Mucopolysaccharidosis type I (MPS I): Assessment of disease severity, therapeutic options and early diagnosis

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General introduction
Chapter 1

GENERAL INTRODUCTION

History of mucopolysaccharidosis type I

Hurler syndrome, later named mucopolysaccharidosis type I or MPS I, was described for the first time in 1919 by the German pediatrician Gertrud Hurler, who reported on two patients who displayed an unusual combination of congenital abnormalities, including corneal clouding, skull deformities and other skeletal defects, disproportionate dwarfism strongly resembling that of hypothyroidism, and other features such as mental defect and inguinal and umbilical hernia [1]. In 1936, Ellis and co-workers introduced the name ‘gargoylism’ because of the resemblance of the gross features with the gargoyles of the Gothic architecture [2]. Soon after, the name dysostosis multiplex of the Hurler-type was proposed for the bone changes in MPS I, also causing the facial features, and considered to be a more suitable name [3].

Hurler syndrome was initially considered a lipid storage disease, based on microscopic findings in post-mortem material [4]. In 1952, Brante identified the storage material as a mucopolysaccharide, and proposed the term mucopolysaccharidosis [5]. The chemical nature of the abnormal storage material became clear when Dorfman and Lorincz isolated large quantities of heparan sulfate and dermatan sulfate from the urine of a Hurler patient [6]. Subsequently, the relationship between the excretion of these substances to the storage material in tissues was confirmed by Meyer and co-workers [7,8] and Brown [9]. In the decade following these reports, the general concept of ‘inborn lysosomal diseases’ was formulated by Hers et al., based on their studies on Pompe’s disease [10]. As predicted by this concept, ultra-structural studies of hepatocytes of Hurler patients disclosed enlarged lysosomes (Figure 1) [11]. Matalon and Dorfman suggested that the mucopolysaccharidoses could result from an excessive biosynthesis of mucopolysaccharides [12]. In parallel, interest was paid to the measurement of lysosomal hydrolases involved in the breakdown of these macromolecules. That Hurler syndrome (mucopolysaccharidosis type I, MPS I) is caused by a profound deficiency of the lysosomal hydrolase α-L-iduronidase (IDUA) was first suggested by Matalon and co-workers in 1971, based on studies in cultured fibroblasts [13]. Additional studies confirmed these data [14,15]. The concept of storage of heparan sulfate and dermatan sulfate in MPS I was understood since both these mucopolysaccharides contain iduronic acid. It was also demonstrated that the same lack of IDUA-activity was found in the Scheie syndrome, first described in 1962 [16], and up to then classified as MPS V, and that types I and V thus were allelic disorders [17]. In addition, the classification Hurler-Scheie syndrome was used to describe a clinical phenotype that is intermediate between the Hurler and Scheie syndromes. In 1990, Scott and co-workers reported the localization of the IDUA gene on chromosome 4p.16.3 [18].

The feasibility of hematopoietic stem cell transplantation (HSCT) in the treatment of Hurler patients was first investigated in animal studies. Subsequently, extensive clinical
experience following the first report of Hobbs and co-workers in 1981 confirmed its efficacy on the central nervous system (CNS) in humans [19]. HSCT has become the treatment of choice in the severely affected group of patients, being the only treatment modality that can preserve cognition if performed at an early stage [20].

Following the development and subsequent highly successful clinical introduction of intravenous supplementation of recombinant glucocerebrosidase, which was genetically modified to improve cellular and lysosomal uptake for Gaucher disease (another lysosomal storage disorder, LSD), studies on the feasibility of this approach in MPS I were initiated [21-25]. The first clinical study was conducted in the late nineties of the previous century [26]. Based on the results obtained, recombinant IDUA (laronidase, Aldurazyme®) was granted marketing approval in 2003. Recombinant IDUA is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of MPS I to treat the non-neurological manifestations of the disease. Subsequent studies showed that intravenous therapy with laronidase may significantly ameliorate several of the somatic disease symptoms [27-29].

