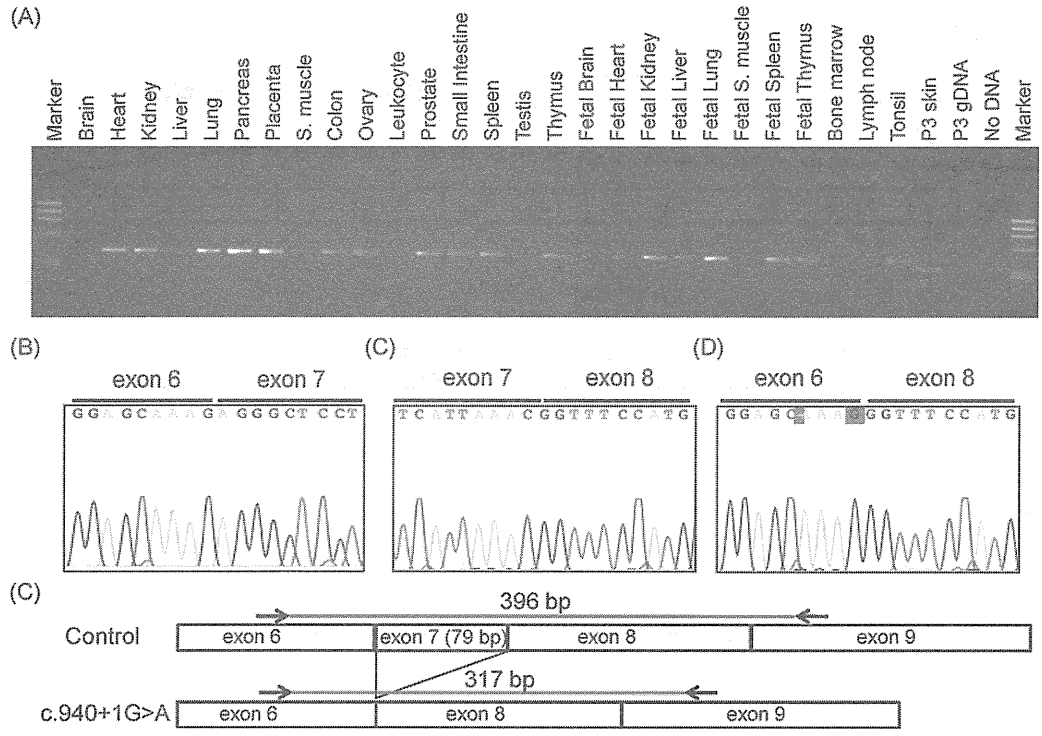

Fig. 3. Splice site mutation c.940+1G>A causes loss of exon 7 in *SLCO2A1* mRNA. (A) RT-PCR product amplified between exon 6 and exon 9 in *SLCO2A1*. Although *SLCO2A1* mRNA of the expected size is expressed in a wide variety of human tissues, only a smaller PCR product was obtained from the skin biopsy specimen taken from P3 who was homozygous for the c.940+1G>A SS mutation. (B–D) Sequence analysis of the PCR products generated between exon 6 and exon 9. The exon 7 region was detected in the exon boundaries of RT-PCR products from lung tissues (B, C). No exon 7 sequence was detected in the PCR product derived from skin mRNA of P3 (D). (E) Schematic representation of the exon 7 skipping. The *SLCO2A1* c.940+1G>A SS mutation located in the splice donor site of intron 7, which results in the loss of exon 7 and a truncation of PGT.

gene would cause the failure of PGE re-uptake, resulting in high PGE2 levels in the skin tissue, serum, and urine.

Of the 4 PDP patients screened, 1 carried a homozygous mutation, where as the other 3 carried compound heterozygous mutations in the *SLCO2A1* gene. All 4 PDP patients who possessed *SLCO2A1* mutations showed typical PDP phenotypes which are classified into the complete or incomplete forms. However, no significant mutations in the *SLCO2A1* gene were identified in the sole patient with CVG. Among the 8 alleles of *SLCO2A1* identified in this study, 4 (50%) included the same SS mutation (c.940+1G>A), which would be derived from a single founder allele. The other 4 *SLCO2A1* mutations were found in one of mutations in compound heterozygotes (summarized in Table 1). Analysis of *SLCO2A1* transcripts in P3, who was homozygous for the c.940+1G>A SS mutation, showed that the mutation resulted in the loss of exon 7 and a truncation of the PGT protein.

Among the 5 types of *SLCO2A1* mutations we identified, the NS mutation p. G104*and the c.940+1G>A SS mutation are considered to be severe mutations, as they result in truncations of the PGT protein. The p.Q556H mutation is located in the highly conserved 11th transmembrane domain adjacent to 1 of 3 critical amino acid residues (Glu78, Arg561, or Lys614) for PG transport activity [18] (Fig. 4). No information has been reported in previous investigations of PGT with regard to the potential functional impacts of the 2 mutations p.T347I and p.E427-P430del. Thr-347 is located in the extracellular region between the 7th and 8th transmembrane domains and is highly conserved in human, mouse, chicken, frog, and zebrafish (Fig. 4). The amino acid sequence containing the p.E427-P430del mutation (EVYP) is located in the extracellular region between the 9th and 10th transmembrane domains. The amino acid sequence (V/I)YP is conserved in human, mouse, chicken, and zebrafish, but not in frog (Fig. 4). Therefore, it is possible that the amino acid deletion mutation p.E427-P430del could have a less severe effect on PG transport activity.

Collectively, we deduced that the homozygous status of the c.940+1G>A SS mutation observed in P3, would have the most severe impact on PGT function. Compound heterozygotes with an c.940+1G>A SS mutation and a p.Q556H mutation, for example P5, would also be expected to have hindered PGT function, although to a lesser extent than c.940+1G>A homozygotes.

For *ZNF98*, we found a single heterozygous c.217delA mutation in 2 of the 4 PDP patients in one of their parents who did not have PDP. Phenotypic comparison indicated that no specific phenotype was associated with PDP patients who possess a single heterozygous c.217delA mutation. Therefore, we deduced that the c.217delA mutation of *ZNF98* does not have a modifier effect on PDP.

4.2. Genotype–phenotype correlation in PDP

SLCO2A1 mutations and clinical phenotypes of 6 patients are summarized in Table 1. Interestingly, P3, diagnosed with the complete form of PDP, was homozygous for the severe c.940+1G>A SS mutation, whereas P1, P2, and P5 were all found to be compound heterozygotes for *SLCO2A1* mutations represented both the incomplete form (P1, P2) and the complete form (P5) of PDP, carrying a severe mutation (either c.940+1G>A SS mutation or NS mutation) and another *SLCO2A1* mutation. The severity of pachydermia and associated histological changes was also correlated with *SLCO2A1* genotypes (Fig. 1 and Table 1). In addition, serum and urinary PGE2 levels in P3 were much higher than those observed for other PDP patients. Together, clinical data and genetic analyses showed that *SLCO2A1* genotypes in PDP patients were closely associated with serum PGE2 levels, suggesting that *SLCO2A1* mutations contribute to the severity of clinical phenotypes in PDP.

It was previously reported that transgenic mice with the K5 promoter – PTGS2 (also known as Cox2) transgene, exhibit high

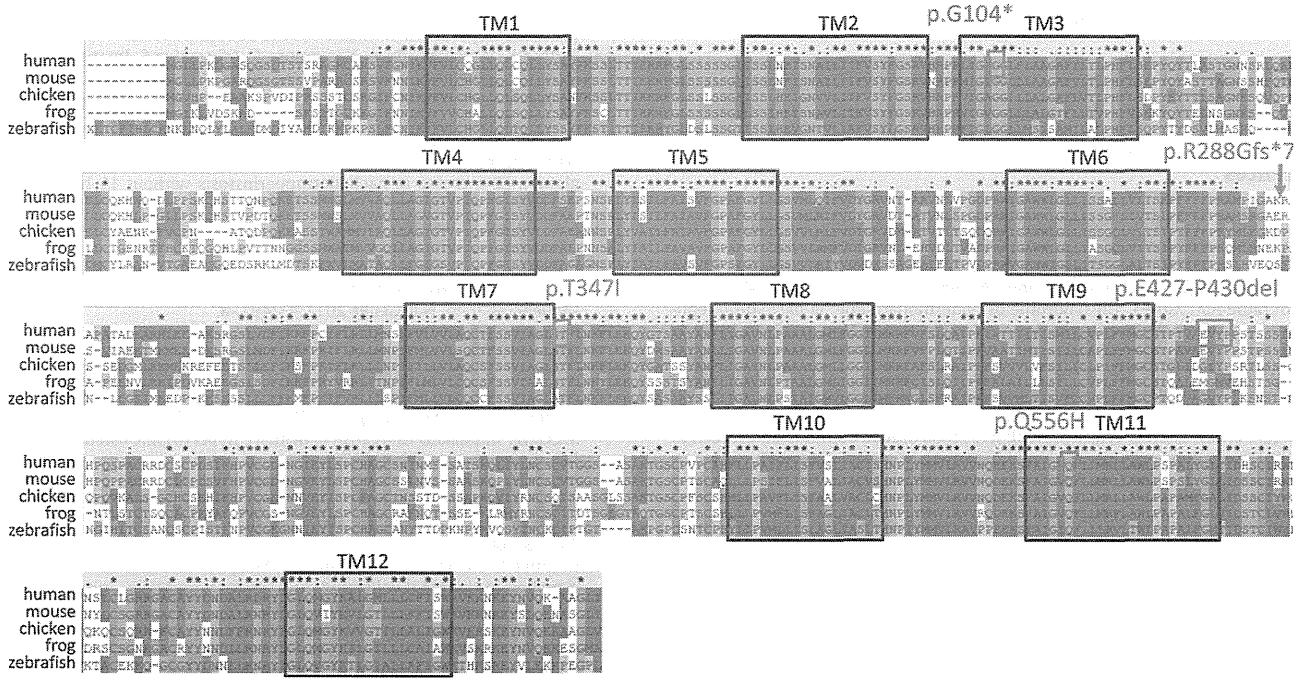

Fig. 4. Amino acid sequence alignments of PGT orthologs and mutations in PDP patients. Amino acid sequence alignments of PGT sequences of human (NP_005621) and 4 other vertebrate species (NP_201571, ENSGALG00000006471, ENSXETG00000011817, and ENSDARG00000061896) were performed using ClustalX (2.0). Twelve transmembrane regions were predicted using SOSUI ver1.11. The 5 *SLCO2A1* mutations found in this study are shown in red.

mRNA expression level of PGE2 in epidermis, epidermal hyperplasia, and sebaceous gland hyperplasia [22]. These hyperplasia phenotypes are quite similar to those of PDP patients. Furthermore, it was reported that PGE2 inhibits the proliferation of human gingival fibroblasts *in vitro* [23]. Therefore, high concentrations of PGE2 level in the skin tissue would cause epidermal, and sebaceous gland hyperplasia and dermis hypoplasia, and these cell proliferation differences between the dermis and epidermis would determine the magnitude of affected skin in PDP.

