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Chapter 1

General introduction

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Diagnosis, classification and treatment of mucopolysaccharidosis type I

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INTRODUCTION AND HISTORY OF MPS I

This chapter aims to provide a concise overview of the history, pathophysiology, clinical presentation, classification and treatment of mucopolysaccharidosis type I (MPS I).

In 1919 the first cases of MPS I appeared in the medical literature, when a German physician named Getrud Hurler described a boy and a girl with “multiple conditions, mainly affecting the skeletal system” [1]. Soon after this initial report, more and more cases were described of what was at the time known as “polydystrophy-Hurler type” or “gargoylism”, a term derived from the typical facies of these patients [2]. In the early 1930s the term “dysostosis multiplex” was coined to describe the constellation of skeletal abnormalities, that are one of the hallmarks of MPS I. It wasn’t until chemical studies in the 1950s revealed storage of sulphated mucopolysaccharides [3] that Hurler syndrome and the related disorders became known as the mucopolysaccharidoses (MPSs, Table 1). Following work of De Duve and Hers, the MPSs were recognized to be lysosomal storage disorders, where the storage was a result of insufficient degradation of mucopolysaccharides in a specific organelle of the cell; the lysosome. When co-culturing fibroblasts of MPS I and MPS II patients, the group of Elizabeth Neufeld observed that storage in these co-cultured cells resolved and they hypothesized this was the result of “cross-correction” [4]. This discovery eventually led to the identification of α-L-iduronidase (IDUA) as the deficient enzyme in MPS I and triggered the search for therapeutic options, finally leading to the current treatment options of hematopoietic stem cell transplantation and enzyme replacement therapy. Patients with a much more attenuated phenotype that had thus far been classified as MPS V or Scheie syndrome (after Harold Scheie, the ophthalmologist who first described these patients) appeared to be biochemically identical to MPS I and this disorder was renamed MPS I-Scheie (MPS I-S) as opposed to MPS I-Hurler (MPS I-H) [5].

PATHOPHYSIOLOGY

In the MPSs, loss of enzyme activities required for lysosomal degradation of mucopolysaccharides, also known as glycosaminoglycans, or GAGs, leads to intra- and extralysosomal accumulation of incompletely degraded material. GAGs are complex
General introduction

Chapter 1

This chapter aims to provide a concise overview of the history, pathophysiology, clinical presentation, classification and treatment of mucopolysaccharidosis type I (MPS I). In 1919 the first cases of MPS I appeared in the medical literature, when a German physician named Getrud Schuler described a boy and a girl with “multiple conditions, mainly affecting the skeletal system” [1]. Soon after this initial report, more and more cases were described of what was at the time known as “polydystrophy-Schuler type” or “gargoylism”, a term derived from the typical facies of these patients [2]. In the early 1930s the term “dysostosis multiplex” was coined to describe the constellation of skeletal abnormalities, that are one of the hallmarks of MPS I. It wasn’t until chemical studies in the 1950s revealed storage of sulphated mucopolysaccharides [3] that Schuler syndrome and the related disorders became known as the mucopolysaccharidoses (MPSs, Table 1). Following work of the Schus and others, the MPSs were recognized to be lysosomal storage disorders, where the storage was a result of insufficient degradation of mucopolysaccharides in a specific organelle of the cell; the lysosome. When co-culturing fibroblasts of MPS I and MPS II patients, the group of Elizabeth Eufeld observed that storage in these co-cultured cells resolved and they hypothesized this was the result of “cross-correction” [4]. This discovery eventually led to the identification of α-L-iduronidase (IDUA) as the deficient enzyme in MPS I and triggered the search for therapeutic options, finally leading to the current treatment options of hematopoietic stem cell transplantation and enzyme replacement therapy. Patients with a much more attenuated phenotype that had thus far been classified as MPS II or Scheie syndrome (after Harold Scheie, the ophthalmologist who first described these patients) appeared to be biochemically identical to MPS I and this disorder was renamed MPS I-Scheie (MPS I-S) as opposed to MPS I-Schuler (MPS I-S) [5].