Prevalence, pathophysiology and genetics

MPS I (MIM #252800) is an autosomal recessive inborn error of metabolism caused by a deficiency of the lysosomal enzyme IDUA (EC 3.2.1.76) [30]. Its prevalence is estimated at around 4 per 100,000 live births, but varies widely between different regions [31,32]. Highest birth rates were reported for the Irish Republic (1:26,000) [33].

IDUA is involved in the catabolism of the glycosaminoglycans (GAGs) heparan sulfate and dermatan sulfate, and hydrolyzes terminal α-L-iduronic acid residues of these GAGs [30]. Normally, IDUA is synthesized in the rough endoplasmatic reticulum (RER), and then transferred to the Golgi complex. In the Golgi complex, the enzyme is modified by the addition of a mannose 6-phosphate marker, making IDUA recognizable for receptors that direct their transfer to lysosomes. In addition, IDUA may be transported from the extracellular environment to lysosomes through receptor-mediated endocytosis [34].

GAGs are the carbohydrate moiety of proteoglycans, gel-forming components of the extra-cellular matrix. One of the major roles of proteoglycans is to provide structural support to tissues, especially cartilage and connective tissues, but proteoglycans are also found in organs such as the liver, brain, cornea and kidney. Many of the GAGs play an essential active role in tissue and cellular biology. Dermatan sulfate is mainly found in skin, blood vessels, tendon and heart valves. Heparan sulfate is found primarily on cell surfaces, and plays an important role in cellular signaling. GAGs are eventually recycled by uptake in the lysosomes followed by degradation of the GAGs [35]. Historically, it was believed that the accumulation of undegraded GAG fragments in the lysosomes of patients with IDUA-deficiency directly led to the disease symptoms associated with MPS I. However, various studies into the pathophysiology of MPSs have shown that this process is much more complex, and appears to involve diverse secondary biochemical and physiological processes, thereby influencing intracellular targeting pathways, altering activity of other lysosomal enzymes and affecting extracellular signal transduction and inflammation [36].

The IDUA-gene is situated on chromosome 4p16.3 and contains 14 exones [18,37]. To date, more than 150 mutations, including missense, nonsense, and splice site mutations, as well as deletions and insertions, have been reported (HGMD® Professional release 2012.1; http://www.hgmd.cf.ac.uk/). Genotype-phenotype correlations are still limited in MPS I. It is thought that mutations that prevent the production of any functional enzyme will lead to a severe phenotype, whereas the presence of at least one mutation that allows for some residual enzyme activity will lead to a milder phenotype [30,38]. Two common nonsense mutations (p.W402X and p.Q70X) that invariably result in the severe, Hurler phenotype if present in homozygous or compound heterozygous combination have been reported [38-40], and few mutations have been reported which may predict the attenuated Scheie phenotype [39]. However, newly diagnosed MPS I patients often reveal at least one ‘private’ mutation, hampering prediction of the clinical phenotype based on the genotype. In addition, several polymorphisms, likely to modify the MPS I phenotype when present with
disease-causing mutations, have been reported [41]. Central collection of MPS I genotype and phenotype data in the MPS I Registry (www.MPSIRegistry.com), an ongoing, global, observational database that tracks the natural history and outcomes of patients with MPS I, has led to further understanding of genotype-phenotype correlations in MPS I over the recent years [42]. To date, over 1,000 patients have been enrolled in the Registry.

Clinical signs and symptoms and disease phenotypes

The MPS I phenotype has originally been divided into three distinct categories on the basis of clinical signs and symptoms: the Hurler (MPS I-H; severe), Scheie (MPS I-S; mild) and Hurler-Scheie (MPS I-H/S; intermediate) syndromes [30]. All clinical phenotypes are characterized by multi-system involvement and progressive organ dysfunction. The clinical heterogeneity seen in MPS I manifests itself primarily as variability in the age of symptom onset as well as the rate of disease progression. Nowadays, MPS I is recognized as a disease continuum, ranging from severe (MPS I-H) to attenuated (MPS I-H/S and MPS I-S) [20].