Although the serum PGE2s level of patients with the incomplete type PDP patients (P1 and P2) were within the normal range, we found mild sebaceous gland hyperplasia in P1 (Supplementary Fig. 1). These results suggested that the mild *SLCO2A1* mutation found in the patients with the incomplete form of PDP could alter the PGE2 level in affected skin, although serum PEG2 level would be within the normal range.

4.3. *Founder effect of* SLCO2A1 *mutation*

We found that 3 of the 4 patients possessed the c.940+1G>A SS mutation. All of these patients were unrelated and showed no consanguinity. In this study, we have shown that this mutation represents an ancient founder allele rather than a recurrent mutation (Table 3). These results indicated that c.940+1G>A SS mutation is one of major mutation in Japanese PDP patients and c.940+1G>A SS mutation should be analyzed first in all Japanese PDP patients before genetic screening at other *SLCO2A1* mutation. During manuscript preparation, 2 papers describing the identification of *SLCO2A1* mutations in PDP patients were published (MIM#614441) [19,20]. In one of these papers, Chinese PDP patients, who possess c.940+1G>A SS mutation, were reported. These results indicated that c.940+1G>A SS mutation would occur before divergence between Chinese and Japanese population, and currently spread in Asian area.

In this study, we identified 4 novel mutations of the *SLCO2A1* gene (p.G104*, p.T347I, p.E427-P430del, and p.Q556H) in 3 Japanese patients and also confirmed that parents of 2 of the patients were carriers of these mutations, implicating an autosomal recessive mode of inheritance. This information will be useful for genetic counseling. We also found evidence of genotype–phenotype correlations between *SLCO2A1* mutations and disease severity; however, further analyses are needed to clarify correlations among *SLCO2A1* genotypes, PGE2 level in skin, and the clinical forms. The patients described here with *SLCO2A1* compound heterozygous mutations, including those carrying the founder allele, might be useful for future investigations.

Note added in proof

Additional manuscript for isolation of *SLCO2A1* mutation in PDP patients were published [24] in revision.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2012.07.008.

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Current diagnosis and management of mucopolysaccharidosis VI in the Asia-Pacific region

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ABSTRACT

Introduction: Mucopolysaccharidosis (MPS) type VI (Maroteaux–Lamy syndrome) is a clinically heterogeneous lysosomal storage disorder. It presents significant diagnostic and treatment challenges due to the rarity of the disease and complexity of the phenotype. As information about MPS VI in Asia-Pacific countries is limited, a survey was conducted to assess current practices for diagnosis and management of MPS VI in this region. The participants were selected based on their experience in diagnosing and managing MPS patients.

Methods: The survey comprised 29 structured quantitative or qualitative questions. Follow-up consultations were undertaken to discuss the data further.

Results: Thirteen physicians from eight countries or regions (Australia, China, Hong Kong, Japan, Malaysia, Philippines, Taiwan and Thailand) were surveyed. At the time of the survey twenty-two patients with MPS VI were directly treated by the respondents and most (~80%) had rapidly progressing disease. A wide range of medical specialists are involved in managing patients with MPS VI, the most common being orthopedic surgeons, pediatricians and geneticists. The availability/accessibility of diagnostic tools, therapies and national insurance coverage vary greatly across the countries/regions and, in some cases, between different regions within the same country. Currently, there are national MPS management groups in Australia and Japan. Australia, Taiwan and Hong Kong have local guidelines for managing MPS and local MPS registries are available in Australia, Taiwan, and Japan.

Conclusions: This survey highlights differences in the diagnosis and management of MPS VI between Asia-Pacific countries/regions. Important barriers to advancing the identification, understanding and treatment of MPS VI include the paucity of epidemiological information, limited access to laboratory diagnostics and therapies, low disease awareness, and a lack of monitoring and treatment guidelines. There is a clear need to facilitate communications between physicians and establish regional or national disease registries, a multidisciplinary referral network, and a centralized diagnostic and management framework.

Abbreviations: ARSB, arylsulfatase B gene; ASB, arylsulfatase B; BMT, bone marrow transplantation; DBS, dry blood spot; dx, diagnosis; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; HSCT, hematopoietic stem cell transplantation; LSDP, Life Saving Drugs Program; MDAC, Mucopolysaccharidosis Disease Advisory Committee; MPS, mucopolysaccharidoses; NK, not known; NA, not applicable; SCC, spinal cord compression; uGAG, urinary glycosaminoglycan.

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1. Introduction

The mucopolysaccharidoses are a heterogeneous group of lysosomal storage diseases. There are currently 11 known enzyme deficiencies that cause seven distinct mucopolysaccharidosis (MPS) disorders [1]. MPS type VI, or Maroteaux–Lamy syndrome, is an autosomal recessive lysosomal storage disorder in which mutations in the arylsulfatase B gene (*ARSB; Gene/Locus MIM #611542*) cause defects in N-acetylgalactosamine 4-sulfatase (EC 3.1.6.12), resulting in impairment of the stepwise degradation of the glycosaminoglycan (GAG) dermatan sulfate [2]. This leads to progressive intra- and extracellular accumulation of dermatan sulfate in various tissues and organs. As with other MPS disorders, MPS VI is a clinically heterogeneous condition, and due to the complexity of the disease phenotype it often presents considerable diagnostic challenges to clinicians. Diagnosis of MPS VI occurs through a combination of clinical findings and laboratory test results. Clinical findings for patients with rapidly progressing MPS VI typically include impaired growth, coarse facial features, dysostosis multiplex, restriction of joint movement, flexion contractures, impaired vision and/or hearing, nerve entrapment syndromes such as carpal tunnel syndrome and spinal cord compression (SCC), organomegaly, umbilical and/or inguinal hernias, reduced pulmonary function, and cardiac valve disease. Onset usually occurs before 2 or 3 years of age [3,4]. Without treatment, most of these patients die in their second or third decade of life. Patients with attenuated disease live longer and tend to have close to normal height. Facial or skeletal changes may be absent or mild. Although symptoms appear later in these patients, usually in adolescence or early adulthood [5,6], they ultimately develop severe morbidity or life-threatening symptoms such as cardiopulmonary diseases, hip dysplasia, impaired vision and SCC.

MPS VI is an extremely rare disorder and data on the prevalence of MPS VI in the Asia-Pacific region are limited. Current knowledge about the epidemiology of MPS VI is therefore restricted to reports that describe the birth incidence of the disorder or single center studies. The results from observational studies suggest that the prevalence of MPS VI may be highly variable among different populations and geographic regions [7–9]. The global incidence of MPS VI based on countries ranges from 1 in 238,095 and 1 in 1,505,160 live births [4]. About 1100 individuals may be affected in the developed world [10]. A retrospective survey in Australia reported 18 patients with MPS VI for the period from 1980 to 1996. These data translate to an incidence of 1 per 248,000 live births [11]. An epidemiological study in Western Australia for the period from 1969 to 1996 estimated an incidence of approximately 1 in 320,589 live births for MPS VI [12]. MPS VI accounted for around 9–10.4% of total MPS diseases in Australia. The reported incidence in Taiwan is 1 per 708,589 live births (7% of all MPS births) between 1984 and 2004 [13]. A retrospective study conducted by the Korean Pediatric Society identified 131 patients with MPS between 1991 and 2000, with 69 MPS II, 22 MPS I, 11 MPS III, one MPS IV, one MPS VI and 27 unclassified [14]. In a single center study in Malaysia, of 40 suspected patients, 17 were diagnosed with MPS and one patient was diagnosed with MPS VI [15]. In a single center report from Shanghai, China in 2009, of 47 MPS cases (28 MPS II, 12 MPS IVA and 7 MPS I) no patients were diagnosed with MPS VI [16]. In terms of MPS subtypes, MPS III is the most common in Australia [11,12], whereas in South Korea [14,17], Malaysia [15], Taiwan [13], Japan and China, MPS II appears to be the most prevalent.

The management of patients with MPS VI was traditionally limited to physical and occupational therapy, symptom-based medications, surgical interventions involving orthopedic, otorhinolaryngological, ophthalmological, cardiac and neurosurgical interventions, and hematopoietic stem cell (HSCT) or bone marrow transplantation (BMT) [3]. However, treatment with HSCT or BMT has been limited by the high procedure-related morbidity and mortality risk and the difficulty of finding HLA-matched donors [18,19]. With the advent of disease-specific enzyme replacement therapy (ERT) with the human recombinant ASB galsulfase (Naglazyme®), more patients with MPS VI are now treated effectively and safely, thereby improving health and quality of life [20,21]. However, there are a number of factors that have a major influence on clinicians' approaches to MPS VI such as the rarity of MPS VI and subsequently low awareness of the disease, wide regional variations in national healthcare systems, the availability of testing facilities for the confirmation of diagnosis, differences in, or lack of, regulations regarding rare diseases and orphan drugs, and disparities in affluence both within and between countries. These factors are likely to influence approaches to diagnosis and management of MPS VI.

Therefore, a survey and literature search to assess current MPS VI diagnosis and treatment patterns in the Asia-Pacific region was conducted to identify knowledge gaps and unmet needs that should be addressed, as well as opportunities for research on topics of particular relevance in the region.

2. Methods

2.1. Survey questionnaire and follow-up interviews

The survey was designed in consultation with pediatricians and clinical geneticists in the Asia-Pacific region and with the Mudskipper Business Consulting (Shanghai) Limited. Invitation letters outlining the rationale for conducting the survey were distributed to 15 pediatricians in October 2010 together with the accompanying questionnaire. The participants were selected based on their experience in diagnosing and managing MPS patients. The questionnaire was a quantitative and qualitative survey comprising 29 structured questions that could be completed electronically in approximately 30 minutes once they had accessed all the necessary data. Respondents were required to classify their primary workplace (academic institution/university; government general hospital; regional/ community hospital; private general hospital/private practice or another healthcare setup). The survey was divided into four distinct sections: (1) country-specific information; (2) general diagnosis, treatment and follow-up; (3) available laboratory tests; and (4) the physicians' general opinions about the diagnosis and management of MPS VI in their countries and the Asia-Pacific region. Table 1 shows the particular questions asked in each of the sections. Although many questions could be answered by choosing the appropriate answer, all questions allowed for detailed answers. Each section was followed by a question to assess the respondents' perceived accuracy for his/her answers in that particular section.

