The natural history of MPS I: global perspectives from the MPS I Registry

Michael Beck, MD1, Pamela Arn, MD2, Roberto Giugliani, MD, PhD, MSc3, Joseph Muenzer, MD, PhD4, Torayuki Okuyama, MD, PhD5, John Taylor, MS6 and Shari Fallet, DO6

INTRODUCTION
Mucopolysaccharidosis type I (MPS I) is a rare autosomal recessive disease caused by a deficiency of α-L-iduronidase, an enzyme required for the degradation of the glycosaminoglycans dermatan and heparan sulfate. The estimated incidence of MPS I is 1 in every 100,000 live births. Due to the chronic and progressive accumulation of glycosaminoglycans in the lysosomes of cells throughout the body, patients affected by this devastating disease experience multiorgan dysfunction leading to considerable morbidity in most patients, and early mortality in those most severely affected.1

Like most other metabolic inherited diseases, MPS I displays significant variability in its presentation and course. This may be due to differences among patients in the severity of the underlying mutation(s) and consequent degree of residual enzyme activity; however, other factors may also contribute to the well-known phenotypic heterogeneity.2 Historically, MPS I has been classified into three syndromes—Hurler, Hurler–Scheie, and Scheie—though it is now widely accepted that overlap in symptomatology exists among these subtypes.1 Hurler syndrome, the most severe form of MPS I, typically involves significant developmental delay and cognitive decline, along with characteristic coarse facial features, joint stiffness and contractures, short stature, and respiratory, cardiac, and hepatic disease. Symptoms emerge shortly after birth and progress rapidly, such that most patients with Hurler syndrome die within the first decade of life. At the other end of the MPS I disease spectrum, Scheie syndrome involves later onset of typically milder symptoms and a slower disease progression. While patients with the Scheie phenotype usually develop significant disease-related morbidity, they show normal intelligence and survive into adulthood. Hurler–Scheie syndrome represents an intermediate phenotype that is characterized by mild or no cognitive impairment but includes somatic symptoms that reduce life expectancy into the second or third decade of life. Delineation of the different MPS I phenotypes can be challenging and is largely driven by consideration of the age of symptom onset and rate of disease progression as well as a patient’s genotype.3

Historically, treatment of MPS I was restricted to palliative care and symptom-based interventions, including surgery (e.g., adenotonsillectomy, hernia repair, ventriculoperitoneal shunt, cardiac valve replacement, carpal tunnel release, and spinal decompression); physical, occupational, and speech therapies; respiratory support; hearing aids; and medications for pain and gastrointestinal disturbances. Since 1981, hematopoietic stem cell transplantation (HSCT) has been used to treat MPS I. When successful, it is a one-time procedure that can prolong survival, preserve cognitive function, and reduce some somatic features of the disease.4,5 However, due to its significant...
be used, corresponding to “onset” or “age first reported.” In addition, if the same symptom was reported multiple times, the earliest age was used. When symptoms were not explicitly reported, they were considered to be absent, and frequencies were calculated as the number of patients with the symptom present divided by all patients in each region and/or phenotype. This assumption means that the reported frequencies may underestimate the true frequency for each symptom. Descriptive statistics were computed for age of onset of each symptom (as indicated by the earliest age each symptom was reported) among patients who experienced the symptom. For those patients with the same symptom reported multiple times, the earliest age was used, corresponding to “onset” or “age first reported.”

RESULTS

Global occurrence of MPS I phenotypes

A total of 987 MPS I patients with evaluable natural history information were enrolled in the Registry as of August 2013.
(Table 1). The largest proportion of patients was from Europe (45.5%), with the next largest from North America (34.8%), followed by Latin America (17.3%) and Asia Pacific (2.4%).

The overall phenotypic distribution was 601 (60.9%) for Hurler, 227 (23.0%) for Hurler–Scheie, and 127 (12.9%) for Scheie. Another 32 (3.2%) patients met the criteria for inclusion in this analysis, but their phenotypes were not reported in the Registry and were therefore considered undetermined or missing. Of note, North America (71.4%) and Europe (61.5%) had higher proportions of patients with the severe Hurler phenotype than Latin America (42.7%) or the Asia Pacific region (29.2%).

Table 1 Distribution of MPS I phenotypes by geographic region—all evaluable patients

| Geographic region | Hurler,a n (%) | Hurler–Scheie,a n (%) | Scheie,a n (%) | Undetermined,a n (%) | Total,b n (%) |
|-------------------|---------------|-----------------------|---------------|----------------------|--------------|
| All regions       | 601 (60.9)    | 227 (23.0)            | 127 (12.9)    | 32 (3.2)             | 987          |
| Asia Pacific      | 7 (29.2)      | 5 (20.8)              | 12 (50.0)     | 0                    | 24 (2.4)     |
| Europe            | 276 (61.5)    | 102 (22.7)            | 63 (14.0)     | 8 (1.8)              | 449 (45.5)   |
| Latin America     | 73 (42.7)     | 57 (33.3)             | 22 (12.9)     | 19 (11.1)            | 171 (17.3)   |
| North America     | 245 (71.4)    | 63 (18.4)             | 30 (8.7)      | 5 (1.5)              | 343 (34.8)   |

MPSI, mucopolysaccharidosis type I.

