2 and GM3) in the brain, causing microglial activation [24–29], which activates the inflammatory response pathway in the brain [23].

While genotype variations can cause some of the clinical heterogeneity (extensive range of signs and symptoms) a specific mutation does not necessarily coordinate with the observed phenotype [30]. Patients are currently categorized, in the most general terms, as having either attenuated (no CNS impairment) or severe (CNS impairment) [25,18, 31,] The severe phenotype of MPS II is more prevalent (60%) [31]. Typically, hydrocephalus develops before any behavioral changes indicative of CNS involvement [33,34]. This is followed by behavioral difficulties and hyperactivity at around 3.5 years of age, although CNS manifestation can occur much later. Attention difficulties, particularly in school aged children are prevalent, potentially due to abnormal corpus callosum volumes [37–39]. Scholastically, children with severe MPS II develop normally until around 3 to 4 years of age when cognition begins to decline [35,36,32]. Language skills are typically slow to develop due to the cognitive decline and hearing loss that frequently occur in conjunction with other symptoms. Mild to moderate conductive deafness results from frequent ear infections, as well as inner and middle ear abnormalities including deformity of the ossicles (Fig 1) [40]. Frequent epileptic seizure is another common consequence of CNS involvement.

There is evidence of both gray and white matter being involved in behavioral deficits in MPS II patients. White matter abnormalities (WMA) consist of diffuse or focal areas prolonged in T1 (longitudinal relaxation time) and T2 (transverse relaxation time) relaxation times. Periventricular white matter exhibits more frequent abnormalities [34]. Gray matter signal intensity abnormalities have been found in the basal ganglia [41, 34]. Brain magnetic resonance imaging (MRI) scans have revealed brain atrophy typical in patients with seizures [42]. MPS II patients with CNS involvement often display a “honeycomb-like appearance” in the brain which describes the patchy areas of increased and decreased signals in the T1 and T2 regions (Figure 2). This imbalanced distribution of white and gray matter is a potential cause for the epileptic seizures seen in MPS II patients [43, 34, 44].

Patients with attenuated phenotypes do not have CNS involvement, allowing normal intellectual development. Nevertheless, long-term follow-up examination in some patients with an attenuated phenotype shows a slow progression of CNS involvement and/or retinal degeneration in cases where patients might have previously been considered to have no CNS involvement [37]. For this reason, prognosis and diagnosis of clinical severity should be made carefully in favor of a more robust and comprehensive outlook.

Dental Abnormalities—Patients with MPS II often show dental abnormalities. Teeth are typically abnormal in number, shape and form including malocclusion and enamel defects (both milk and definite teeth), anterior open bite, undershot jaw, and other orthodontic problems. Patients typically need to be followed by an oral specialist before symptoms begin. Patients are more prone to developing cysts and abscesses due to increased rates of oral infection [45–47].

1.3.1 Ear, nose, and throat—Patients often have ear, nose, and throat (ENT) problems including noisy breathing, recurrent otitis, sinusitis, and upper respiratory infections with atypical mucosal discharge [48–50]. These disturbances are caused by an enlarged and swollen tongue, redundant trachea, and thickened and copious mucosal secretions in

addition to an increased inflammatory immune response. Breathing difficulties, often accompanied by sleep apnea, are caused by engorged tonsils and adenoids, narrowed trachea, and thickened vocal chords (Fig. 2) [48,51].

Frequent respiratory infections typically lead to limited endurance including intolerance of activity and decreased activity of daily living (ADL), which is a standard measure of independence in completing routine activities. Superficial, loud, and rapid breathing are typical results. The restrictive airway disease is exacerbated by bone and joint pathology including an abnormally shaped ribcage and thoracolumbar deformities (Fig. 3). Progressive deposition of GAGs in the soft tissue of the throat and trachea leads to a narrow and difficult airway [52]. These breathing abnormalities often occur in conjunction with cardiovascular disease [49,52].

1.3.2 Cardiovascular involvement—The MPS II outcome survey revealed that valvular heart disease (63%), followed by left ventricular hypertrophy (48%) and elevated blood pressure (25%), are common cardiovascular abnormalities [37,28,53]. Valvular thickening leading to insufficient cardiac activity accounts for most of the observed cardiovascular effects [54,53].

General findings upon examination are fatigue, cardiac murmur, cardiomyopathy, and aortic or mitral regurgitation [53]. A recent report evaluating the cause of death for 129 deceased MPS II patients showed that airway involvement was the primary cause of death (65%) followed by cardiac involvement (16%) [55]. These rates do not take into consideration deaths in which cardiac involvement is listed as a secondary cause of death suggesting that that actual role cardiac disease plays in patient mortality rates is even greater than reported [55,56].