In addition, each respondent was asked a post-hoc question regarding the assessment and management of SCC. Spinal cord compression is a potentially serious complication of MPS VI resulting in debilitating muscle weakness or paralysis. However, early diagnosis by means of MRI can identify clinical features suggestive of SCC and treatment, to prevent or forestall SCC, can be initiated early on [22]. From our survey responses it was clear that patients generally undergo a skeletal survey at diagnosis, and we wanted to assess whether MRI for the detection of SCC is done routinely or as a result of abnormal results during the skeletal survey. The question regarding the assessment and management of SCC was therefore posed.

We also provided an opportunity for further discussion of the data by means of follow-up e-mails, telephonic contact or face-to-face meetings. The survey was divided into four distinct sections: (1) country-specific information; (2) general diagnosis, treatment and follow-up; (3) available laboratory tests; and (4) the physicians' general opinions about the diagnosis and management of MPS VI in their countries and the Asia-Pacific region. The study was completed in April 2012.

2.2. Analysis

Collection and analysis of the survey information was done by the Mudskipper Business Consulting (Shanghai) Limited.

Table 1
Questions in each of the four sections of the survey questionnaire.

Survey questionnaire	
Question sections	Specific questions
A: Country specific	1. Are there any national MPS study groups in your country? 2. Are there any national MPS registries? 3. Are there any national guidelines for MPS management? 4. National insurance coverage of diagnostics and therapies related to MPS for: urine GAG; enzyme assay; molecular test; imaging test; enzyme replacement therapy; hematopoietic stem cell transplantation or bone marrow transplantation; surgical management procedures (such as hernia repair, carpal tunnel release, spinal procedure, etc.). 5. In the past five years, has your center been involved in any clinical trials for MPS (multi- or single-center, or investigator initiated studies)?
B: General diagnosis, treatment and follow-up	6. How many MPS patients are you aware of in your country (total number of patients)? 7. How many MPS VI patients are you aware of in your country (total number of patients)? 8. Of those patients, how many MPS VI patients are being treated at your center? 9. Of these MPS VI patients, how many are: (male; female). 10. Of these MPS VI patients, how many are of the: (rapidly progressing form; slowly progressing form). 11. What is the earliest age at which they are diagnosed with the condition? 12. What is the oldest age at which they are diagnosed with the condition? 13. Diagnostic test used for these MPS VI patients: (clinical diagnosis; urine GAG; enzyme assay; mutation test; detail of others). 14. What is the common initial clinical presentation in MPS VI patients in your center? (Short stature, abnormal facial features, skeletal abnormalities, limited range of motion, corneal clouding, recurrent otitis media, noisy breathing, valvular cardiac disease, umbilical/inguinal hernia, carpal tunnel syndrome, others.) 15. Of all MPS VI patients treated at your center, which of the following specialties have these patients consulted at any time based on your knowledge? (Pediatrician, cardiologist, respiratory specialist, geneticist, ophthalmologist, orthopedic specialist/surgeon, metabolic specialist, general surgeon, neurosurgeon, others.) 16. Which guidelines are applied in your institute for the management of MPS? 17. How many patients have been treated by: (hematopoietic stem cell transplantation; bone marrow transplantation; cord blood transplant). 18. How many patients receive: (regular[a] follow-up; no regular follow-up; regular follow-up post-transplant; no regular follow-up post-transplant). 19. Provide details regarding the routine schedule of assessment for patients with MPS VI.
C: Laboratory test availability	20. Do you run urine GAG as a screening test? (Yes, own lab/hospital; third party; academic lab; commercial lab; no.) 21. Methods used to detect urine GAG (toluidine blue spot test; CTMA turbidity test; chromatography; electrophoresis; other). 22. Do you routinely confirm diagnosis of MPS VI by examining arylsulfatase B (ASB) activity? (Yes, own lab/hospital; third party; academic lab; commercial lab; no.) 23. What is the source of the sample for enzyme assay? (Plasma; leukocytes; fibroblasts; dry blood spot; others.) 24. Methods used to perform enzyme assay (fluorometry; mass spectrometry; others). 25. Do you routinely perform mutation analysis for patients suspected of MPS? 26. Who performs the mutation test? 27. Methods used to detect mutation (direct sequencing; D-HPLC; ASO-PCR; pyrosequencing; others).
D: General opinion	28. In your country, what do you consider to be the greatest challenges and opportunities in the diagnosis of MPS VI? 29. In your country, what do you consider to be the greatest challenges and opportunities in the management of MPS VI?

[a] Regular follow-up is considered one medical check-up at least once a year.

3. Results

Data collection was done from October 2010 to April 2012. Most respondents (85%) felt that they had completed the survey with 'very good' or 'near 100%' objective reliability.

3.1. Respondent demographics

A total of 14 physicians from eight countries/regions in the Asia-Pacific region completed the survey (China, n = 2; Hong Kong, n = 2; Japan, n = 2; Malaysia, n = 2; Thailand, n = 2; Australia, n = 1; Philippines, n = 1 and Taiwan, n = 2). At the time of the survey, respondents were based at academic institutions or university-affiliated hospitals (n = 7), government hospitals (n = 5) or government hospitals affiliated to an academic institution (n = 2).

3.2. National management groups/registries and access to diagnostics and therapies

Based on the responses received, there are currently national MPS management groups in three of the eight countries/regions surveyed, namely Australia, Japan and Taiwan. The Mucopolysaccharidosis Disease Advisory Committee (MDAC) provides advice to the Department of Health and Ageing on the treatment of MPS patients with ERT through the Australian Government's Life Saving Drugs Program (LSDP). The MDAC meets twice annually to review patients' eligibility to receive, or to renew their Australian government-subsidized ERT treatment for MPS disease. The Japanese Society for Mucopolysaccharidosis established the Research Group for Therapy of MPS VI on February 12, 2007.

Australia [23], Hong Kong and Taiwan have local guidelines for the use of ERT in patients with MPS. In Hong Kong these guidelines have been prepared by the Expert Panel on ERT for Rare Metabolic Diseases under the auspices of the Hospital Authority (the statutory body responsible for managing Hong Kong's public hospitals). At the time of publication treatment guidelines for MPS were being drafted in Malaysia. Formal national registries/databases for MPS are available in Australia (the LSDP stores summaries of data from 6 monthly clinical assessments, collected from treating physicians), Taiwan (MPS I, HOS and MOR-001 studies) and Japan (organized by the MPS Advisory Board). In Hong Kong, a registry for patients with rare metabolic diseases, including MPS, was set up in 2010. The National Committee on Enzyme Replacement Therapy in Malaysia does not maintain a formal MPS VI registry but this committee collects case reports. Initiatives for national and regional registries have been discussed in Malaysia and Taiwan and have been initiated in the Philippines.

Four of the 13 respondents (38%) have been involved in MPS-related clinical trials in the previous 5 years. Two Japanese physicians were involved in national multicenter Phase 3 studies on idursulfase and laronidase, while two physicians from Taiwan were

Table 2
National insurance coverage of MPS VI diagnostics and therapeutics.

Country/region	Diagnostics				Therapeutics		
	uGAG	Enzyme assay	Molecular test	Image test	Surgical procedures[a]	HSCT/BMT	ERT
Australia	Covered	Covered	Covered	Covered	Covered	Covered	Covered
China	Not covered	Not covered	Not covered	Partially covered	Partially covered	Not covered	Not available
Hong Kong	Covered	Not covered	Not covered	Covered	Covered	Covered	Covered
Japan	Not covered	Not covered	Not covered	Covered	Covered	Covered	Covered
Malaysia	Covered	Partially covered	Partially covered	Covered	Covered	Covered	Case-by-case
Philippines[b]	Not covered	Not covered	Not covered	Covered	Covered	Not covered	Not available
Taiwan[c]	Covered	Covered	Partially covered	Covered	Covered	Covered	Covered
Thailand	Covered only in some hospitals; not nationally	Not covered	Not covered	Covered	Covered	Not covered	Not available

[a] E.g. hernia repair, carpal tunnel release, spinal procedure.
[b] Enzyme assay and uGAG are available through collaboration with National Taiwan University Hospital.
[c] Tests are free to patients but are not reimbursed by the government. Private sponsorship is obtained to cover the associated costs.

involved in an under-5 study on idursulfase, a MPS I registry and a Hunter Syndrome Outcome study. One Australian physician has conducted a single center galsulfase Phase 3 sibling study [24]. In addition, one patient from Taiwan participated in the multicenter phase III trial on galsulfase in the United Kingdom.

The coverage of various diagnostic tests and therapies under national insurance programs in the Asia-Pacific region was assessed (Table 2). In Australia, all the tests and procedures for MPS VI are available free of charge under public medical coverage and some, excluding enzyme studies and molecular tests, are available with a government rebate under private medical coverage. In Taiwan tests are free to patients but are not paid for by the government. Physicians in this country must therefore secure funding for these tests from other resources, for instance institutional research grants. In Thailand there is no national coverage for the assessment of urine GAG (uGAG) levels although it is available in some hospitals. HSCT/BMT in Thailand is only covered for patients with thalassemia. In Malaysia coverage is available for certain diagnostic tools and therapies for the first child, but not necessarily for affected siblings.

In Australia, to be eligible for subsidized access to ERT through the LSDP, a patient must meet the requirements listed in the LSDP guidelines for the treatment of MPS VI. All applications for ERT in Hong Kong are subject to review and approval by an expert panel within the Hospital Authority. Once the application is approved, the Hospital Authority will cover the cost of ERT. There is a similar application process in Taiwan and Japan. ERT is generally unavailable in Thailand, except on a named patient/compassionate use basis for certain types of MPS. It is noteworthy that only physicians from public sector were invited to the survey, thus, the data does not necessarily reflect the situation in the private sector. As the data comes from only one or two metropolitan centers in a country, the presented insurance coverage in countries like China and the Philippines may not reflect the nationwide situation.