In the MPSs, loss of enzyme activities required for lysosomal degradation of mucopolysaccharides, also known as glycosaminoglycans, or GAGs, leads to intra- and extralysosomal accumulation of incompletely degraded material. GAGs are complex carbohydrates that can be found in various quantities on cell surfaces and in the extracellular matrix in all tissues throughout the body. Virtually all organ systems may therefore be involved in MPSs. In MPS I the deficiency of IDUA results in impaired degradation of the GAGs heparan sulfate (HS) and dermatan sulfate (DS). The key mechanisms contributing to the clinical pathophysiology in MPS I are the following. First, intracellular and extracellular accumulation of GAGs may directly lead to enlargement of various organs. Hepatomegaly for example, is a common finding in untreated MPS I patients. Also, the leptomeninges may become thickened, contributing to a narrowed spinal

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canal, with a risk of spinal cord compression, and to reduced cerebrospinal fluid reabsorption, which may lead to high pressure hydrocephalus [6-8]. GAG depositions directly lead to thickened cardiac valves [9], to thickened transverse carpal ligaments, resulting in median nerve compression [10,11], and to corneal clouding [12].

Second, next to the direct effects of accumulating HS and DS, several complex and not fully elucidated downstream effects play a pivotal role in the pathophysiology of MPSs. One of these downstream effects is secondary accumulation of gangliosides (GM2 and GM3) in affected neurons which is related to disease progression [13,14]. Intra-lysosomal storage of GAGs in combination with altered pH may lead to binding and partial inactivation of lysosomal enzymes and it is hypothesized that peroxisomal dysfunction may contribute to ganglioside accumulation [15–17].

Another downstream effect that may occur in lysosomal storage diseases is impaired autophagy [14,18,19]. Autophagy is an essential degradation pathway, through which the cell regulates turnover of proteins and organelles. Autophagy serves as a pro-survival mechanism when cells are damaged and in case of nutrient deprivation autophagy can provide a source of macromolecules from which the cell can generate ATP. Suppressed autophagy leads to cell stress and death, especially in post mitotic neurons and chondrocytes [20–22], and may thus significantly contribute to the clinical pathology in patients with MPSs.

Furthermore, extracellular GAGs play a key role in many biological processes including cell-cell signaling. This is achieved through binding of various protein partners such as chemokines, cytokines and growth factors. DS enhances anti-coagulation properties of heparin cofactor II, while HS mediates cell adhesion, regulation of cellular growth and cell surface binding of proteins [23–25]. Their extracellular accumulation may thus lead to a disturbance of homeostasis. HS for instance acts as a co-receptor of the FGF receptor, facilitating efficient binding and signaling of FGF2. The excess HS in MPS leads to impaired proliferation and high rates of apoptosis [26].

Finally, inflammatory processes have been observed in various tissues of patients and in animal models of MPS I and VI and is generally regarded as an important factor in the pathology in the central nervous system (CNS), bones and joints [14,27–30]. Extracellular
GAG-fragments lead to non-physiologic activation of signal transduction receptors, such as TLR4, and prompt an immune response [31].

**CLINICAL PRESENTATION AND DIAGNOSIS**

**CLINICAL PRESENTATION**

MPS I is a multisystem disease and the presenting signs and symptoms are highly variable. Patients with the severe Hurler syndrome may appear normal at birth, although a thoracolumbar kyphosis and inguinal or umbilical herniae may already be present [32,33]. Most of the clinical signs and symptoms arise within the first few months of life and consist of a combination of recurrent upper respiratory tract infections, inguinal or umbilical herniae, cardiomyopathy, valvular dysfunction, hydrocephalus, hepatosplenomegaly and skeletal abnormalities. Untreated Hurler patients develop course facial features in the first year of life, characterized by frontal bossing, a depressed nasal bridge, full lips and macroglossia accompanied by corneal clouding [34–36] and the median age of diagnosis of MPS I-H is 0.8 years [37]. Patients with Hurler syndrome may be unusually large in infancy, only to be severely stunted afterwards and final heights may vary from average to minus five standard deviations [38–41]. The skeletal deformities are the result of defective endochondral and membranous growth, collectively known as dysostosis multiplex. Typical features are hip dysplasia, thoracolumbar kyphosis secondary to vertebral body hypoplasia, bullet shaped metacarpals, stunted growth of the long bones and broad oar shaped ribs (figure 1A-D) [42–44]. The presence of a thoracolumbar kyphosis and abnormally shaped vertebrae as well as ligamentous and dural hyperplasia contribute to a risk of developing compression myelopathy [40,45]. Other complications include carpal tunnel syndrome, trigger fingers, tendon shortening (mostly of the Achilles tendon) and early arthrosis, secondary to dysostosis multiplex. Untreated Hurler patients will inevitably develop severe cognitive decline and death ensues in adolescence [45,46].