*Percentages are based on the number of patients in each region enrolled in the Registry who met the criteria for inclusion in this analysis as of 2 August 2013.

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Chronology of symptom onset, diagnosis, and treatment by region

Median ages at symptom onset, MPS I diagnosis, and first treatment (ERT or HSCT, if applicable) are presented by region and phenotype in Figure 1. Across all regions, patients with Hurler syndrome, the most severe phenotype, were diagnosed and treated earliest, as expected. The median age at symptom onset for these patients was 6 months, and diagnosis and treatment initiation followed quickly thereafter, at median ages of 12 and 18 months, respectively. Patients with Hurler–Scheie and Scheie syndromes, which have the more attenuated presentations, typically experienced initial symptoms sometime after infancy and exhibited a 2- to 4-year gap between onset of symptoms and diagnosis, respectively, and a 4- to 8-year gap between diagnosis and treatment initiation, respectively.

Analyses of age of symptom onset, diagnosis, and treatment initiation based on phenotype and geographic region generally mirrored the results in the overall Registry population, with a few notable exceptions. In North America, treatment initiation for patients with Scheie syndrome was earlier than in the other regions. The median age for treatment initiation for patients diagnosed with Scheie syndrome in North America was 11.7 years, whereas in Europe and Latin America it was 16.9 and 17.7 years, respectively. The Asia Pacific region had an even higher median age of 31.5 years for treatment initiation. The median age of treatment initiation in patients with Hurler–Scheie was also higher in the Asia Pacific region (23.8 years) compared with the overall Registry population (8 years). Another notable finding was the rate of patients with an undetermined or missing phenotype in Latin America (11.1%), which was much higher compared with the other regions. The median ages of symptom onset, diagnosis, and treatment initiation for patients in Latin America with an undetermined phenotype were 0.7, 1.3, and 3.3 years, respectively, which is highly comparable to the median ages for patients in Latin America with the Hurler phenotype (0.7, 1.7, and 3.6 years, respectively), suggesting that some portion of the patients with undetermined phenotypes may, in fact, have Hurler syndrome.

Natural history of MPS I by phenotype

Symptom frequency by phenotype. Coarse facial features were the most predominant characteristic of all functional and anatomic abnormalities for both the Hurler and the Hurler–Scheie phenotypes, occurring in 86.4 and 72.7% of these patients, respectively. The symptoms occurring in at least 25% of patients are summarized by phenotype in Figure 2, and all symptoms, including those occurring in less than 25% of patients, are summarized by phenotype in Supplementary Table S1 online. Among patients with the Scheie phenotype, 48.0% presented with coarse facial features. Corneal clouding was noted in all three phenotypes at approximately the same rate: 70.9, 68.3, and 70.1% for Hurler, Hurler–Scheie, and Scheie, respectively.

Hepatomegaly was present in the majority of patients with Hurler (70.0%) and Hurler–Scheie (66.5%) phenotypes and in approximately half (48.0%) of those with the Scheie phenotype. Similarly, splenomegaly was present in 50.9% of patients with Hurler syndrome and 47.1% of patients with Hurler–Scheie syndrome but in only 27.6% of those with the Scheie phenotype. The incidences of hernias were more evenly distributed among the phenotypic groups, with 58.9% in Hurler, 59.9% in Hurler–Scheie, and 53.5% in Scheie patients.

In terms of musculoskeletal abnormalities, kyphosis/gibbus was the only abnormality present in the majority (70.0%) of patients with Hurler phenotype, and it was reported much less frequently in patients with Hurler–Scheie (33.5%) and Scheie (21.3%) phenotypes. Conversely, joint contractures and carpal tunnel syndrome were present in the majority of Scheie patients (69.3 and 51.2%, respectively) but were less common in Hurler–Scheie patients (57.3 and 27.8%, respectively) and even less frequent in Hurler patients (37.9 and 7.8%, respectively).

Cardiac valve abnormalities were observed in 67.7% of Scheie patients, 59.0% of Hurler–Scheie patients, and 48.9% of...
Airway-related symptoms, such as sleep disturbances/snoring were observed in 51.6% of Hurler patients, 48.9% of Hurler–Scheie patients, and 26.8% of Scheie patients. Cognitive impairment was observed in 46.4, 31.3, and 9.4% of patients with Hurler, Hurler–Scheie, and Scheie phenotypes, respectively.