3.3. Demographics of MPS VI

There were large variations in responses regarding the number of patients with MPS in the region. At the time of the survey, 22 patients with MPS VI were being directly treated by the participating physicians. A respondent from Hong Kong previously treated one additional patient who died prior to our survey and 2 patients from Taiwan were known to have died (Table 3). Similar proportions of male and female patients were identified. According to the survey responses most MPS VI patients (~80%) had rapidly progressing disease. (MPS VI can present as rapidly or slowly progressing disease. Rapidly progressing MPS VI is characterized by undetectable enzyme activity, onset before 2 or 3 years of age, impaired mobility by 10 years of age, absent or delayed onset of puberty, cervical spinal cord compression, respiratory insufficiency, and surgical complications. Without treatment these patients often die from heart failure in their 2nd or 3rd decade of life. Slowly progressing MPS VI presents with a later onset of symptoms. These symptoms may not develop in a specific order and they usually become noticeable in adolescence or early adulthood. Without treatment, patients with slowly progressing MPS VI usually survive into adulthood [1–4].)

3.4. Diagnosis of MPS VI

Patients with MPS VI initially present with a variety of clinical presentations; the most common were abnormal facial features and skeletal abnormalities (Fig. 1).

In addition to clinical phenotype, various laboratory assessments are used to diagnose MPS VI including uGAG, enzyme activity, and mutation analysis. Multiple laboratory assessments are often requested by a physician (Table 4). Quantitative and/or qualitative uGAG analysis is often the first step in the evaluation of a patient with suspected MPS, and it is primarily performed in-house or, in

Table 3
The number of MPS VI patients and their ages at the time of diagnosis at responding physicians' clinics[a].

	Australia (n=1)	China (n=2)[b]	Hong Kong (n=2)	Japan (n=2)	Malaysia (n=2)	Philippines (n=1)	Taiwan (n=2)	Thailand (n=2)
MPS VI patients that respondents are aware of in their own country	13	20 and 2	6[c]	5 and 8	2 and 5	1	13 (2 deceased)	4 and 4–6
Patients managed at each respondent's center	4	1 and 2	3 and 2 (1 deceased)	1 and 1	1 and 5	1	2 and 6 (1 deceased)	0 and 0
Age (months) of youngest diagnosed patient	8 (clinically); 1 patient by enzyme studies in utero	24 and 84	10	At birth	36 and 24	69	42 and 12	72 and 72
Age (months) of oldest diagnosed patient	60	228 and 144	132	60 and 69	NK and 60	69	48 and 114	108 and 180

[a] In countries where there was more than one respondent, both responses have been provided.
[b] Responses are from Beijing and Shanghai, respectively.
[c] Both respondents are aware of the same six patients.

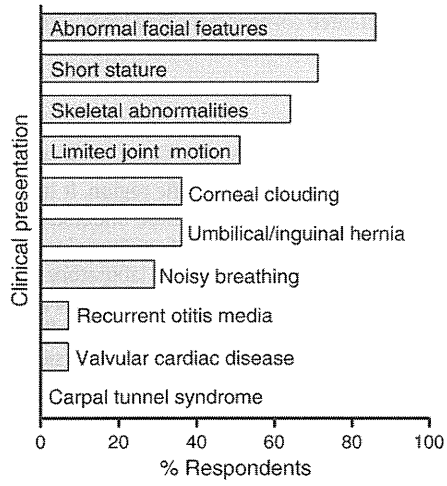

Fig. 1. Initial clinical presentation of patients with MPS VI.

the Philippines, in another academic laboratory. Diagnosis is usually confirmed by examining ASB enzyme activity, which is primarily undertaken in the local laboratory/hospital or in another academic or commercial laboratory if necessary. More than half the respondents do not routinely use mutation analysis to support diagnosis, mainly due to the prohibitive costs involved. Molecular analysis is mainly conducted for carrier testing and subsequent genetic counseling. Direct sequencing is the only method used to detect mutations.

3.5. Management and follow-up of patients with MPS VI

Medical specialists from different disciplines are involved in the management of patients with MPS VI in this region, most commonly: orthopedic specialists/surgeons, pediatricians, geneticists, metabolic physicians and respiratory specialists (Fig. 2). (In Australia, the treating doctors are mainly metabolic pediatricians/physicians who are also qualified in genetics).

Transplantation of cord blood, bone marrow and hematopoietic stem cells are fairly common among MPS VI patients in this region. ERT is not available in all of the countries represented in this survey. In those countries in which ERT is available, the funding for this therapy has become available relatively recently, compared to North America and Europe. In countries without access to ERT, transplant remains the appropriate therapy. In total, 12 of the 22 patients were given a transplantation: Two patients from Hong Kong had cord blood transplantation, four patients in Japan, one patient in Taiwan, one patient in Australia and one in Hong Kong received BMT, and of three patients in China, two received BMT and one received HSCT.

Most patients with MPS VI (>90%) reported in this survey are followed up on a regular basis. This usually consists of various evaluations, including: physical examination, ophthalmological and audiometric assessments, joint range-of-movement and pulmonary function tests, electrocardiogram, X-rays and uGAG. The availability of these assessments and the frequency at which they are carried out at the centers are given in Table 5.

With regards to SCC: If there are clinical features suggestive of SCC, a magnetic resonance imaging (MRI) scan of the head and neck

Table 4
Laboratory diagnosis used for MPS VI.

Survey questions	Survey responses							
	Australia (n = 1)	China (n = 2)	Hong Kong (n = 2)	Japan (n = 2)	Malaysia (n = 2)	Philippines (n = 1)	Taiwan (n = 2)	Thailand (n = 2)
uGAG screening: methods used								
Toluidine blue spot		2					2	
Chromatography					1			1
Electrophoresis	1	1		1	2		2	1
Spectrophotometric			1					
Others			1 (cetyl pyridinium chloride precipitation test)			Sent to other countries		
None				1 (assesses uronic acid)				1
Enzyme assay: sample source								
Plasma			1				1	
Leukocytes	1	2	2	2	2	1	2	2
Fibroblasts	1						2	1
Dry blood spot	1					1	2	1
Enzyme assay: methods used								
Fluorometry		2		2	1		1	1
Mass spectrometry					1			
Others	Radioisotopic/ spectro-photometric		Sent to other countries			Sent to other countries		
Mutation analysis								
Only for prenatal dx	1			1	1			
Yes		1	1				2	If indicated
No		1	1	1	1	1		

Note: Shaded cells indicate a positive response. The number in a shaded cell indicates the number of positive responses in a particular country/region; dx, diagnosis.

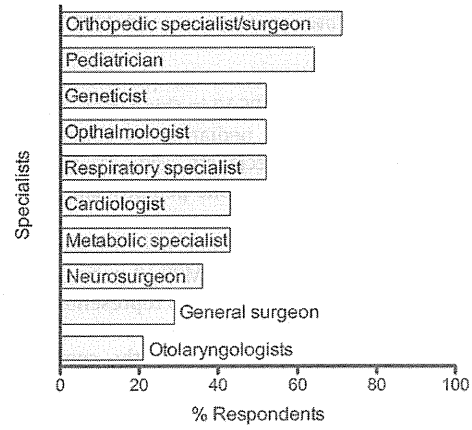

Fig. 2. Specialties consulted during management of patients with MPS VI.

will be performed for confirmation. In Taiwan, X-ray imaging is used for regular monitoring, while MRI imaging of the brain and spine is performed when neurologic signs are suspected. In the Philippines, a patient's neurologic status would be closely monitored after the initial MRI, since serial MRI is considered costly. Currently, SCC is not commonly monitored at diagnosis and follow-up in China.

The inclusion of an ophthalmologist in the medical management team for MPS VI patients was emphasized by a respondent from Taiwan. In Taiwan, three MPS VI patients required cornea transplantations (5 procedures in total). Even though these transplantation procedures did not improve visual acuity satisfactorily because the patients already had permanent visual damage as a result of their medical condition, the transplanted corneas remained clear with the patients receiving weekly ERT.

4. Discussion

This survey was conducted to better understand the diagnosis and management of MPS VI in the Asia-Pacific region. It highlights important barriers to advancing the identification, understanding and treatment of MPS VI, including the paucity of epidemiological information, low disease awareness, limited capacity in laboratory diagnostics, and a lack of monitoring and treatment guidelines. The survey was optional, unmonitored, and the responding physicians were all from the public health sector. The survey was structured so that physicians could complete it within 30 min once they had all the required information at hand. However, we cannot exclude the possibility that some respondents answered some questions from their general knowledge rather than by referring to patient records.

However, even though the overall sample size was small, our data provide an insight into experience from across the Asia-Pacific region and a snapshot of current practice in major urban centers. Our findings should, however not be generalized as there are important differences between countries and regions within a country. Insight into these differences would require a more in depth analysis.

As our survey is based on responses from one or two centers in each country, the actual number of affected individuals is difficult to determine and is likely underestimated. It is clear that MPS VI is an uncommon form of MPS in Asian countries/regions with the published relative frequency of MPS VI among all MPS patients being: China 0% [16], Korea 1% [14], Malaysia 6% [15] and Taiwan 7% [13] which is similar to most of the other regions with the published range being 2–18.8%

Table 5
Follow-up assessments.

Frequency (months) and type of assessments utilized by respondents in various countries

Test / Country (respondents)	Physical examination	Tanner stage	Photographs	Endurance		Opthalmologic / audiometric assessment	Echocardiogram	Pulmonary function test	Sleep study	Joint range of motion test	Skeletal survey (X-ray)	uGAG
				6/12 MWT	3 MSC							
Hong Kong (2)	3 3-4	3 3-4	Occasionally X	6 X	6 X	As per ENT/ opthalmologist X	12 X	6 X	12 X	6 X	As needed X	3 X
Phillipines (1)	6	12	12	6	X	6/as needed	As needed	As needed	As needed	Every visit	First visit	First visit
Taiwan** (1)	Every visit	X	X	6	6	As needed / 12	6	12	12	12	12	3
Australia (1)	Weekly to annually$	-	12	6	X	12	12	12	12 (unless normal)	6	As needed	6
China*	+	+	+	X	X	+	+	X	X	+	+	+
Japan (2)	1 12	12 12	60 X	12 X	X 12	12 24	12 12	X 24	12 24	12 12	12 12	24 X
Malaysia (2)	6 X	12 X	X 1st visit only	X X	X X	As needed 12	12 12	As needed 24	As needed X	6 6	As needed 1st visit only	At diagnosis 1st visit only
Thailand (2)	6 6	6 X	24 - 36 X	X X	X X	12 12	12 12	12-24 X	X X	6 X	12 - 48 12	X 12

*One of the respondents from China indicated that none of these assessments are routinely conducted.
**One of the Taiwanese respondents did not indicate whether these assessments are conducted.
$Various from patient to patient, depending on individual circumstances.
X = not assessed as part of routine management.
+ = assessment is conducted, but the frequency as indicated by the respondent is unclear.