1.3.3 Gastrointestinal tract—Gastrointestinal involvement often leads to discomfort and a decreased quality of life. The protuberance of the abdomen is often one of the first noticeable symptoms for MPS II [57] (See supplemental data). Progressive and degenerative hepatosplenomegaly is seen due to excessive storage of GAGs. Hepatosplenomegaly causes increased intra-abdominal pressure, leading to inguinal and umbilical hernias (Fig. 3). Patients are often plagued by chromic watery stool that does not appear to be associated with malabsorption. In older patients, loss of bowel movement and loss of muscle strength can lead to constipation.

1.3.4 Skeletal, joint and muscle disease—Patients often present with coarse facial features as one of the first recognizable symptoms. Skeletal involvement typically occurs earlier in the more severe form and is characterized by dysostosis multiplex [58]. Short stature, present in most types of MPS, is thought to be a result of the failure of endochondral ossification in growth plates which are secondary to GAG storage. The delay in ossification centers results in many of the characteristic features associated with the skeletal manifestations of this disease including thoracic kyphosis, scoliosis, and odontoid hypoplasia, with the latter leading to atlantoaxial instability [59,60].

Inflammatory events affect chondrocytes, osteoblasts, and their extracellular matrix; often resulting in severe arthroplasty. Although there is GAG storage in and potentially around all joints, the hip is particularly susceptible [23]. Hip inflammation and erosive damage are painful and significantly decrease mobility and quality of life. Decreased mobility exacerbates problems seen in other organs.

Myopathy caused by GAG storage in muscle cells and around tendons leads to muscular dysplasia in MPS II patients. The destruction of the articular and epiphyseal cartilage layers of deformed bones leads to rigidity of joints and increased pain [61, 58]. These effects culminate in restriction and contraction of the hips, knees, toes, shoulders, wrists, and elbows (see supplemental data). In the spine, the skeletal and joint manifestations result in ovoid contour and the humpback characteristic of this disorder (see supplemental data). This results in sagittal deformity and instability, axial deformity and instability, and spinal cord and root compression. As the disease progresses, these factors reduce mobility. Cervical myelopathy often leads to bowel and bladder dysfunction, decreased endurance and eventually quadriparesis. If the compression becomes substantial, these orthopedic deformities can result in death [37].

The skeletal manifestations also affect hand motion. Claw hand deformities (Fig. 5) develop due to joint stiffness and contractures. The inability to hold and grip leads to a significant loss of mobility and thus a loss of independence. This is in part caused by ossification delay. GAG accumulation in and around tendons and nerve sheaths leads to carpal tunnel syndrome which causes further pain [25].

1.4. Diagnosis

1.4.1. Clinical—The initial signs and symptoms of MPS II are typically physical rather than psychological or developmental. Coarse facial features are often the first and most indicative appearance of MPS and occur in both phenotypes of MPS II, to varying degrees of severity. Other early clinical manifestations include bone deformity, abnormal gait, and difficulty of joint movement. The average age at onset of symptoms in untreated children has been reported as 1.5 years old for severe phenotype and 4.3 years old for attenuated phenotype [62]. Some patients with an attenuated form of MPS II might not show symptoms until later in childhood or even early adolescence. Patients with attenuated MPS II are most frequently diagnosed between the ages of 4 and 8 [37] Frequent ear nose and throat infections as well as snoring, difficulty sleeping, and hearing loss are also often present from early onset [63].

Some patients might present early cognitive dysfunction including difficulty sleeping, hyperactivity, pervasive chewing, seizures, and inappropriate bowel and bladder training [38]. Often these inappropriate behaviors become more identifiable after the initial diagnosis. Due to the heterogeneity of signs and symptoms, more than 60% of patients are seen by at least three physicians to obtain an accurate diagnosis [64].

1.4.2. Biochemical and Molecular findings—The gold standard in diagnosis of MPS II is the measurement of IDS [4]. Enzyme activity can be measured in a variety of samples: cultured fibroblasts, leukocytes, plasma/serum, dried blood spots (DBS), and chorionic villi

for prenatal analysis [65–73]. Wang's group used a novel approach with the addition of a synthetic substrate for the enzyme to a buffer rehydrated with 2 disks from a DBS. The enzyme-generated product was then measured by tandem mass spectrometry (MS/MS) [68,74]. To exclude multiple sulfatase deficiency, other lysosomal enzymes should be measured [75,76].

