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

de Ru, M.H.

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SUMMARY OF THE THESIS

Mucopolysaccharidosis type I (MPS I; MIM #252800) is a rare autosomal recessive inborn error of metabolism caused by a deficiency of the lysosomal enzyme IDUA (EC 3.2.1.76). The resulting defective catabolism and subsequent continuous accumulation of the glycosaminoglycans (GAGs) heparan sulfate and dermatan sulfate leads to progressive, multi-system disease. Its clinical spectrum ranges from the severe Hurler phenotype (MPS I-H) to the more attenuated phenotypes, Hurler-Scheie and Scheie (MPS I-H/S and MPS I-S). Disease modifying treatment options comprise of hematopoietic stem cell transplantation (HSCT) for the MPS I-H phenotype and enzyme replacement therapy (ERT) for the attenuated phenotypes. Indications, optimal timing, safety and efficacy of these treatment options are subject of continuous debate. Early diagnosis and start of treatment appears to be essential to optimize treatment outcomes. However, a diagnostic delay in MPS I is common and early delineation of the different phenotypes based on clinical signs and symptoms and on genotype often proves to be difficult. The identification of reliable biomarkers would provide the clinician with a tool to facilitate the evaluation of disease burden as well as an objective measure of treatment response. Implementation of newborn screening (NBS) for MPS I will facilitate earlier diagnosis and initiation of therapy. However, several relevant ethical issues need to be considered.

Chapter 2 presents the results of a modified Delphi procedure that was organized to reach consensus about the indication and optimal timing of the two available treatment options for MPS I. Eight European specialists for metabolic disorders and seven bone marrow transplant physicians, all with substantial expertise in MPS I, reached full agreement on important issues related to therapeutic choices, including the following: 1) The preferred treatment for patients with MPS I-H diagnosed before age 2.5 yrs is HSCT; 2) In individual patients with an intermediate phenotype HSCT may be considered if there is a suitable donor. However, there are no data on efficacy of HSCT in patients with this phenotype; 3) All MPS I patients including those who have not been transplanted or whose graft has failed may benefit significantly from ERT; 4) ERT should be started at diagnosis and may be of value in patients awaiting HSCT. This consensus document constitutes an important step towards an international, collaborative approach on MPS I.

In chapter 3, the results of a consensus procedure, aimed to develop a numerical severity scale for classifying different MPS I phenotypes at diagnosis based on clinical signs and symptoms, are described. Sixteen international MPS I experts participated in this process. Full consensus was reached on six key clinical items for assessing severity at diagnosis: age of onset of signs and symptoms, developmental delay, joint stiffness/arthropathy/contractures, kyphosis, cardiomyopathy and large head/frontal bossing. However, despite considerable effort in analyzing all data, a reliable numerical scale could not be
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constructed. This was due to the highly variable expert opinion on phenotypic severity at diagnosis, which was considered to be the ‘gold standard’. This emphasizes the need for validated biomarkers and improved genotype-phenotype correlations in order to guide phenotypic severity assessments at diagnosis.

Newborn screening (NBS) techniques have been developed for several lysosomal storage disorders (LSDs), including MPS I. As expansion of NBS programs raises complex ethical issues, we performed an interview study (chapter 4) in order to explore the experiences of MPS I patients and their parents with the timings of their diagnoses. The goal of this study was to fuel this ethical discussion about NBS for MPS I. A qualitative research approach was used, consisting of 17 interviews with the parents of patients with all MPS I phenotypes and with patients with attenuated forms of MPS I. Five important themes, focusing on the experienced disadvantages of delayed diagnosis and the advantages and disadvantages of a hypothetical earlier diagnosis, were identified in our group of participants: 1) delayed diagnosis causing parental frustration; 2) delayed diagnosis causing patient frustration; 3) early diagnosis enabling reproductive decision-making; 4) early diagnosis enabling focusing on the diagnosis; 5) early diagnosis enabling timely initiation of treatment. These five themes support an early diagnosis in MPS I, and are highly relevant to the ethical discussion on expanding NBS programs for MPS I.

In chapter 5, the results of a study on the concentrations of disaccharides derived from heparan sulfate and dermatan sulfate, the primary storage substrates in MPS I, in both urine and plasma and the total urinary GAG (uGAG) levels, at different time points relative to the infusion of ERT, are presented. All seven included patients had been treated with ERT for more than 2.5 years. We show that, despite a very strong decrease after the initiation of ERT, the concentrations of urinary heparan and dermatan sulfate derived disaccharides (HS and DS, respectively) were still significantly elevated in all MPS I patients and plasma DS levels were still significantly elevated in all but one patient. In contrast, total uGAGs excretion, which is currently the most frequently used biomarker in MPS I, was normal in the large majority of these patients. We therefore conclude that plasma and urinary HS and DS are more sensitive biomarkers than total uGAG levels for monitoring the biochemical treatment efficacy of ERT. In addition, we were able to show that the timing of sample collection with respect to the ERT infusion is not relevant at the current dose of 100 IU/kg once weekly. The observed lack of full (biochemical) efficacy may be related to the labeled dose and, in some patients, to the generation of antibodies against the recombinant enzyme.

The aim of the study presented in chapter 6 was to determine levels of HS and DS in dried blood spots (DBS), and to investigate its ability to reliably separate newborn patients from controls and heterozygotes. Newborn DBS of 11 MPS I, 6 MPS III patients, with
phenotypes ranging from severe to relatively attenuated, and of 1 MPS II patient with the neuronopathic phenotype were collected and levels of HS and DS in these DBS were compared with levels in DBS of newborn MPS I and MPS III heterozygotes and controls. We showed that levels of HS and DS were clearly elevated in all newborn DBS of MPS I and II patients, and that levels of HS were clearly elevated in all newborn DBS of MPS III patients compared to controls and heterozygotes. We therefore conclude that measurement of HS and DS in DBS may be suitable for NBS for MPS I, II and III, and we hypothesize that this same approach will also detect other MPSs in which heparan sulfate and/or dermatan sulfate are also the primary storage products. However, we could not detect clear differences in HS and DS levels in MPS I DBS between severe and attenuated patients, which demonstrates that this technique probably cannot be used for early assessment of the MPS I phenotype within the scope of NBS.

Chapter 7 focuses on the question whether the concentrations of HS and DS and non-reducing end (NRE) disaccharides in plasma and urine samples of MPS I patients collected prior to the initiation of treatment correlate with clinical disease severity. Concentrations of HS and DS were determined in plasma of 22 untreated MPS I patients and in urine of 15 untreated MPS I patients, and were subsequently corrected for the age-related decline of the values in controls. HS and DS levels were compared with age-corrected levels of total uGAGs, generally considered to be of limited value other than as a simple diagnostic screening test for MPS I. Total uGAGs were available from 23 untreated patients. In addition, levels of NRE disaccharides were measured in the plasma and urine samples. Levels of HS and DS and total uGAGs were clearly elevated in MPS I patients prior to initiation of treatment compared to control subjects. We show that plasma HS and DS levels seem to correlate with disease severity in MPS I, but do not separate all MPS I-H patients from patients with more attenuated phenotypes. Surprisingly, total uGAGs, as measured by the dimethylene blue (DMB) test, show a better correlation with disease severity and an improved distinction between different phenotypes.

Finally, chapter 8 presents a general discussion on the current status and a description of future perspectives.