[4]. Published epidemiologic data for MPS VI in the Asia-Pacific region is only available for Taiwan (incidence 1 in 833,000) [25] and Australia (1 in 248,372 live births) [11]. These data are similar to published data from other countries, which range from 1 in 238,095 and 1 in 1,505,160 live births [3,4]. Moreover, the age at diagnosis, clinical features at diagnosis, diagnostic tests used, involvement of sub-specialists and monitoring schedules, reported in other published data and guidelines [2–4,10,26,27], are similar to those reported in many of the centers that took part in this study. Exceptions to this were reported by the centers where ERT is not available. These centers were less likely to have 1) access to appropriate diagnostic tests, 2) comprehensive monitoring schedules and 3) proper monitor for SCC. These differences are discussed in the following paragraphs.

On average the youngest age at diagnosis of the MPS VI patients, identified in this survey, was around 3 years old. This is older than the median age at diagnosis of 1.9 years that was reported in a review of Italian MPS VI patients [26], but similar to the mean age at diagnosis of 48.4 months reported by a Brazilian study [27]. The patients included in the Italian review all had severe MPS VI and 88% of the patients included in the Brazilian study had an onset of symptoms before 3 years of age [26,27]. In our study, about 80% of patients had rapidly progressing disease; this is in line with the available literature [3,4]. Some of the patients were diagnosed as late as 19 and 15 years of age. These patients likely suffered from slowly progressing disease, but our survey respondents did not categorically specify the kind of MPS VI these patients had when reporting the oldest age at which a diagnosis was made.

The most commonly reported clinical features at presentation were abnormal facial features, short stature, skeletal deformities and limited joint motion. These are similar to the presentation of patients from other regions [2–4,10,26,27].

Accurate and early diagnosis of MPS VI remains a serious problem in the region. A wide range of medical specialists are involved in the diagnosis and management of patients with MPS VI, although many physicians are unfamiliar with the common signs and symptoms. Thus, they may not be aware of the differential diagnosis of the disease, which laboratory tests to order or where to refer the patient, and they may undertake procedures without full knowledge of the underlying diagnosis. This may be particularly relevant for patients living in rural areas, as local hospitals often lack adequate knowledge and facilities to diagnose MPS, leading to delayed diagnosis and referral. Some physicians believe that the condition is non-treatable and therefore may not refer the patient at all.

In most of the countries/regions surveyed, analysis of uGAG is performed as a screening tool and assessment of enzyme activity is a critical component of diagnosis. A study from Malaysia presented experience with quantification of uGAGs and high resolution electrophoresis as initial screening tests for isotyping MPS, followed by specific enzyme diagnostics [15]. Dry blood spot (DBS) is currently available in Australia [28] and Taiwan, but only Taiwan uses it for routine MPS screening. Fluorometry is the common method employed to examine whole blood enzyme activity. In the present survey, less than 50% of the respondents routinely perform a confirmatory mutation analysis of the ARSB gene in patients with suspected MPS VI. Some physicians (from Australia, Japan and Malaysia) use the mutation test for prenatal diagnosis only.

Although it is widely agreed that using a combination of clinical findings and laboratory test results is critical for an accurate diagnosis of MPS VI [4], some types of analysis are not available or accessible in every country or in all areas of a country. In certain regions of countries, such as China, Malaysia, the Philippines and Thailand, the diagnosis of MPS VI might still be made based on the presence of typical MPS VI clinical features only. This is primarily due to the lack of diagnostic capacity and prohibitive costs. For example, in the Philippines diagnostic tests such as uGAG analysis and enzyme assay are not readily available. In China there are only three diagnostic centers located in Beijing, Shanghai and Guangzhou (http://www.chinararedisease.cn/3-jianjie.html). In most parts of western China, where there are large areas with limited medical services, especially in rural and low-income regions, laboratory facilities for diagnosis of genetic diseases are very scarce. Although diagnostic centers in Australia and Taiwan provide laboratory-testing support to other countries, shipment costs, long shipment duration leading to a decrease in enzyme activity, non-standardized sample collection and transport procedures can have a negative impact on the quality of the results. It is therefore important to establish diagnostic testing in more centers across the region and to improve training, collaboration and communication between different laboratories as well as between physicians and laboratories. The development of more efficient, straightforward and less expensive diagnostic tests is also warranted.

Treatment patterns for MPS VI differ across the Asia-Pacific region. The availability and accessibility of galsulfase vary considerably between countries/regions. Galsulfase is designated as an orphan drug in Australia, Japan and Taiwan. However, in China, Hong Kong, Malaysia, the Philippines and Thailand, orphan drug legislation is not yet formally established. ERT is currently covered by government funding in Australia, Hong Kong, Japan, Malaysia and Taiwan. One of the issues associated with ERT is that weekly 4-hour intravenous infusions can be burdensome, especially when the patient lives in a rural area and has to travel to the city medical center for ERT. Unlike in the US and UK [29,30], where patients may have their ERT at home, this is not yet an option for patients in Asia-Pacific countries and all infusions are performed in the hospital setting. Investigation of the feasibility of home infusion will be beneficial for the patients and their families as it may improve compliance to treatment. In countries where ERT is not currently available, symptomatic management remains the primary treatment option. There is also wide regional variation in the monitoring patterns of MPS VI.

Spinal cord compression (SCC) is one of the severe clinical complications of MPS VI, which may lead to lower-extremity weakness, spastic paraplegia or quadriplegia and, ultimately, early death if left undetected and/or untreated. Horovitz et al. (2011) recently highlighted the importance of monitoring MPS VI patients for SCC before and after the introduction of ERT. An increase in joint mobility, associated with ERT, may well lead to, or unmask, underlying SCC. In addition Horovitz et al. showed that neurophysiological abnormalities sometimes precede changes in MRI images and should, therefore, be accessed in MPS VI patient evaluations, so as to allow for timely intervention and better prognosis [22]. SCC is monitored in most of the countries surveyed, for example, it is monitored by MRI in Taiwan. However, in China it is rarely evaluated and monitored at diagnosis or follow-up. In countries such as China, Malaysia, Philippines and Thailand, regular visits can be challenging for some patients and their families, because there are only a few centers experienced in managing MPS patients. In these countries patients often have to travel far to reach a specialized medical care and they may well incur major costs in doing so. The lack of treatment options in China, Philippines and Thailand also pose another barrier for the parents to seek medical treatment.

The healthcare systems in each Asia-Pacific country differ greatly in structure and access to diagnostic tools and treatment. There are large variations in insurance coverage in different countries and across regions within a country. For example, there are no government-run reimbursement programs specific for MPS VI in the Philippines and Thailand but these do exist in Australia and Taiwan. In China, access to treatment and healthcare insurance varies depending on the city or province where the patient is a registered permanent resident. Imaging tests are covered in most countries/regions, while uGAG and enzyme assays are covered only in certain countries/regions. Molecular testing to confirm diagnosis is covered only in Australia and in some instances in Thailand. In Taiwan, these tests are free to patients but are not reimbursed by the government. Funding, to cover the cost of the tests, is

therefore sought from sponsors/donors. In terms of treatment, all therapies are available free of charge under public health cover in Australia whereas coverage can be limited in other countries. For example, surgical procedures such as hernia repair and carpal tunnel release are covered in all respondent countries except in China. A lack of resource for effectively managing MPS VI remains a challenge across much of the Asia-Pacific region, where the primary focus may be on treating diseases that affect large numbers of people rather than on managing a few with rare diseases.

Early initiation of treatment can lead to better clinical outcomes for patients with MPS VI [24,25,31,32], highlighting the importance of early diagnosis and the potential value of newborn screening. Some respondents noted that the availability of newborn screening would greatly enhance diagnosis. The National Referral Laboratory in Adelaide, Australia, has developed lysosomal protein profiling as a high throughput method to screen populations for lysosomal storage diseases, including MPS VI in a DBS [32]. However, due to the rarity of MPS VI and technical limitations, newborn screening programs are not generally considered to be practical on a population level.

One of the obstacles to advancing the identification, understanding and treatment of MPS VI identified in this survey is the relative paucity of information. To date, the largest multinational, multicenter disease registry for MPS VI has enrolled 132 patients over 5 years to track the long-term clinical outcomes [29]. However, only 3% of patients in this registry are Asian. Therefore, regional or national disease registries are urgently needed to facilitate a better understanding of the natural history of the disease, and to generate long-term data for evaluating existing and new therapies for this clinically heterogeneous disease. This is especially pertinent for MPS VI as it often begins in childhood, becomes progressively more debilitating and life-threatening throughout life, and is difficult to diagnose. Registries would need to be structured so that they accommodate different clinical practices in different countries/regions, because data are sometimes requested from procedures that are not routinely performed in a particular country. One example would be a request for MRI to measure hepatosplenomegaly in a country where abdominal palpation is a standard practice that is commonly used to assess organomegaly.

A further challenge is that in most countries there is a lack of specialized healthcare personnel to provide adequate and comprehensive care for patients with MPS VI. Although the management of some clinical problems associated with the disease may seem routine, management is typically complex and requires physicians to be aware of the specific issues. A multidisciplinary approach is also needed. As shown in this survey, subspecialties such as orthopedics, respiratory medicine, cardiology, ophthalmology, anaesthesiology, otorhinolaryngology and metabolic genetics all have a specific role in patient management. Therefore, it is important to establish an expert infrastructure in each country and within the Asia-Pacific region, to improve the specialist training and communications.

Conflict of interest

W-L Hwu and S-P Lin have received honoraria and research grants from BioMarin. L-H Ngu has received honoraria from Biomarin for speaking at a meeting organized by Biomarin. Staff members from J McGill's medical unit received educational grants from BioMarin, and BioMarin also funded the treatment of some of J McGill's patients in research trials. WM But, SC Estrada, X Gu, J Hui, M Kosuga, H Shi, A Tanaka, M-K Thong, T Okuyama, P Wasant, and D Wattanasirichaigoon have no conflicts of interest.