Although there is no clear correlation between residual levels of enzyme and disease severity, typically patients with the severe form have very low or undetectable levels of IDS [77–81].

Correlations between genotype-phenotype are challenging due to variation between patients and a large number of mutations [87,88].

1.5. GAGs as a biomarker

Urinary GAGs have been used as biomarkers for several forms of MPS and as a surrogate marker for IDS activity in a clinical trial [9, 89]. Oguma et al. first developed a method to assay specific GAGs including DS, HS, and KS using liquid chromatography tandem mass spectrometry (LC/MS/MS) [90, 94]. Screening of MPS positive patients using LC/MS/MS showed significant elevation of plasma HS and DS in MPS I, II, III and IV patients as opposed to the controls [91]. Auray-Blais et al. developed DS and HS quantification in urine by ultra-pressure liquid chromatography (UPLC) tandem mass spectrometry (MS/MS) post methanolysis [92].

Measurement of urinary GAGs can be limited due to small changes in levels over time, variations in anthropometry, and renal status [82,83,80,84]. The exact correlation between urinary GAG and clinical severity or therapeutic efficacy remains unclear [77–80] and sometimes attenuated forms, and less severe disease cannot be detected resulting in false negatives [81,77,86,84,].

Shimada et al. have also established a GAG assay by high-throughput mass spectrometry (HT/MS/MS) with RapidFire system (Agilent Technologies) allowing discrimination of phenotypes and measurement of treatment efficacy in ERT and HSCT treated patients [93].

1.6 Other Biomarkers

Heparin cofactor II thrombin complex (HCII-T) is elevated in MPS II and decreases post-ERT treatment [94,80,95]. Secondary elevation of keratan sulfate (KS) has been reported in MPS II suggesting its use as a biomarker [96,97,98,93,92]. Alternative biomarkers including pro-inflammatory cytokines and the ratio of dermatan to chondroitin sulfate [99,100, 101] are under investigation.

2.7 Incidence

Globally, MPS II occurs in 1: 100,000 to 1: 170,000 male births. MPS II is the most prevalent MPS in East Asian regions, accounting for 54% of MPS patients in Japan (Fig 4), 52% in Taiwan [102], 50% in South Korea [103], and 47.4% in Eastern China [104]. Incidence is lower in European regions [105], examples include accounting for only 7.6% of

diagnosed MPS patients in the Netherlands between 1970 and 1996 [106], and 7.6 % in Portugal between 1982 and 2001 [107] (Fig 4).

2. Treatment

2.1. 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 [108]. Suppression of metabolic inflammation with anti-inflammatory agents can help patients manage this discomfort, thereby improving their quality of life [109]. Pentosan polysulfate (PPS), an anti-inflammatory drug approved by FDA for interstitial cystitis, is currently under investigation. The exact mechanism by which PPS decreases GAG levels and stimulates chondrocyte formation remains under investigation [111].

2.2. 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 [112]. These somatic improvements result in a better quality of life for some patients [29, 113]. However, conventional ERT does not alter the course of neurological decline [37,33, 112,114].

Conventional ERT has been approved in many countries, including the United States, Canada, EU, and Japan, as a treatment option for patients who have a confirmed diagnosis of MPS II. Treatment before six years old provides the positive effects of somatic improvement [28,115]. This method of treatment has been available since 2006, although guidelines for use vary between nations. In Australia, for example, only patients with an attenuated phenotype are eligible to receive ERT whereas in the UK all patients with MPS II are eligible to receive ERT regardless of phenotype [113]. In Latin America, there are approved guidelines stating that ERT should be offered to all patients older than five years of age with an attenuated phenotype, despite the current data suggesting that ERT is more effective when started earlier [61]. When The Hunter Syndrome European Expert Council suggests that all MPS II patients are eligible for ERT unless patients are at a disease terminal stage. ERT should be continued unless ineffective after 6 months of clinical observation [40].

When Elaprase® is denied to patients with the cognitive decline, it is primarily because recombinant enzyme does not cross the blood-brain barrier (BBB) when administered intravenously and consequently provides a little impact on cognitive impairment and retinal degeneration.