The MPS I-H phenotype, representing the severe end of the spectrum, is the best described phenotype. MPS I-H patients often appear normal at birth, but first signs and symptoms will appear in the first few months of life. A combination of symptoms, generally consisting of recurrent upper respiratory tract infections, umbilical and inguinal hernia, coarsening of facial features, growth delay, skeletal deformities (joint contractures, gibbus/kyphosis), hepatosplenomegaly and enlarged tongue leads to a relatively early diagnosis at a median age of 9 months [20,30,43,44]. Cardiac disease (including cardiomyopathy, valvular insufficiency and coronary artery involvement) can occur early in the disease course, and may lead to heart failure at young age [45]. Some degree of (often combined conductive and perceptive) hearing loss is common. Developmental delay is usually apparent before 24 months of age. Hydrocephalus is a common finding, resulting in increased head circumference [20,30,43]. A potentially life-threatening complication is spinal cord compression, which is likely caused by a combination of bone disease, cervical instability, spinal disc disease, ligamentous thickening and spinal meningeal thickening [20,46,47]. If MPS I-H patients are left untreated, the maximum obtainable developmental age is 2 to 4 years, followed by progressive deterioration. Untreated children with MPS I-H usually die during the second decade of life, as a result of progressive neurologic disease and cardiorespiratory failure [20,30].

The MPS I-S phenotype is characterized by a much later onset of clinical disease and a slower disease progression. Symptom onset is usually around the age of 5, and consists mainly of skeletal problems (joint contractures, especially of the fingers and hands). Other common features include corneal clouding, cardiac valve abnormalities, carpal tunnel syndrome and hernia. Recurrent upper respiratory tract infections, obstructive sleep apnea syndrome, facial dysmorphism, growth problems, hearing deficits and hepatomegaly also have been reported. Mental development is normal, but a delay of gross motor mile
stones due to the skeletal problems is a common observation. Hydrocephalus may occur, but is more common in severely affected MPS I patients [20,30,43,48,49]. As in MPS I-H, cervical cord compression is a potentially life-threatening complication. The generally milder symptoms often cause a delay in diagnosis. The diagnosis in this phenotype has been reported to be established at a median age of 9 years [44]. Life expectancy can be normal, however, MPS I-S patients typically have significant disabilities. Therefore, the term ‘attenuated’ instead of ‘mild’ seems to be more appropriate [20].

MPS I-H/S patients have a clinical phenotype that is intermediate between MPS I-H and MPS I-S. Symptom onset is earlier than in MPS I-S, with a median age at diagnosis of around 4 years of age [44]. Skeletal disease, corneal clouding, deafness and valvular heart disease can cause significant disabilities in teenage years. Severely affected MPS I-H/S patients can exhibit intellectual dysfunction [30,49]. As in the other phenotypic subgroups, cervical cord compression is a potentially life-threatening complication. Many patients survive into adulthood, but life expectancy may be reduced, with death occurring due to cardiovascular and respiratory complications [20,30].

Diagnostic approach

Due to the often non-specific presenting signs and symptoms in MPS I and the rarity of the disease, a diagnostic delay is common, with a median age at onset of symptoms to diagnosis ranging from several months for MPS I-H patients to several years for MPS I-S patients. Early diagnosis and accurate delineation into the different phenotypes at diagnosis are indispensible for optimizing treatment decisions and improving outcomes. Unfortunately, median age at diagnosis has not decreased over the recent years, despite the available treatment options [44].

Undegraded GAGs are excreted in large quantities in the urine of untreated MPS I patients, and measurement of total urinary GAG (uGAG) levels is therefore usually the first step in the diagnostic process. This rapid but non-specific method is based on semi-quantification of glycosaminoglycan-dye complexes in solution [50]. Definite diagnosis is established by measurement of IDUA activity in leucocytes or fibroblasts, and subsequent analysis of the IDUA gene [30]. Excess urinary GAG excretion and deficient IDUA activity in leukocytes are seen in patients with all phenotypes, but supposedly do not reliably predict disease severity in all patients. In addition, as discussed previously, genotype-phenotype correlations are still poor. As there is no validated clinical severity scale for MPS I available, measuring disease severity based on the clinical signs and symptoms may be difficult. Therefore, other methods to reliably assess disease severity are warranted.