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ORIGINAL ARTICLE

Diagnosis and treatment trends in mucopolysaccharidosis I: findings from the MPS I Registry

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Abstract Our objective was to assess how the diagnosis and treatment of mucopolysaccharidosis I (MPS I) have changed over time. We used data from 891 patients in the MPS I Registry, an international observational database, to analyze ages at symptom onset, diagnosis, treatment initiation, and treatment allocation (hematopoietic stem cell transplantation, enzyme replacement therapy with laronidase, both, or neither) over time for all disease phenotypes (Hurler, Hurler–Scheie, and Scheie syndromes). The interval between diagnosis and treatment has become shorter since laronidase became available in 2003 (gap during 2006–2009: Hurler—0.2 year, Hurler–Scheie—0.5 year, Scheie—1.4 years). However, the age at diagnosis has not decreased for any MPS I phenotype over time, and the interval between symptom onset and treatment initiation remains substantial for both Hurler–Scheie and Scheie patients (gap during 2006–2009, 2.42 and 6.71 years, respectively). Among transplanted patients, an increasing proportion received hematopoietic stem cells from cord blood (34 out of 64 patients by 2009) and was also treated with laronidase (42 out of 45 patients by 2009). *Conclusions*: Despite the availability of laronidase since 2003, the diagnosis of MPS I is still substantially delayed for patients with Hurler–Scheie and Scheie phenotypes, which can lead to a suboptimal treatment outcome. Increased awareness of MPS I signs and symptoms by primary care providers and pediatric subspecialists is crucial to initiate early treatment and to improve the quality of life of MPS I patients.

Keywords Mucopolysaccharidosis I · Hurler · Hurler–Scheie · Scheie · Laronidase · Enzyme replacement therapy · Hematopoietic stem cell transplant

Introduction

The Mucopolysaccharidosis I (MPS I) Registry was created in 2003 with the purpose of characterizing the natural history and long-term health and treatment outcomes of this rare, life-

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threatening genetic disorder [25]. This report looks at how diagnosis and disease-specific treatment of MPS I have changed over time by analyzing aggregate data from nearly 900 patients enrolled in the MPS I Registry.

MPS I (McKusick 607014) is an autosomal recessive lysosomal storage disorder that is caused by deficient enzyme activity of α-L-iduronidase (IDUA), leading to lysosomal accumulation of glycosaminoglycans (GAGs) in multiple tissues throughout the body. MPS I is a chronic, progressive disease affecting the heart, eyes, bones, joints, respiratory system, facial appearance, viscera, and often the central nervous system. It has historically been classified clinically into three syndromes based on age of onset, rapidity of progression, and presence and degree of cognitive involvement [23]. Hurler syndrome describes patients with the most severe form of MPS I, with signs and symptoms typically appearing in infancy and a median age of death of 6.8 years when untreated [20]. Patients with Scheie syndrome present later in childhood and demonstrate slower symptom progression with preservation of cognition and survival into adulthood [30]. Hurler–Scheie describes an intermediate form with no or mild cognitive impairment and death usually occurring in adolescence or early adulthood when untreated. Patients with Hurler–Scheie and Scheie syndromes also have been referred to as having attenuated MPS I. Collectively, these forms represent different degrees of severity along a disease spectrum without strict clinical, biochemical, or molecular diagnostic criteria in place to differentiate them.

With an overall prevalence of 1:100,000 live births [19, 20, 27] and significant variability in presentation, diagnosis of MPS I in all its forms poses a true challenge [8, 32]. Initial diagnosis is primarily based on physician recognition of signs and symptoms. Deficient IDUA activity and excess urinary GAG excretion are seen in all patients, but do not accurately predict disease severity or form. Although some genotype–phenotype correlations have been established [11, 29], most known disease-causing mutations (over 100 to date) are individually unique ("private") and uncharacterized. Treatment of MPS I has also proven challenging as disease-specific treatment options are limited, intensive, and not curative. Hematopoietic stem cell transplantation (HSCT) has been used to treat more than 500 patients with MPS I since 1981 [1, 18] and is typically recommended for patients with Hurler syndrome under 2 years of age with normal cognition (DQ>70), as it can prolong survival, preserve neurocognition, and ameliorate some somatic features [21]. However, due to its significant morbidity and mortality, HSCT is reserved for the most severe form of MPS I [5, 6, 28]. The allogenic stem cell infusion is given following conditioning with chemotherapeutic agents used to suppress the immune response; when successful, the transplant is a one-time procedure, though graft failure may necessitate subsequent transplants. Enzyme replacement therapy (ERT) with laronidase (recombinant human α-L-iduronidase; Aldurazyme®, BioMarin Pharmaceutical and Genzyme, a Sanofi Company) was approved in 2003 to treat the non-neurologic manifestations of MPS I and is the primary treatment option for patients with Hurler–Scheie and Scheie syndromes. Laronidase is also used to treat Hurler patients who are not candidates for HSCT because of age, health status, access to transplant, or parental choice. Laronidase must be given as a weekly peripheral or central intravenous infusion and is a lifelong therapy.

The timing of treatment initiation, and therefore of diagnosis, is thought to be an important factor for the success of both HSCT and laronidase. Developmental outcomes are better when transplant occurs before 24 months of age [26]. Laronidase may also be more beneficial when started early, as suggested by a case report of a sib pair with Hurler–Scheie syndrome [15]. Other than laronidase and HSCT, additional management of MPS I is symptom-based and largely supportive, such as surgical interventions (e.g., adenotonsillectomy, hernia repair, ventriculoperitoneal shunt, cardiac valve replacement, carpal tunnel release, spinal decompression); physical, occupational, and speech therapies; respiratory support (e.g., continuous positive pressure ventilation with oxygen supplementation); hearing aids; and medications for pain and gastrointestinal disturbances.

With the intent of improving the long-term health outcomes and quality of life of patients with MPS I worldwide, we report how the chronology of symptom onset, diagnosis, and treatment initiation with HSCT and laronidase have evolved over time among Registry patients. We also analyze treatment trends among patients in the MPS I Registry with regard to the use of HSCT and laronidase by reported phenotypes. Although there are some genotype–phenotype correlations in MPS I [29], genotype information was not included in the analysis since treatment decisions are usually based on clinical manifestations, as newborn screening is not yet available.

Methods

Variables analyzed and statistical methods

Data entered into the Registry as of March 2010 were analyzed. The 891 MPS I patients came from 179 sites in 33 countries (Table 1). Regionally, 46.6% of the patients came from Europe and the Middle East, 35.1% from North America, 14.9% from Latin America, and 3.4% from Asia Pacific. MPS I forms (Hurler, Hurler–Scheie, Scheie, and unknown phenotypes) were analyzed by year of treatment initiation and year of diagnosis with respect to the following treatment groups: HSCT, ERT with laronidase, both laronidase and HSCT, or neither treatment. A phenotype designation of "unknown" signifies that the reporting physician either checked

Table 1 Enrollment in the MPS I Registry by region and country

Region	Country	Number of patients
Europe and Middle East (47%, n=415)	Belgium	9
	Czech Republic	11
	Denmark	5
	France	63
	Germany	28
	Hungary	2
	Ireland	9
	Italy	26
	Netherlands	37
	Norway	1
	Poland	20
	Portugal	5
	Russia	1
	Saudi Arabia	2
	Slovakia	1
	Spain	25
	Sweden	4
	Turkey	3
	UK	163
North America (35%, n=313)	Canada	54
	USA	259
Latin America (15%, n=133)	Argentina	17
	Brazil	82
	Chile	7
	Colombia	6
	Mexico	20
	Venezuela	1
Asia Pacific (3%, n=30)	Australia	1
	Japan	8
	Korea	13
	New Zealand	1
	Singapore	1
	Taiwan	6
		Total 891

"undetermined" or left the field blank on the Patient Enrollment form. Treatment chronology was determined by analyzing age at symptom onset, diagnosis, and first disease-specific treatment (either HSCT or ERT) in relation to reported phenotype and year of diagnosis. These analyses excluded patients who reported symptom onset after diagnosis, as occurs in siblings of children already carrying an MPS I diagnosis, whose diagnosis and treatment chronology are not representative of the general MPS I population. Three time periods were examined: patients diagnosed before 2003 (prior to laronidase approval), patients diagnosed in 2003–2005, and patients diagnosed in 2006–2009. The latter two time periods are not event-specific but were chosen to allow for sufficient numbers of patients in each group for meaningful comparison. Among Hurler patients who underwent HSCT, age at first HSCT was analyzed by year of first HSCT.

Treatment initiation was defined as the initial laronidase infusion or the initial HSCT, whichever treatment modality was used first. Among transplanted patients, the stem cell source (bone marrow, umbilical cord blood, or peripheral blood) was determined. Among transplanted patients receiving laronidase, the timing of laronidase with respect to transplant was analyzed. Peri-transplant ERT was defined as laronidase given at any time during the interval 6 months prior and 3 months after HSCT. With respect to use of ERT in conjunction with transplantation, the distribution of patients by number and location (country) of treatment centers was also determined. Variables are summarized using descriptive statistics, including mean, median, standard deviation, designated percentiles, and minimum and maximum values. As data are not available for all variables in every patient, the number of observations is always designated.

Results

Patient demographics

The demographic profiles of the 891 Registry patients are shown in Table 2. Patients classified as having Hurler syndrome made up more than half of the study population, while patients with the Hurler–Scheie and Scheie forms made up one quarter and one tenth, respectively. Caucasian patients made up >80% of the Hurler and Scheie groups, but only 61% of the Hurler–Scheie group. Approximately 9% of patients had an unknown form. Males and females were equally distributed in this MPS I population, as expected for an autosomal recessive disorder. Consistent with clinical severity, the median ages of symptom onset, diagnosis, and treatment initiation (HSCT or laronidase) were earliest for Hurler patients (0.5 year, 0.8 year, and 1.4 years, respectively), intermediate for Hurler–Scheie patients (1.9, 3.8, and 8.6 years), and latest for Scheie patients (5.4, 9.4, and 17.1 years). The intervals between median age at onset of symptoms to diagnosis and from diagnosis to treatment initiation were on the order of several months for Hurler patients, a few years for Hurler–Scheie patients, and several years for Scheie patients.