Intrathecal injections (IT) of enzyme were proposed to overcome this barrier [117]. Infusion of IT-ERT was administered directly into the cerebrospinal fluid (CSF) of patients using an

indwelling intrathecal drug delivery device (IDDD). In 16 males with neurodegeneration, patients were randomly divided into four treatment groups to receive monthly infusions (0, 1, 10, or 39 mg idursulfase-IT) (clinical trial No: NCT00920647) [118]. IT-ERT appeared to slow the progression of cognitive decline. Neurodegeneration did continue for all patients, but progression was slower and less severe in treated patients. However, due to safety concerns, only older patients (average age 8.2 with neurological impairment already present) were included in the study, limiting interpretation of the results. GAG buildup in CSF was reduced by 80–90%, but more than 80% of the patients showed serious adverse effects related to the IDDD [117]. The difficulties experienced by patients as a result of IDDD malfunction fell into two main categories; device breakage and catheter migration from the spinal canal. These severe side effects were unrelated to use of enzyme that was well tolerated [117]. As it is impossible to reverse neuronal decline, younger patients may benefit more from IT- ERT before clinical signs appear. A clinical trial for younger patients (3 to 18 years old) who tolerated at least 4 months of IV-ERT previously is in progress to test the effectiveness of 12 monthly doses of IT- ERT on neurodevelopmental status (Clinical Trail No. NCT02055118 and NCT02262338). It is not yet clear whether IT-ERT will be an appropriate strategy to treat CNS involvement in patients with MPS II.

2.3. Hematopoietic stem cell transplantation (HSCT)

In hematopoietic stem cell transplantation (HSCT) healthy donor cells are obtained from bone marrow (BM), cord blood (CB), or peripheral blood stem cells (PBSC), and transplanted into patients to provide cross correction of enzyme in deficient tissues [119–123, 138]. The first patient with MPS II to undergo treatment with HSCT was treated in 1982. Before 2000, HSCT had high mortality rates due to poor donor selection, rigorous conditioning and high risk of, graft-versus-host disease (GVHD) [124–128, 31,35,32].. Nevertheless, improvements in donor-selection and regimens have decreased mortality rates of HSCT for MPS to less than 5% [130].

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 [132,36,32,123]. Knowledge of the effects of HSCT on bone growth is somewhat limited. A comparative study, which examined the difference of HSCT, conventional ERT and combined ERT and HSCT on long bone growth found that HSCT and ERT were equally effective in restoring growth of MPS II patients [37]. Although this study included some patients between the ages of 4 and 12, it is expected that HSCT will have a greater efficacy if given before the age of 2. It would be prudent to conduct a similar study with younger patients, if newborn screening allows younger patients to be identified. HSCT should be a one-time procedure, and consequently cost considerably less than ERT.

Recently it has been found that donor cells cross the blood-brain barrier (BBB) [131]. Tanaka et al. demonstrated that when HSCT is carried out before developmental delay becomes apparent, it is effective in certain aspects of CNS manifestation as measured by

both intellectual and imaging analyses. They also found that speech deterioration was significantly less severe in patients who underwent HSCT versus the untreated group. While other studies indicated that HSCT does not have a clear impact on neuropsychological outcomes, the positive comparative results seen in this study indicate that HSCT could have some effect on CNS manifestations if conducted at early disease stages, and HSCT is likely to have similar or superior effects on somatic symptoms when compared to ERT.

While the strong preconditioning regimen prior to HSCT causes severe side effects including increased susceptibility to infection, particularly in immunocompromised patients, a recent murine study suggests that the establishment of a milder conditioning regimen could be as effective while limiting the risk of side effects for the patients. In this study, MPS II mice were pre-treated with anti-c kit antibody 2 (ACK2) followed by low lose irradiation. 59% donor chimerism was achieved 16 weeks after transplantation in the peripheral blood of the mice [135]. This study did not show any effect of the treatment on CNS symptoms; however, it did suggest a potential new pre-conditioning treatment for patients with attenuated MPS II who are unable to tolerate the harsh preconditioning treatments that are currently necessary before HSCT. With the decreased risk of HSCT for patients, comparative studies involving both severe and attenuated patients, should be conducted. This is especially important for patients who can be treated before clinical symptoms of MPS II are apparent.

2.4. 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 [136,137]. Motas et al. used adeno-associated virus 9 (AAV9-Ids) delivery injected directly to the CSF through intracisternal injections in 2-month-old MPS II mice [138]. IDS activity was significantly increased throughout the CNS with full reversal of CNS and somatic pathology post-treatment. The improvement was also seen in behavioral deficits and survival rates [138].

Another study investigated the use of AAV-9 by CSF injections in MPS II mice and found a dose-dependent resolution of brain storage lesions and decreased GAG storage in the visceral organs. Behavioral testing showed some improvement although the limited effect was seen in fear conditioning and attention span [139].. Mice in this study were treated when they were between 2 and 3-months old when clinical symptoms had developed. The purpose of this later treatment was to determine if neurological and somatic manifestations could be reversed. Although reversal of CNS pathology is less likely in humans, delivery of AAV vectors directly into the CSF is a potential treatment option to prevent further CNS pathology for MPS II patients [139].