Over recent years, several studies on MPS I biomarkers have been performed. This resulted in the detection of several promising primary (representing the primary storage material) and secondary (reflective of altered cellular and tissue homeostasis) biomarkers, such as the serum heparin cofactor II-thrombin complex (HCT-II) [51-53], plasma and urinary
heparan sulfate and dermatan sulfate derived disaccharides [54], and the urinary dermatan sulfate:chondroitin sulfate ratio [53,55]. However, the true value of these biomarkers for differentiating between phenotypes and for detecting treatment efficacy has not been established.

Finally, a number of studies have focused on the optimal approach for newborn screening (NBS) in MPS I [56-59], enabling diagnosis at an early, often presymptomatic, stage of the disease. In this respect, ethical issues are being raised, such as the possible drawbacks of identification of novel or adult-onset variants [60-62]. These questions still remain unanswered. However, several NBS pilot programs that include MPS I screening have recently been initiated [63-65]. With the prospects of NBS for MPS I, the availability of reliable tools to predict the clinical phenotype in newly diagnosed MPS I patients becomes even more important.

Treatment and clinical management

Two treatment options, hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT), have become available for MPS I patients over the last three decades. The rationale of both treatment options is to provide the patient with active IDUA, either through intravenous infusion or through synthesis and subsequent release of the enzyme by transplanted stem cells, thereby increasing the catabolism of accumulated GAGs and preventing further accumulation. Although HSCT and ERT can significantly ameliorate the course of the disease, both treatment modalities are not a complete cure for the disease.

After the first successful bone marrow transplantation in 1980 [19], several hundreds of MPS I-H patients have been transplanted. Umbilical cord blood derived stem cells are increasingly used as graft source [66]. Successful HSCT results in increased life expectancy and improvement of clinical parameters, such as respiratory and cardiac function. HSCT is currently the only treatment that can prevent or halt the MPS I CNS-manifestations [67-70]. Therefore, HSCT is considered the treatment of choice in MPS I-H patients [20,66,71]. The best outcomes have been reported in those patients who had a HSCT under the age of 2 with a developmental quotient (DQ) > 70 [67]. To achieve maximum long-term benefits, it is therefore important to perform the HSCT early in the disease course, if possible before the onset of irreversible signs and symptoms (Figure 5). Due to new protocols for chemotherapeutic conditioning and stem cell source, transplant-related mortality, although still considerable, has declined significantly, with current survival and engraftment rates exceeding 90% [66]. Musculoskeletal manifestations unfortunately appear to respond poorly to HSCT, and many patients still have progressive skeletal disease, often requiring multiple orthopedic interventions in the years following HSCT [69,70].

In 2003, the recombinant form of human IDUA (laronidase, Aldurazyme®) received marketing approval in the US and the European Union. Laronidase is indicated for long-term
ERT in MPS I patients in order to treat the non-neurological manifestations of the disease. Laronidase is safe and effective across a wide range of ages (young children to adults) and disease severity (severe to attenuated), and is labeled for weekly infusion. Improvement of several clinically relevant outcome parameters, such as pulmonary function and the distance walked in six minutes, was shown in the pivotal clinical trials [27,28]. In addition, significant reductions in liver volume and urinary GAG excretion and improvements in joint range of motion, growth patterns and cardiac disease were reported [26-29,72]. A 26-week dose optimization study showed similar efficacy and the lowest rate of adverse events and infusion-associated reactions in the group of patients receiving the approved dose of 0.58 mg/kg (100 IU/kg), when compared to alternative regimens [73]. However, all studies are limited by the small number of patients studied, and by the relatively short term of the follow-up.

It is generally considered that early initiation of ERT, prior to the onset of significant disease manifestations, favors clinical outcome. This is supported by a case history on siblings started on ERT at different ages [74]. Early diagnosis and start of ERT seem therefore essential to optimize outcome. One major disadvantage of intravenous laronidase is its inability to prevent cognitive decline or prevent and improve other CNS symptoms in MPS I-H patients, as the enzyme is not able to cross the blood-brain barrier in sufficient quantities. Other challenges are the formation of antibodies which may interfere with efficacy and uptake of the infused enzyme [75], and disease manifestations in regions were the infused enzyme does not penetrate in sufficient quantity, such as bone, heart valves and cornea.