Patients with the intermediate Hurler-Scheie phenotype may display many of the same signs and symptoms as Hurler patients. However, the clinical symptoms are generally less severe and the disease progression is slower. Median age at diagnosis is 3.8-4 years [37,47] and
Figure 1. Dysosotosis multiplex.

A Anterior beaking of vertebral bodies and gibbus deformity.
B Thickened clavicles and broad, oar-shaped ribs.
C Acetabular dysplasia, flattened femoral heads, osteoarthritis.
D Bullet-shaped metacarpals and phalanges.

Survival into adulthood is common [37,46]. Symptoms at clinical presentation often consist of stiff joints, delayed motor milestones or recurrent ear, nose and throat (ENT) symptoms, rather than the severe cardiac and neurological complications observed in patients with MPS I-H. The course of the disease is further dominated by the musculoskeletal manifestations, with progressive arthropathy reported in up to 86% of patients [47]. MPS I-H/S patients may have CNS involvement with developmental delay [47]. However, the prevalence of cognitive impairment in MPS I-H/S has not been studied in any large cohort.

In the most attenuated MPS I patients, MPS I-S, there is no CNS involvement, although cervical myelopathy due to cord compression in a narrowed cervical spinal canal may occur [48]. Presenting symptoms are joint stiffness, corneal clouding, recurrent ear infections and cardiac valve disease. The diagnosis is made at a median age of 7-9.4 years, and survival is near normal [37,47].
Biochemical and Molecular Diagnosis

Laboratory testing to confirm a diagnosis of MPS I is usually a step-wise procedure. Traditionally, the first step is an analysis of total excretion of GAGs in the urine by a dimethylmethylene blue binding assay followed by two-dimensional electrophoresis [49,50]. After the initial screening, and confirmation of increased GAG levels, final diagnosis is made by analysis of enzyme activity. This is usually done in leucocytes or cultured skin fibroblasts. Mutation analysis is, if feasible, the final step in diagnosis. Over 200 mutations of the IDUA gene have been reported, and compound heterozygosity is a frequent finding [51–54]. Determining the underlying molecular defect may be used for carrier screening within families and phenotypic characterization of the patient.

Newborn Screening

An alternative approach is detection through newborn screening (NBS) programs and several methods have been reported, including enzyme activity assays and enzymatic digestion of GAGs followed by disaccharide analysis via tandem mass spectrometry [55–60]. There are two major advantages of NBS over detection on clinical signs and symptoms. First, early detection by NBS allows for early initiation of disease modifying treatment which is essential for optimal treatment efficacy [61–65]. In addition, NBS will significantly shorten the often long and burdensome diagnostic odyssey in MPS I [37,66]. NBS for MPS I has recently been introduced in Taiwan and is considered for nationwide screening in a number of other countries, including the US and the Netherlands [57,60,67,68]. Some drawbacks and challenges remain however. NBS almost invariably leads to the identification of individuals with low enzyme activity with previously unreported genetic variants of unknown significance and identification of more cases than expected on historical grounds. Indeed, in a pilot study on NBS for MPS I in over 100.000 newborns 3 patients were identified [57], which resulted in a prevalence of MPS I three fold greater than based on clinical diagnosis. The interpretation and clinical significance of some of these findings need careful evaluation. Also, decisions on treatment initiation can be complicated in pre-symptomatic patients and a robust phenotypic prediction is essential.
CLASSIFICATION

Traditionally, MPS I is classified into one of three phenotypes: the severe Hurler syndrome, intermediate Hurler-Scheie and attenuated Scheie syndrome. However, it is now recognized that the disease presents with a continuous spectrum of severity.

Although some form of phenotypic classification is warranted in all patients, no precisely defined, consensus-based delineations of each phenotype are available. In clinical practice, classification is often based on age of onset of symptoms, signs of cognitive impairment and overall impression of severity. A summary of criteria reported by Venturi et al. [52] represent the most common classification. They define the phenotypes as: MPS I-Hurler (severe), when onset of symptoms are before 12 months of age, and, in the absence of disease modifying therapy, survival is < 10 years and mental retardation manifests before the age of 3 years; MPS I-Hurler/Scheie (intermediate), when onset of symptoms is between 1 and 6 years, survival is variable, and mental retardation is absent or mild but not present before 3 years of age and MPS I-Scheie (mild), when onset of symptoms are after 5 years of age, survival is normal, and mental retardation is absent.