Lentiviral vectors in *ex vivo* gene therapy have been used as a clinical option for several genetic diseases [140–143] and have been shown to be effective for correcting some aspects of neuronal defects in mouse models of MPS I and IIIA [144,140,145]. Lentiviral *ex vivo* HSC gene therapy improves biochemical abnormalities in tissues, rescues autophagic flux

retardation, reduces neurofunctional impairments in the CNS, and decreases deterioration of the neuronal function of MPS II mice [140]. While there are risks, this therapy shows stronger efficacy against neurological defects in MPS II than other treatment regimens [149].

In the future, genome editing may be of value for correcting IDS deficiency in MPS II. Although integration efficiency of this technique is often low, this may be sufficient for MPS II where expression of even very low levels of IDS will lead to a dramatic clinical improvement.

In summary, gene therapy is expected to be superior to both ERT and HSCT due to greater efficacy in the treatment of CNS symptoms. Gene therapy would be a potential one-time treatment offering greater potential than either conventional or intrathecal ERT and may also avoid some of the most serious complications of HSCT. More pre-clinical studies and clinical trials are needed to elucidate safety and long-term effects of this treatment approach.

2.5 Substrate reduction therapy

Another treatment option is substrate reduction therapy (SRT). This methodology aims to reduce GAG synthesis which allows for correction of the imbalance between the formation and breakdown of GAGs [151–153]. Genistein (4′ 5,7 trihydroxy isoflavone) is a soy isoflavone which has been investigated in the context of MPS II as capable of decreasing the expression of genes coding for one or more enzymes involved in GAG synthesis [152–157].

Genistein was shown first to reduce GAG accumulation in the fibroblasts of MPS II patients [152]. Experimental data on the effects of Genistein in an MPS II mouse model showed decreased storage of GAGs in several peripheral tissues with some signs of reduction in brain storage [153]. The complete mechanism for the observed effects was originally thought to be due to the inhibition of the epithelial growth factor (EGF) receptor (EGFR or ErB1), which inhibits trypsin specific protein kinase activity. EGF is required for GAG synthesis so without this the synthesis is significantly decreased [152–154].

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 [157].

Previous data has suggested that high does genistein is safe in patients [155]. Genistein was also associated with an improvement in connective tissue elasticity and range of motion in joints of MPS II patients [154]. There is not yet conclusive data to indicate that this treatment can cross the BBB sufficiently to improve neurological symptoms. However, it was shown to cross the blood-brain barrier in an MPS II mice model, with histochemical evidence of GAG reduction at the choroid plexus of the ventricular region [153].

3.6 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 [54]. Regular echocardiograms should be given to MPS II patients to monitor for cardiac arrhythmia due to cardiomyopathy. Some success has been seen in physical therapy slowing the decline of exercise-induced endurance in patients.

Respiratory problems in patients with MPS II can lead to upper airway complications (Fig. 2). Chronic upper respiratory tract infections from very early childhood and increased mucosal secretion make more complications for the MPS II patient. The difficulty of breathing leads to sleep apnea which must be treated in severe cases with supplemental oxygen to avoid hypercapnia. Children will often have tonsillectomy and removal of the adenoids to decrease airway obstruction [158]. Recurrent ear infections often lead to infection of the middle ear and subsequent hearing loss. Many patients, therefore, require ear tube placement which will add an otolaryngologist to their team of specialists.

The mechanism that causes the watery stool in many patients with MPS II is not fully understood [9,69]. This diarrhea can be chronic and/or episodic and severely impacts the quality of life for patients and caretakers. Anti-motility drugs as well-planned diet control should be used to remedy this. Abdominal and inguinal hernias, classic manifestations seen in most MPS types, including MPS II, are fixed with surgery although this surgery is a temporary solution and recurrence typically occurs [37].

3. Activity of daily living

Learning disability and psychological well-being of patients must be closely and carefully monitored. It is critical that patients, particularly patients with a severe phenotype, receive a stimulating and enriching environment at an early age, as early enrichment helps with skill retention and delay of the disease progression. For patients with the attenuated phenotype who do not have involvement of the CNS, physical difficulties in school result from a lack of stamina. Pain when sitting and deafness cause learning in a traditional school environment to be very challenging.