Chronology of symptom onset, MPS I diagnosis, and treatment initiation

Figure 1 shows the median age at symptom onset, diagnosis, and initiation of treatment with either HSCT or laronidase for each disease form by year of diagnosis: <2003, 2003–2005, and 2006–2009. Several notable trends were observed. The

Table 2 Mucopolysaccharidosis I Registry: patient demographics

Baseline characteristics	Hurler	Hurler–Scheie	Scheie	Undetermined	Missing	Overall
Number of patients (%)	508 (57)	209 (23.5)	97 (10.9)	28 (3.1)	49 (5.5)	891
Male (%)	255 (50)	95 (46)	47 (49)	14	31	442 (50)
Caucasian (%)	405 (81.2)	127 (61.4)	81 (83.5)	21	3	637 (76.3)
Black (%)	16 (3.2)	13 (6.3)	2 (2.1)	0	0	31 (3.7)
Hispanic (%)	38 (7.6)	14 (6.8)	1 (1)	4	1	58 (6.9)
Asian (%)	13 (2.6)	37 (17.9)	7 (7.2)	1	1	59 (7.1)
Other ethnicity (%)	27 (5.4)	16 (7.7)	6 (6.2)	1	0	50 (6)
Median age at last data entry (range) [total number]	6.3 (0.4–35.9) [508]	13 (1.9–49.8) [209]	22.2 (5.4–64.3) [97]	6.9 (0.3–46.7) [28]	8.2 (0.9–40.1) [49]	8.6 (0.3–64.3) [891]
Median age of symptom onset (range) [total number]	0.5 (0–6.5) [485]	1.9 (0–12.4) [187]	5.4 (0–33.8) [87]	0.8 (0.1–7.2) [24]	1.6 (0.6–5.7) [4]	0.8 (0–33.8) [787]
Median age of diagnosis (range) [total number]	0.8 (0–23.8) [508]	3.8 (0–38.7) [209]	9.4 (0–54.1) [97]	1.3 (0–43.9) [28]	1.6 (0.3–33) [49]	1.3 (0–54.1) [891]
Median age of first treatment (range) [total number]	1.4 (0.1–31.2) [438]	8.6 (0.3–47.2) [197]	17.1 (3.1–62.9) [85]	2.9 (0.3–44) [23]	6.6 (0.5–34.8) [27]	2.8 (0.1–62.9) [770]
Median age at death (range) [total number]	3.8 (0.4–27.2) [156]	17.4 (7.5–30.3) [16]	29 (17.4–46.6) [4]	5.1 (1.8–9.7) [4]	0	5.1 (0.4–46.6) [180]

median age at symptom onset remained relatively stable for Hurler and Scheie patients over time, whereas it decreased by approximately 1.5 years for Hurler–Scheie patients after 2003. On the other hand, the age at diagnosis was stable over time for all forms. The interval between median age at diagnosis and initiation of treatment decreased for all groups after 2003, when laronidase was approved. The decrease was more notable for Hurler–Scheie and Scheie patients (several years) than for Hurler patients (several months). During 2006–2009, the median interval between age at diagnosis and initiation of treatment for individuals with Hurler–Scheie was 0.5 year, and for Scheie patients, 1.4 years. However, even after the 2003 approval of laronidase, the median interval between the age of symptom onset and the age of treatment initiation between 2006 and 2009 for the Hurler–Scheie and Scheie patients was 2.42 and 6.71 years, respectively.

Disease-specific treatment allocation by MPS I phenotype

The allocation of disease-specific treatments over time for the 770 treated patients is shown in Fig. 2. HSCT has been used primarily in Hurler patients, but especially so since 2003. Since laronidase became available, the proportion of patients treated with laronidase has increased in all disease forms. Among Hurler patients, almost half of those who began treatment in 2006–2009 received laronidase alone, and approximately two thirds of those who were transplanted also received laronidase.

Analysis of untreated MPS I patients

Of the 891 MPS I patients, 116 (13%) were listed as untreated with either laronidase or HSCT. Over time, the proportion of untreated patients has decreased. When analyzed by year of diagnosis, 83 of the 534 patients (16%) diagnosed before 2003 were untreated, as compared with 21 of the 197 patients (11%) diagnosed in 2003–2005, and 11 of the 159 patients (7%) diagnosed in 2006–2009. Among untreated patients, all three disease forms as well as patients with an undetermined/missing phenotype were represented. Of the 115 total untreated patients who had a date of diagnosis, 56 (49%) were Hurler patients diagnosed before 2003.

HSCT and laronidase treatment trends

Among all patients with Hurler syndrome receiving HSCT, the median age at first transplant has not changed over time (Fig. 3) though the proportion of patients receiving stem cells from cord blood or peripheral blood rather than bone marrow has increased from 26 out of 158 patients (16.5%) before 2003 to 33 out of 65 patients in 2003–2005 and 39 out of 64 patients in 2006–2009 (Fig. 4). Among patients receiving stem cells from bone marrow or peripheral blood, the majority of donors were unrelated and the proportion of

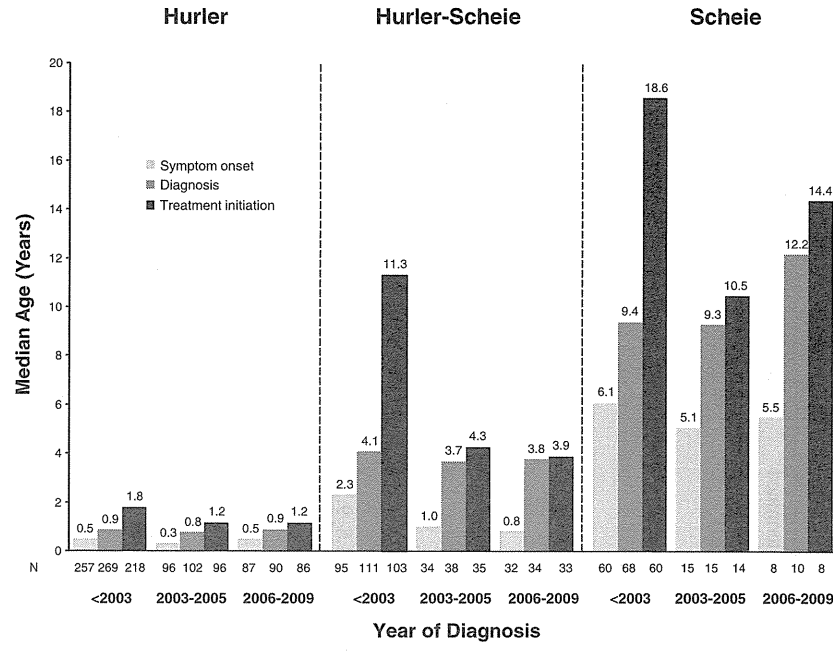

Fig. 1 Median age at symptom onset, diagnosis, and initiation of treatment. *Numbers* below each *bar* denote the number of Registry patients in each analysis and year of diagnosis. All data are as of March 2010. Median age is given in years

related versus unrelated did not change appreciably over time, although small sample sizes and missing donor information may have masked any trends.

The use of laronidase has greatly increased over time among patients receiving HSCT, the vast majority of whom have Hurler syndrome (Fig. 5). Since 2007, 42 out of 45

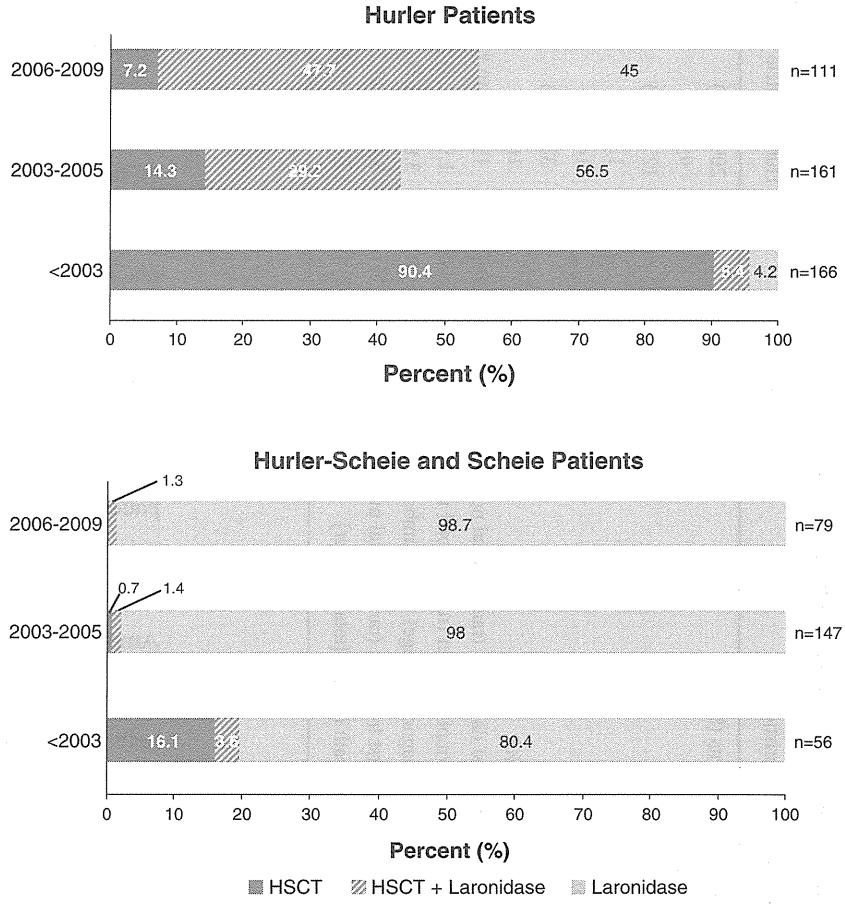

Fig. 2 Distribution of treatment modalities over time. *Data* represent all patients enrolled in the Registry as of March 2010 who report treatment with either HSCT, laronidase, or both. An additional 116 patients reported no treatment

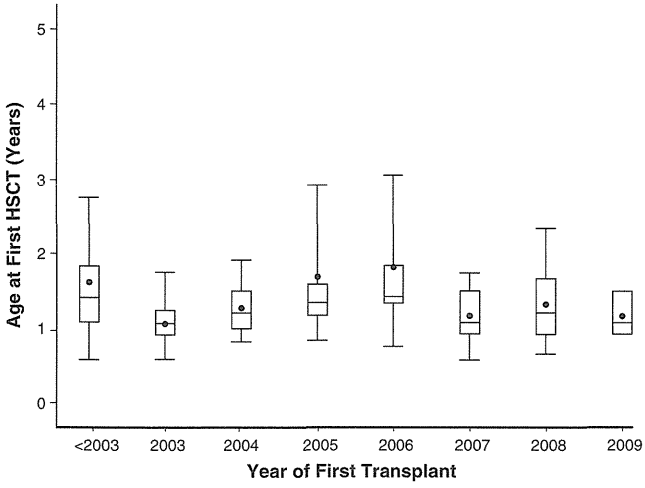

Fig. 3 Median age at first transplant by year of first transplant in Hurler patients. All data are as of March 2010. *Horizontal lines* within in each *box* represent the median age, and *dots* represent the mean age. *Lower and upper box edges* represent the 25th and 75th percentiles; *lower and upper whiskers* represent the 5th and 95th percentiles