One major drawback of a classification based on clinical symptoms is that it can only be applied after disease manifestations have occurred and this classification cannot be used in pre-symptomatic settings. When a diagnosis is made through newborn screening, assessment of disease severity is needed for prognosis and treatment allocation. Alternative strategies to categorize disease severity in MPS I patients have therefore been explored, such as classification by residual enzyme activity, by genotype or by quantification of storage compounds [54,69–71].

TREATMENT

DISEASE MODIFYING TREATMENTS

Two treatment modalities are currently available for MPS I, both aimed at correcting the enzyme deficiency: hematopoietic stem cell transplantation (HSCT) and enzyme replacement
therapy (ERT). Both approaches rely on the principle of cross-correction; cells have the capacity to take up extra-cellular enzyme by a mannose-6-phosphate receptor.

The beneficial effect of HSCT can be attributed to the enzyme released by circulating leukocytes as well as macrophages that infiltrate peripheral tissues [72]. In addition, the changes in cellular microenvironment may lead to immune modulation and the mitigation of inflammation [73]. The first successful bone marrow transplantation in a Hurler patient was reported by Hobbs et al in 1980 [74]. Since then, more than 500 patients with MPS I have received a stem cell transplantation [37,75].

A unique benefit of HSCT is that it may treat the CNS and if HSCT is performed before the clinical onset of CNS disease, neurocognitive decline can be prevented, at least to a significant extent [40,45,76–79]. Other reported beneficial effects include reduction of hepatomegaly, improved hearing, improved cardiomyopathy, improved obstructive airway disease and variable attenuation of corneal clouding [40,76,80,81]. Linear growth is also positively affected, although final height generally remain well below minus two standard deviation of the normal population [39,40,76]. This is in concordance with the observation that other skeletal manifestations, such as hip dysplasia, kyphosis and genu valgum do not respond to HSCT and contribute significantly to the residual disease burden observed in transplanted patients [44,76,82,83].

HSCT is not the first choice of treatment for all patients, as it carries considerable risks of morbidity and mortality and requires a highly specialized medical setting. ERT by weekly infusion of recombinant IDUA is therefore the preferred treatment for patients who are not at risk for progressive mental retardation [84,85]. The first clinical trial with ERT was initiated in 1997, and over 500 patients have been treated since then, including Hurler patients in the peri-transplantation period [37,86].

Generally, the initial response to ERT consists of improved forced vital capacity, improved apnea-hypopnea index (AHI), a reduction of liver and spleen size, reduction of urinary GAGs and improved joint mobility [86–88]. Long-term follow up studies report a maintained biochemical response, stable lung capacity, reduction of hepatosplenomegaly and stable or improved AHI for up to 3,5 years of treatment [89]. The 6 minute walk test showed an initial improvement in all subjects, but this was only maintained in a subset of patients [89]. Pre-
existing left-ventricular hypertrophy resolved in most patients on initiation of ERT, but mitral and aortic valves remained thickened and in some patients showed disease progression [89–91]. Dysostosis multiplex generally does not respond to ERT, with the possible exception of very early treatment initiation [61,64,92].

RESIDUAL DISEASE AND SUPPORTIVE CARE

Despite the treatment options available for correcting the enzyme deficiency, patients with MPS I may still suffer from a significant disease burden. Facilitating supportive care is therefore essential and a multidisciplinary approach is warranted [84]. Regular follow up by ENT specialists, neurologist/neurosurgeons, ophthalmologists, orthopedic surgeons and cardiologists is necessary to diagnose, follow up and treat specific clinical problems. Additional supportive care from rehabilitation specialists, physiotherapists, occupational therapists and family support will be required for optimizing the health related quality of life.

Several of the residual disease manifestations will require surgical intervention and carry specific peri-operative risks [93,94]. The most prominent feature of residual disease in both HSCT as ERT treated patients is dysostosis multiplex [40,44,82,95,96]. Progressive hip dysplasia is seen in nearly all MPS I-H patients [44,76,82,83,97] and may lead to painful subluxation of the femoral head, early arthritis and limited mobility and this may require surgical intervention [40,82,98]. In up to 20% of MPS I patients, progressive thoraco-lumbar kyphosis, or gibbus deformation, requires fusion of the spine [99,100] as untreated kyphosis may lead to neurological compromise [101]. Dysostosis multiplex may also contribute to a narrowed spinal canal, which in combination with thickened meninges may lead to cord compression and myelopathy in both severe and attenuated patients, necessitating decompression surgery [48,95,102,103]. In some cases, this might be further complicated by atlanto-axial instability resulting from dens hypoplasia [102]. Other often reported orthopedic surgeries include valgus correction, tendon release for trigger fingers and carpal tunnel release [10,94]. Umbilical and inguinal herniae may require multiple repairs and in up to 14% of MPSI patients, cardiac valve replacement is indicated [94]. The most frequently performed procedures are ENT surgeries. These mostly consist of myringotomies with placement of grommets and adeno-/tonsillectomies as a majority of patients suffers from hearing loss and airway compromise [40,94,104]. Upper airway involvement may also lead
to sleep disordered breathing, requiring positive airway treatment and/or supplemental oxygen. In some cases, a tracheostomy is required to secure the airway [105].