Recent development of the MPS II specific questionnaire to measure the activity of daily living (ADL) as described by both the patient and their caregiver(s) has made significant progress in understanding the psychology of MPS II patients (37,64,32]. Attenuated patients, in particular, tend to suffer from depression and withdraw with the onset of adolescence. Caretakers report difficulty in some MPS II patients with hyperactivity which can be controlled via behavioral therapy and classroom accommodations. The educational personnel involved with the MPS II patients should be trained in the manifestations of this disorder so that they are aware of behaviors that are expected. Therapy for the patient can also help with the depression and withdrawal that result from the disorder. Psychological support should also be given to the families of the patient from the onset of diagnosis.

4. Conclusions

MPS II is typically detected in young children once they begin displaying characteristic somatic symptoms including course facial features, inguinal and umbilical hernias, delayed bone growth and missed milestones, both physical and mental. While physical abnormalities are typically the first sign or symptoms detected, over half of the cases with MPS II have substantial CNS involvement leading to progressive mental retardation. Current therapies include both conventional ERT as well as HSCT. Conventional ERT and HSCT improve somatic symptoms as well as ADL. IDS from ERT does not cross the BBB so does not affect CNS symptoms while HSCT has limited effect on CNS symptoms and no effect if performed after cognitive decline has begun. Both therapies were less effective against skeletal symptoms if performed after symptoms were detected.

Intrathecal ERT, currently under investigation, is expected to have a greater effect on the CNS involvement of the disease, but recent studies showed severe side effects occur due to the IDDD device. The breadth and efficacy of the initial data are also limited, as safety concerns allowed only older patients to be included in the first clinical trial. Safety of intrathecal enzyme delivery for MPS II and other conditions needs to be improved substantially before this technique can be considered as a treatment.

Gene therapy shows great promise as a possible one-time treatment to solve CNS, skeletal and somatic manifestations of the disease. The best route of administration and most effective vectors to minimize side effects are currently under investigation.

Early treatment is critical for any of these options as all treatments are less effective as the disease progresses. Figure 5 shows the scheme from diagnosis via DBS through treatment. Both current treatment options and those under investigation are shown.

As no therapy currently available completely corrects disease manifestations, orthopedic surgical interventions and supportive treatments are needed. Surgical interventions predominately address mobility, airway and cardiac malfunctions.

The team of specialists necessary for treatment of this disease includes members in the fields of orthopedics, anesthesiology, gastroenterology, genetics, auditory function, orthodontic specialist, ENT specialist, neurologist, speech therapist, ophthalmologist, pulmonologist, and cardiologists. Geneticists, in conjunction with the patient’s medical team offer guidance

in treatment options and provide genetic counseling for patients and their families. Psychologists can provide support for patients and families.

Regardless of what treatment option is chosen, the key to a successful outcome is early treatment which can only be provided if early diagnosis is made. Establishment of affordable and efficient newborn screenings will likely lead to early diagnosis and early treatment [18, 74, 159].

5. Expert Opinion

MPS II is an X-linked disease caused by enzyme deficiency due to mutations in the *IDS* gene. Treatments currently available include ERT and HSCT coupled with surgical intervention and palliative care. However, both treatments are limited by age of start and disease status (e.g. neurological and heart impairment) at the time of treatment. ERT does not provide continuous relief from symptoms, and must be administered at intervals throughout the patient's life span. This continuous administration can cause both financial burden and negative impact on the quality of life for patients and caregivers. Furthermore, if immune reactions such as antibody formation occur during treatment, the efficacy will be compromised, and severe side effects can occur. Intrathecal ERT under clinical trial involves intrathecal injections of the deficient enzyme directly into patient's cerebrospinal fluid using an IDD device. While this method has been shown to improve some CNS symptoms, the indwelling device needs to be improved for patient safety. As with conventional ERT, IT-ERT will be also required continuous administration throughout a patient's life.

Gene therapy is scheduled for clinical trial and seems to have the most promise as an effective and permeant solution if it proves to be as safe and effective as seen in animal models. The recent evidence from animal trials suggests that it is possible to reverse CNS and somatic pathology from MPS II through intrascisternal injection. If this technique can be performed safely, it appears to have the greatest potential for treatment of CNS symptoms of MPS II. As treatment for CNS manifestations remains the most elusive task for MPS II research, this potential cannot be understated. Gene therapy offers the potential for a greater quality of life for both caretaker and patient as this method is self-sustaining and does not require indefinite applications. Research into gene therapy also offers potential financial incentives for its use in patient treatment. ERT is known to be an incredibly expensive treatment, and expense that follows the patient through adulthood. In many cases, the high cost of ERT prevents patients from seeking treatment. Insurance companies and governmental programs are hesitant to pay in many instances due to the high per patient yearly cost.