ERT is indicated as treatment in those patients not qualifying for HSCT, as it may improve quality of life and relieve pain. A limited number of trials have shown that the use of ERT prior to HSCT is safe, and has the potential to improve the clinical condition of patients before the HSCT procedure, which may improve HSCT-related morbidity and mortality [76-79].

Given the complex and multisystemic nature of this disorder, regular multidisciplinary follow-up of MPS I patients is important, and treatment of systemic complications (e.g. hernia repair surgery or hearing aids) should be considered in addition to the disease-specific treatments [20,71]. A recommended schedule of assessments for all MPS I patients was published by Muenzer et al. [20].

The clinical heterogeneity in MPS I can present a challenge for optimal treatment decisions in individual patients. To improve outcome and quality of life, better disease recognition and up-to-date management and treatment guidelines are indispensable. Currently, new therapeutic options are being investigated, including intrathecal ERT, small-molecule therapies and gene therapy [71].
Outline of the thesis

Since its first description in 1919, much progress has been made in the understanding of the epidemiology, pathogenesis and natural history of MPS I. Considerable improvement in the outlook for MPS I patients was achieved during the last three decades, with the emergence of the disease-modifying treatment options. To optimize outcomes in MPS I patients, timely recognition of presenting symptoms and early diagnosis of MPS I and its different phenotypes are indispensable. In addition, continuous efforts should be made to keep disease management and treatment guidelines up-to-date. This thesis focuses on several of these aspects.

In an ultra-orphan disorder such as MPS I, advances in management and treatment strategies can only be obtained through international collaboration between expert centers. The results of a European, multi-disciplinary consensus procedure, mainly focusing on the indication and optimal timing of the different MPS I treatment options, are described in chapter 2. To be able to better define the MPS I phenotype at diagnosis, and thus assist in decision making on the optimal treatment strategy, the availability of a validated severity scale based on clinical signs and symptoms would be of high value, since clear criteria to delineate the different phenotypes are currently lacking. In chapter 3, the results of an international, collaborative study, aimed at designing a reliable and validated severity scale for phenotypically classifying newly diagnosed MPS I patients are reported.

NBS for MPS I may facilitate early diagnosis and start of treatment. However, several ethical issues need to be addressed. In chapter 4, we present the results of an interview-based study, exploring experiences of MPS I patients and their parents with diagnostic timing, and revealing five important themes that can fuel the ethical discussion on expanding NBS programs for MPS I.

The availability of validated biomarkers would provide physicians with a useful tool to facilitate diagnosis and monitor treatment efficacy. Therefore, we extensively studied the potential value of the primary storage substrates in MPS I, heparan sulfate and dermatan sulfate, as biomarkers for monitoring treatment response and disease severity. In chapter 5, levels of heparan and dermatan sulfate derived disaccharides in MPS I patients after long-term ERT were measured in relation to the timing of ERT, and compared with the ‘gold standard’ (total uGAGs as measured by the DMB-test).

Defining the MPS I phenotype in presymptomatic newborn patients is complicated by the fact that genotype-phenotype correlations are still limited. Chapter 6 reports on a study focusing on the potential diagnostic value of levels of heparan sulfate and dermatan sulfate derived disaccharides in dried blood spots (DBS) of newborn MPS I patients. Furthermore, the results of a study, in which attempts are made to relate levels of heparan and dermatan sulfate derived disaccharides and non-reducing end disaccharides in plasma and urine at the time of clinical diagnosis, prior to initiation of ERT, with the clinical phenotype are described in chapter 7.
Finally, **chapter 8** focuses on future prospects in the management and diagnosis of MPS I, and **chapter 9** summarizes this thesis.

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**Figure 5.** Treatment algorithm for patients with a diagnosis of MPS I. Muenzer J, Wraith JE, Clarke LA. Mucopolysaccharidosis I: management and treatment guidelines. Pediatrics 2009;123:19-29.
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