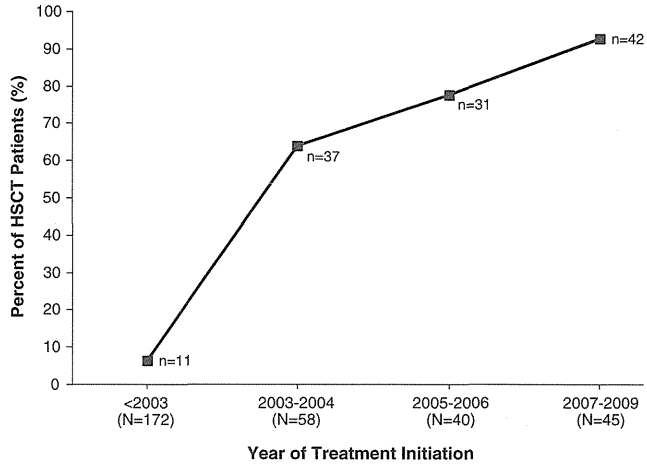

Fig. 5 Use of laronidase with HSCT by year of first treatment. First treatment is defined as either HSCT or laronidase, whichever occurred first. For all treatment periods, 92% of Registry patients who received both HSCT and laronidase received laronidase during the peri-transplant period, defined as any time during the interval 6 months before and 3 months after HSCT. All data are as of March 2010

transplanted patients also reported receiving laronidase. While this analysis included laronidase given to HSCT patients at any time in their disease course, nearly all patients (102 out of 111; 91.9%) who received both treatments after 2003 received laronidase in the peri-transplant period. The 42 patients who received laronidase and HSCT, with first treatment in 2007–2009, came from ten centers (18 patients) in the USA and seven centers (24 patients) in Europe (Spain, Belgium, Italy, UK, Netherlands, Czech Republic). Ten of the 17 centers reported only one patient, while the maximum number of patients treated at any one center was 11. The three patients who underwent their first transplant in 2007–2009 and did not receive laronidase came from different centers in Europe.

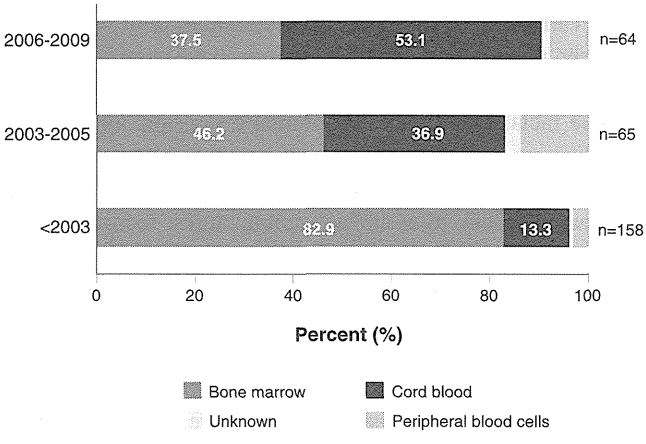

Fig. 4 Hematopoietic stem cell source by year of first HSCT in transplanted patients. Depicted are the relative proportions of various sources of stem cells used for HSCT. All data are as of March 2010

Discussion

Analysis of data from the MPS I Registry has allowed for improved understanding of the natural history of MPS I and will enable evaluation of the impact of therapeutic advances on morbidity and mortality [2, 3, 25, 30]. Limitations of observational registries such as the MPS I Registry, in which anonymized data are submitted voluntarily, include incomplete, missing, or inaccurate data, as well as losses to follow-up and lack of standardization of patient assessments. The voluntary nature of the Registry may also lead to biased data as not all physicians who manage MPS I patients use the MPS I Registry. Despite these potential biases, the data presented here offer insight into diagnosis and treatment trends in the largest cohort of MPS I patients ever evaluated.

Our data show that the median age at diagnosis has not decreased over time for any form of MPS I, despite available treatment options. Although Hurler patients tend to be diagnosed within a few months of symptom onset, Hurler–Scheie and Scheie patients still remain undiagnosed for years after symptom onset (Fig. 1). This gap not only represents years of reduced quality of life that would likely be ameliorated by treatment, but also a lost opportunity for preventing or delaying irreversible disease manifestations, as well as for genetic counseling about the risk of future siblings being affected. Sibling case studies and studies in the MPS I dog model suggest that starting enzyme replacement therapy with laronidase shortly after birth can significantly improve clinical outcome [13–15, 33]. Most patients who begin treatment at a very young age have an older sibling with a known diagnosis of MPS I. While studies of affected sib pairs will certainly provide more information

about the potential impact of early laronidase treatment, prompt clinical diagnosis will be imperative for the majority of MPS I patients to benefit from this information. Demonstration of substantial improvement in clinical outcomes with earlier diagnosis and treatment of MPS I along with an enhanced ability to predict phenotype at birth through genotype–phenotype correlations and/or disease biomarkers will underscore the need for broad implementation of a newborn screening program for this rare, life-threatening disorder and will aid in decisions of which patients to treat with what therapies, and how early to treat them.

As would be expected, the time interval from diagnosis to initiation of disease-specific treatment decreased following the availability of laronidase in 2003, especially for Hurler–Scheie and Scheie patients, who until then had generally been offered only palliative, symptom-based treatments. Prior to 2003, ERT with laronidase was available only through clinical trials, the largest of which enrolled mostly older children, adolescents, and young adults with a mean duration of 13 years since symptom onset [9]. In addition, the proportion of untreated patients has decreased over time. Despite the decrease in time from diagnosis to treatment, there still exists a delay of 0.5 year and 1.4 years between median ages at diagnosis and treatment for Hurler–Scheie and Scheie patients, respectively, during the most recent time interval of 2006–2009. In comparison, for patients with the Hurler form, there was almost no delay between diagnosis and treatment. This may be due to parents and/or diagnosing physicians perceiving the attenuated phenotypes as milder, or less urgent, thereby further delaying time to treatment. In addition, it may represent time needed for laronidase approval by reimbursement authorities [7]. There may also be regional differences in the delay between diagnosis and treatment, given that laronidase was not approved outside the European Union and the USA until 2005.

Interestingly, when looking at Fig. 1, the age of symptom onset appears to have decreased somewhat in both the Hurler–Scheie and Scheie populations. Rather than a true change in the natural history of MPS I disease, this finding is more likely to be secondary to small patient numbers and the retrospective awareness that certain common early symptoms (such as hernia and chronic otitis media) are often related to MPS I. Also, while the actual age of diagnosis has not greatly improved, parents and physicians may have improved in the retrospective recognition of the common early manifestations of the disease, which led to younger ages of symptom onset in the attenuated patient populations.

Of note, patients with an unknown disease form tended to present with MPS I symptoms between the ages of patients classified as Hurler and Hurler–Scheie. Similarly, they were typically diagnosed and treated at ages in between those of Hurler and Hurler–Scheie patients as well. This suggests that patients in the Registry with an unknown disease form are more likely to be on the more severe end of the MPS I spectrum.

This analysis identified several shifts in clinical practice, such as the increasing use of laronidase among transplanted patients, particularly in the peri-transplant period, and the increasing use of cord blood as a stem cell source. The proportion of unrelated versus related donors for HSCT has remained relatively stable as unrelated bone marrow donors have been replaced by unrelated cord blood donors. Use of laronidase in the peri-transplant period has been reported to be safe and well tolerated without interfering with engraftment or increasing the risk of graft-versus-host disease [6, 12, 16, 17, 31, 34]. Laronidase treatment may be particularly beneficial in patients in poor clinical condition prior to HSCT, to help improve their eligibility for transplant and tolerance of the full-intensity transplant conditioning [12, 16, 17, 24, 31].

In addition, an increasing proportion of Hurler patients in the Registry is receiving laronidase alone (Fig. 2), reflecting the fact that HSCT is not available in many parts of the world, while the majority of transplanted patients are from North America and Europe. A recent MPS I Registry analysis comparing patients from Latin America to those from the rest of the world found that less than 1% of patients in Latin America had been transplanted, compared to 27% of patients from the rest of the world [22]. Our MPS I Registry patients came from over 30 countries in Europe and the Middle East, North America, Latin America, and Japan and Asia Pacific (Table 1). Regional differences in treatment availability would also impact the ages at treatment initiation as well as the proportion of untreated patients. For example, in Brazil, which has a universal-access public health care system, neither laronidase nor HSCT is covered by government or specialized pharmaceutical programs [7].

Narrowing the gap between symptom onset and MPS I diagnosis is of the utmost importance and largely relies on increased recognition of clinical red flags by community physicians and pediatric specialists managing the many MPS I-related symptoms, such as otolaryngologists, orthopedists, rheumatologists, and ophthalmologists. While there is significant variability of first presenting symptom both within and between phenotypes, certain symptoms have been consistently noted to appear earlier than others in the MPS I population. Coarse facial appearance, abdominal distension, and corneal clouding are among the most common presenting symptoms in children with Hurler syndrome [4, 10]. In the patients with attenuated forms, joint stiffness/contractures, recurrent ENT symptoms, corneal clouding, and umbilical hernias are the most prevalent initial symptoms [4, 30, 32]. In addition, certain constellations of symptoms should raise a physician's suspicion of MPS I. In a 2009 study of surgical procedures in 544 MPS I Registry patients representing all clinical forms, 72% had had at least one surgical procedure, with a median of 3 to 4 surgeries per patient, and with nearly half of the patients reporting two or more surgeries by age 4 years [2]. Surgeries often appeared unrelated, such as combinations of ear tubes,

hernia repair, and tendon releases in the same patient, and often preceded the patient's MPS I diagnosis, particularly in the attenuated phenotypes. Many procedures were also performed at ages atypical for the general pediatric population, such as younger ages of tonsillectomy/adenoidectomy, and older ages of hernia repair in patients with MPS I.

Given the rarity of MPS I, increased efforts to educate community pediatricians and pediatric surgical subspecialists on clinical red flags that should prompt a genetics referral is of the utmost importance. An MPS I Registry analysis of early presenting symptoms for each MPS I form is underway to aid the front-line clinicians with earlier symptom recognition. Furthermore, future analysis of MPS I long-term therapeutic outcomes is merited, as large-scale evidence of improved outcomes with earlier diagnosis and treatment would reinforce the need for increased recognition of clinical red flags, allow better understanding of the therapeutic potential of current treatment modalities, and underscore the need for newborn screening for this disorder.

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