It is critical to note that beneficial effects of gene therapy have not yet been elucidated in human patients. While mouse models have shown dramatic improvement, reduced risk when compared to other treatments, and complete reversal of symptoms in many cases, it has not been established whether this will be the case in humans. It is also necessary for further longitudinal studies to examine the safety and long-term effects of gene therapy. As this treatment option is in its infancy, no studies, have yet proven the safety of this particular treatment. While the potential for gene therapy is great, it should also be understood that is

likely to have the greatest impact in reliving or preventing the symptoms in very young patients. Gene therapy is unlikely to completely reverse damage already caused in older children and adult patients. Therefore, this therapy must be investigated in conjunction with continued efforts to establish affordable and effective newborn screening to allow for the earliest diagnosis and treatment.

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Article highlights

- MPS II is an X-linked recessive disorder manifesting in multi-systemic manifestations present in the CNS, skeletal, and somatic systems.
- Current treatments include conventional ERT and HSCT coupled with palliative care.
- Current treatments are limited in their efficacy on CNS impairment which decreases a patient's quality of life.
- Intrathecal ERT is currently under clinical investigation and has shown evidence of some efficacy in the CNS although serious side effects related to the indwelling device are reported.
- Gene therapy is expected to provide self-sustaining IDS levels with an evidence of reversal of disease manifestations in mouse models
- Any treatment proposed will increase in efficacy if administered to patients before clinical symptoms of the disease are present, suggesting importance of newborn screening

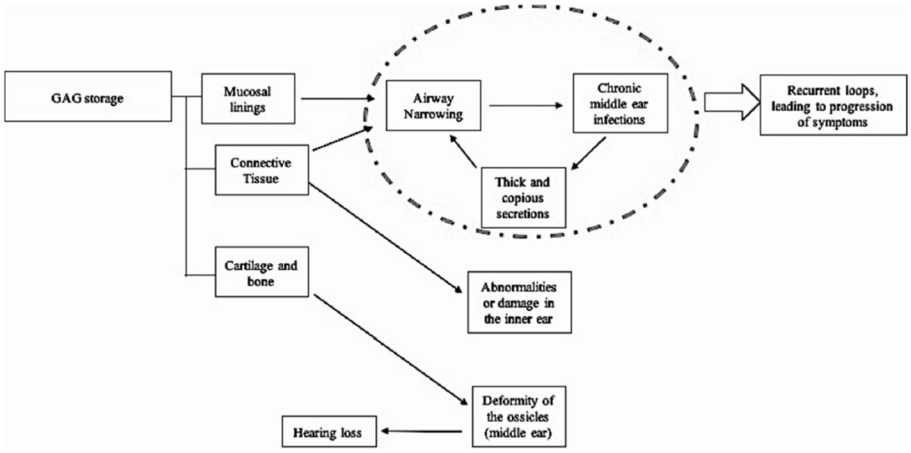
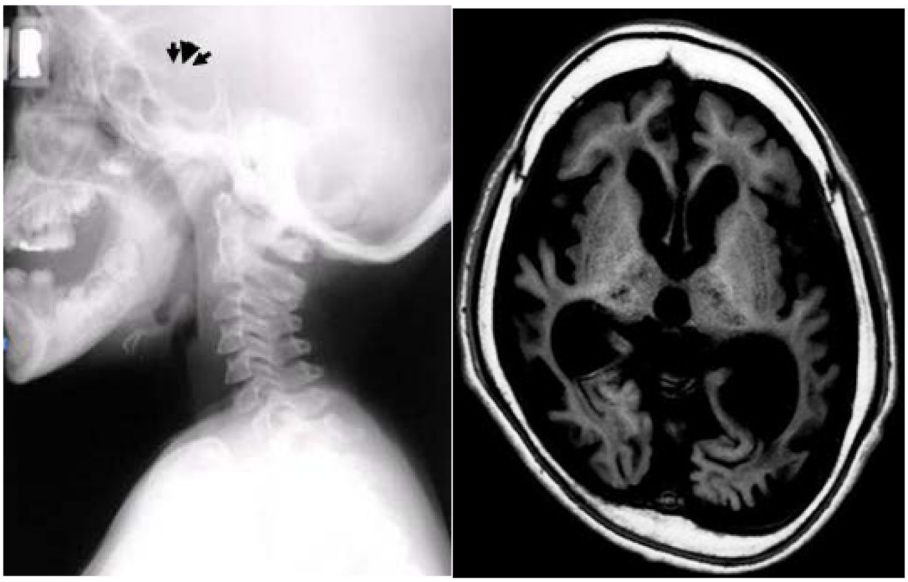


Figure 1.