The observed upper airway manifestations, as well as spinal cord compression, significantly complicate the anesthetic management of MPS I patients [106–108].

**Figure 2.** Residual disease manifestations in a transplanted MPS I-H patient.

A boy of 12 years old who received a successful HSCT at the age of 2 years, with macrocephaly, typical facial features of MPS I, depressed nasal bridge, macroglossia, abdominal distension, a small umbilical hernia, anterior pelvic tilt, short stature, dysplasia of the long bones, most prominent in the under arm, short broad hands and flexion contracture of the fingers (“claw hand”). The clinical course was further complicated by the development of obstructive sleep apnea and progressive cervical myelopathy. Severe hip dysplasia with luxation of the right hip necessitated a girdlestone procedure with removal of the femoral head on that side. Cervical decompression surgery was complicated by a high thoracic myelum infarction.
Chapter 1

This thesis focusses on several aspects related to the residual disease observed in MPS I patients despite the currently available treatment modalities.

Many of the disease manifestations in MPS I are irreversible, especially the skeletal dysplasia. Consequently, one of the key issues is prevention of irreversible tissue or organ damage or dysfunction. Although the rarity of the disease and the significant intra-individual variation are great challenges, early diagnosis and subsequent early start of disease modifying treatments will very likely improve the long term outcomes. In part I of this thesis we focus on improving the diagnosis and classification of MPS I, to facilitate early treatment. The feasibility of including MPS I in newborn screening programs is currently investigated in many countries in order to identify patients as early as possible. However, very early classification of disease severity and therefore treatment allocation, is complicated in presymptomatic patients. In chapter 2 we present an algorithm that allows phenotypic classification of exactly these patients, combining molecular, biochemical and clinical characteristics from the first four weeks of life. Despite its potential benefits, the implementation of newborn screening for MPS I in the near future might not be an option in many countries. As the currently used diagnostic methods for diagnosing MPSs have some shortcomings, new strategies are being explored. We provide an assay that can easily identify patients with all MPS subtypes and shows superior test performance in comparison with the conventional methods in chapter 3. This new method significantly reduces the number of false-negative test outcomes, and may therefore shorten the time to correct diagnosis.

In addition to the prevention of disease manifestations, thorough evaluation of currently available therapies is needed. Insight in mechanisms contributing to suboptimal treatment outcomes will facilitate potential improvements and this is addressed in part II of this thesis. As the accumulation of GAGs is the instigator of a complex pathophysiological cascade, suboptimal clearance may be correlated with a suboptimal clinical outcome. In chapter 4 we provide an extensive evaluation of metabolic correction in MPS I patients treated with ERT and correlate the biochemical response to antibody response to the infused enzyme. Furthermore, in chapter 5 we show that long term outcomes of sleep disordered breathing

Chapter 7

describes in detail the progression of radiological features of a large cohort of MPS I-1 patients who received an ERT. The best treatment options for patients currently suffering from this severe hip dysplasia is evaluated in an international Delphi consensus meeting that is described in chapter 8.

Finally, all findings are discussed and future perspectives are provided in chapter 9.
are correlated with substance clearance and immune response. Finally, in chapter 6 a potential modification of ERT by lysosomal encapsulation is evaluated in an MPS I mouse model.

While prevention of residual disease is still under investigation, a detailed understanding of the residual disease manifestations and of the implications for clinical practice are much needed. In part III we focus on hip dysplasia, as a hallmark sign of dysostosis multiplex in MPS I Hurler patients. We feel that understanding the natural history of this hip dysplasia will aid clinical decision making and, at the same time, will provide a reference for future therapies addressing this issue. Chapter 7 describes in detail the progression of radiological features of a large cohort of MPS I-H patients who received an HSCT. The best treatment options for patients currently suffering from this severe hip dysplasia is evaluated in an international Delphi consensus meeting that is described in chapter 8.

Finally, all findings are discussed and future perspectives are provided in chapter 9.
REFERENCE LIST


General introduction


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