As expected, first symptoms appeared earlier (within the first 2 years of life) in patients with the Hurler phenotype; whereas, in patients with the Hurler–Scheie and Scheie phenotypes, commonly occurring symptoms were first observed between 3 and 7, and 5 and 13 years of age, respectively. The median ages of symptom onset by phenotype are shown in Figure 1.
onset of symptoms occurring in at least 25% of patients are presented by phenotype in Figure 2, and the median ages of onset of all symptoms, including those occurring in less than 25% of patients, are summarized by phenotype in Supplementary Table S2 online.

Across all phenotypes, hernias were the earliest reported symptom, which was noted at median ages of 0.8, 3.2, and 4.6 years of age in Hurler, Hurler–Scheie, and Scheie patients, respectively. Coarse facial features, the most prevalent symptom in patients with Hurler and Hurler–Scheie phenotypes, were also an early finding, with a median age at onset of 0.9 years in Hurler patients and 3.4 and 8.7 years in patients with Hurler–Scheie and Scheie phenotypes, respectively. Corneal clouding, the most prevalent symptom in patients with the Scheie phenotype, was first noted at a median age of 10.5 years in that subset of patients.

Among patients with the Hurler phenotype, kyphosis/gibbus had a median age at onset of 1.0 year (Figure 2a), and dysostosis multiplex, corneal clouding, and hepatomegaly had a median age at onset of 1.1 years. Several symptoms, including sleep disturbances/snoring, enlarged tongue, cognitive impairment, and splenomegaly had a median age at onset of 1.2 years, whereas cardiac valve abnormalities were noted at a median age of 1.3 years. The symptoms that appeared latest in at least 25% of patients with Hurler syndrome were enlarged tonsils and joint contractures, with a median age at onset of 1.5 and 1.6 years, respectively.

The symptoms reported in Hurler–Scheie patients are shown in Figure 2b. After hernias and coarse facial features, cognitive impairment was the earliest symptom observed, first occurring at a median age of 3.8 years. The median ages of onset for enlarged tongue, sleep disturbances/snoring, enlarged tonsils, joint contractures, and dysostosis multiplex were between 4.0 and 4.2 years. Both corneal clouding and hepatomegaly had a median age at onset of 4.4 years, whereas splenomegaly and kyphosis/gibbus had a median age at onset of 4.6 years. Symptoms appearing later in patients with the Hurler–Scheie phenotype included cardiac valve abnormalities, hip dysplasia, and carpal tunnel syndrome, with median ages at onset of 5.7, 6.2, and 7.4 years, respectively.

Symptoms reported in at least 25% of patients with Scheie phenotype are shown in Figure 2c. After hernias, the earliest symptoms within this phenotype were joint contractures and dysostosis multiplex, with median ages at onset of 7.6 and 8.0 years, respectively. Hip dysplasia was first reported at a median age of 8.4 years. Both sleep disturbances/snoring and coarse facial features had a median age at onset of 8.7 years, and hepatomegaly was observed at a median age of 9.4 years. Symptoms appearing later included corneal clouding at 10.5 years, splenomegaly at 11.0 years, cardiac valve abnormalities at 11.7 years, and carpal tunnel syndrome at 12.5 years.

**DISCUSSION**

MPS I is a rare panethic genetic disorder characterized by a spectrum of disease with variable age of onset, progression, and organ involvement. If left untreated, patients with the most severe phenotype experience progressive deterioration of the musculoskeletal, cardiorespiratory, and central nervous systems and, typically, die before the age of 10 years. Although patients with the least severe phenotype usually have normal...
cognitive functioning and survive into adulthood, more than 50% may be affected by cardiac valve abnormalities, joint contractures, corneal clouding, hernias, and hepatomegaly. The availability of improved disease-specific treatments, including HSCT and ERT, allows patients affected with MPS I to obtain substantial clinical benefit for many disease manifestations, including hepatosplenomegaly, upper airway obstruction (including sleep apnea), cardiac symptoms, and coarse facial features. Importantly, the chances of success from these treatments is improved when initiated prior to the onset of irreversible organ damage.

Due to the rarity of the disease as well as the variability of clinical manifestations, MPS I poses challenges for diagnosis. The MPS I Registry provides the largest global data set for evaluating the natural history, clinical presentation, and potential treatment response of patients with MPS I.

The phenotypic distribution in the Registry data set, with most patients (60.9%) in the most severe phenotypic category, Hurler, and the remaining more attenuated phenotypes, Hurler–Scheie (23%) and Scheie (12.9%), is consistent with existing data, suggesting that ~50–80% of patients have severe MPS I. However, the observed rates of the various phenotypes within the Registry may have been impacted by selection bias; e.g., more attenuated phenotypes could be underrepresented due to preferential identification and enrollment of patients with more severe clinical presentations. In an effort to minimize selection bias, the Registry accepts all patients with a diagnosis of MPS I, regardless of treatment status.