Pathophysiology of hearing loss in MPS II (Reused with permission from [161] permitted by Japanese MPS Society)



10-year-old patient 17-year-old patient

Figure 2.

Images of skull X-ray and brain MRI from a 10-year-old patient and 17-year-old MPS II patients, respectively. The left pane (a 10-year-old patient with severe phenotype): Scaphocephalic form, partial sutural synostosis, and enlarged omega- or 'J-shaped' sella turcica. Right panel (a 17-year-old patient with severe phenotype): T1 image shows severe brain atrophy, cystic or cribriform lesions, white matter signal changes, and ventricular enlargement.

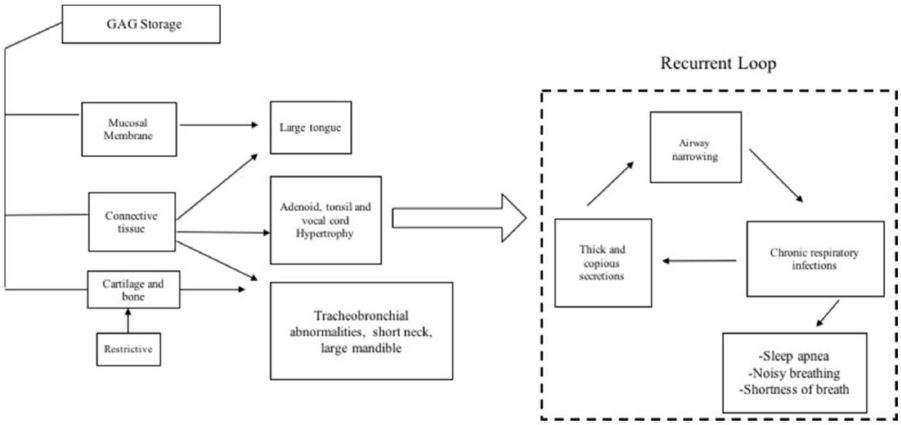


Figure 3.

Pathophysiology of the airway in MPS II (Reused from [161] with permission from Japanese MPS Society)

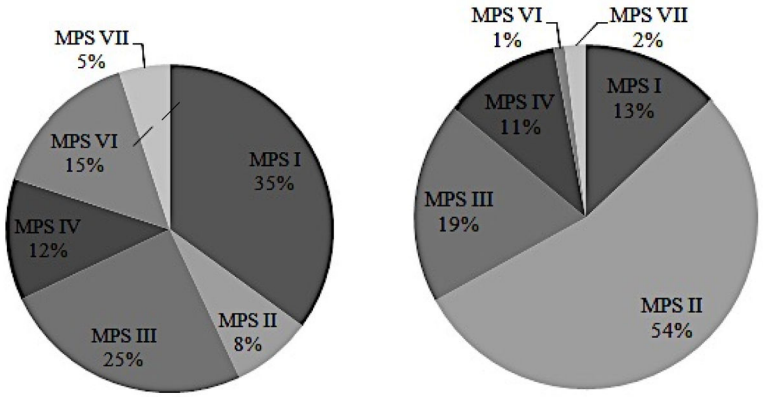


Figure 4.

Incidence of MPS II in Japan (left) and incidence of MPS in Portugal (right) (Reused from [161] permitted by the Japanese MPS Society)

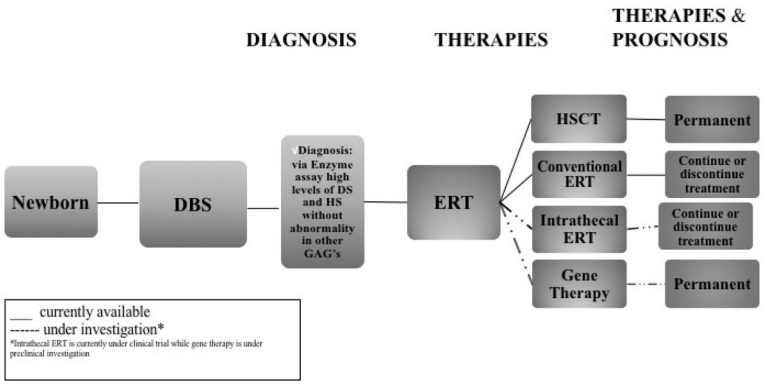


Figure 5.

Progression of disease from diagnosis via DBS to therapies both currently available and under investigation.