Regional differences in phenotypic distribution were also noted. North America and Europe had higher proportions of patients with the Hurler phenotype than did Latin America or the Asia Pacific region. These regional differences could be due to differences in the “genetic landscape” in different geographic regions or may be the result of regional differences in identification and enrollment of MPS I patients in this voluntary Registry. Some evidence exists for regional genetic differences, in that certain severe mutations (common nonsense mutations) identified in North America and Europe have not been observed in the Asia Pacific region.

The profile of MPS I mutations in Brazil also differs from that found in other regions. Based on the similarities in median ages of symptom onset, diagnosis, and treatment initiation, the present study suggests that a substantial proportion of patients in Latin America whose phenotypes were classified as undetermined/missing could have Hurler syndrome.

Early symptom recognition and diagnosis are essential to achieve the best long-term prognosis in patients with MPS I. It is of paramount importance that not only pediatricians, but other specialists as well, are familiar with the clinical manifestations and consider an MPS diagnosis, especially when symptoms are present in combination with each other. Hernias were the earliest presenting symptoms in all three phenotypes. Therefore, the presence of inguinal or umbilical hernias in young children should raise suspicion of MPS I. Likewise, coarse facial features, which are early manifestations and the most prevalent symptom in patients with Hurler and Hurler–Scheie phenotypes, should be considered as an early sign of a potential MPS I diagnosis. Corneal clouding is also a highly prevalent and relatively early manifestation of MPS I across the phenotypes.

Our findings indicate significant delays in diagnosis and treatment, particularly in patients with attenuated phenotypes. Regional differences were evident as well, with attenuated patients in Asia Pacific receiving treatment 18–22 years following the onset of symptoms—a 10- to 12-year delay compared with the 6–12 years between onset of symptoms and treatment in the overall Registry population. This delay may be due, in part, to a lack of access to ERT in some countries.

The data presented here confirm findings from a previous analysis of Registry data published in 2007, shortly after the Registry was established. The current analyses are based on a much larger set of patients (987 vs. 302), provide global and regional breakdowns of the data, and include data from the natural history period only. Regardless, and not surprisingly, there are similarities between the two reports in the age at symptom onset, age at diagnosis, and the rates of prevalence of common MPS I symptoms. However, the current report, based on data from a larger number of patients, provides a more detailed and refined analysis of the earlier findings.

When interpreting results of data analyses from the MPS I Registry, certain limitations common to observational registries should be considered. As with any voluntary registry, incomplete or missing data may affect the results, though a recent analysis of the MPS I Registry using source document verification revealed an overall source-to-database error rate of <4%, with no systematic errors. It is also possible that assessment and data collection methods at the participating sites around the world may not be sufficiently standardized and/or that Registry enrollment biases, perhaps based on regional disease classification, symptom severity, and symptom reporting practices, affected the results. For example, patients who did not have a particular symptom may not have had any information reported for that symptom (i.e., rather than indicating that a patient did not have a symptom, the investigator did not provide information about that symptom). This possibility led us to calculate symptom prevalence rates as the number of patients with a particular reported symptom divided by the total number of patients in each region and/or phenotype. As a consequence, the true symptom prevalence rates are at least what we have calculated, and may be higher. In this study, a slightly higher than expected number of patients with attenuated MPS I had cognitive impairment (31.3% of Hurler–Scheie and 9.4% of Scheie patients). This likely reflects the fact that MPS I presents as a disease continuum, making phenotypic classification of MPS I somewhat subjective. Thus, it is possible that some Hurler and Hurler–Scheie patients may have been misclassified as Hurler–Scheie and Scheie phenotypes, respectively. Although the aforementioned potential limitations are not insignificant, the data compiled in the MPS I Registry provides the largest global data set for evaluating the natural history, clinical presentation, and potential treatment response of patients with MPS I.
Registry are clearly valuable for drawing inferences and generating hypotheses.

Conclusions
The MPS I Registry is the largest global database of information from MPS I patients and provides a useful tool for expanding knowledge about disease presentation, clinical status, and treatment outcomes. Greater understanding of the symptomatology of the disease can lead to earlier diagnosis and initiation of treatment, which may in turn lead to better patient outcomes. Each of the three MPS I phenotypes, Hurler, Hurler–Scheie, and Scheie, is associated with a characteristic constellation of symptoms and disease course. This analysis of data from almost 1,000 patients facilitates definition of the natural history of MPS I across the phenotypic spectrum, which will hopefully increase awareness of the disease and improve early diagnosis. In addition, results from this investigation will be important in establishing benchmarks for future analyses of treatment interventions.

SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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