The diagnostic journey of patients with mucopolysaccharidosis I: A real-world survey of patient and physician experiences

Stefano Bruni [a,*], Christine Lavery [b], Alexander Broomfield [c]

[a] Sanofi Genzyme, Strada Scaglia Est 136, 41126 Modena, Italy
[b] Society for Mucopolysaccharide Diseases, MPS House, Repton Place, White Lion Road, Amersham, Buckinghamshire HP7 9LP, UK
[c] Royal Manchester Children's Hospital, Oxford Road, Manchester M13 9WL, UK

ABSTRACT

Mucopolysaccharidosis type I (MPS I) is an inherited lysosomal storage disease. Affected individuals have disease ranging from attenuated to severe with significant disease burden, disability, and premature death. Early treatment with enzyme replacement therapy and/or stem cell transplantation can reduce disease progression and improve outcomes. However, diagnosis is often delayed, particularly for patients with attenuated phenotypes. We conducted a survey of 168 patients and 582 physicians to explore health care seeking patterns and familiarity of physicians with MPS I symptoms. Patients with attenuated MPS I typically first presented with stiff joints or hernia/bulging abdomen, and patients with severe disease with noisy/difficult breathing, or hernia/bulging abdomen. There was a mean delay from time of symptom presentation to diagnosis of 2.7 years for patients with attenuated disease, with a mean of 5 physicians consulted before receiving a correct diagnosis. MPS I was most commonly misidentified by physicians as rheumatoid arthritis (48–72%), with a wide variety of suspected diseases, including lupus. *CONCLUSION:* Patient and physician real-world surveys show that MPS I is under-recognized and diagnosis of MPS I remains delayed, particularly in patients with attenuated disease. Across regions and specialties, physicians require differential diagnosis education in order to improve early detection and early treatment initiation of MPS I.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Mucopolysaccharidosis I (MPS I) is a life-threatening disease resulting from deficiency of α-L-iduronidase (IDUA), a lysosomal enzyme responsible for glycosaminoglycans (GAGs) dermatan and heparan sulfate metabolism [1]. MPS I is a pan-ethnic, autosomal recessive disease with an estimated incidence of 1/100,000 live births [2]. Disease phenotypes range from severe (Hurler syndrome) to attenuated (Hurler-Scheie and Scheie syndromes) depending on presence or absence of neurocognitive involvement and rate of disease progression [1,3,4].

If untreated, MPS I results in significant disease burden, disability, and premature death from respiratory and cardiac disease, and in the most severe phenotype, neurodegeneration due to GAG accumulation [2]. Treatment options include hematopoietic stem cell transplantation (HSCT) for severe disease, and enzyme replacement therapy (ERT)

with laronidase (recombinant human IDUA; Aldurazyme®) for attenuated MPS I [5–8]. Treatment outcomes depend on disease severity and age at treatment initiation [9,10]. Early treatment considerably improves patient outcomes during long-term therapy and is crucial to reduce disease progression before irreversible damage occurs [10–14]. However, diagnosis of MPS I is often delayed, particularly for patients with attenuated phenotypes [15–17].

Early signs and symptoms of MPS I are non-specific and diverse, and suggestive of many other diseases. While pediatricians and primary care physicians are typically consulted first, cardiac symptoms, ocular clouding, recurrent ear infections and hearing loss, hernias, and spinal deformity often result in referrals to specialists [6,16]. Given the musculoskeletal symptoms associated with MPS I, rheumatologists are often consulted. In order to understand the real-world diagnostic journey for patients with MPS I, we used survey-based data to investigate the patterns of healthcare seeking by patients and the familiarity of pediatricians and rheumatologists with MPS I.

2. Methods

This international, voluntary, quantitative study used purposive, non-random sampling to collect data from surveys administered to patients with MPS I and physicians likely to encounter these patients. No

---

Abbreviations: Card, cardiologist; ENT, ear nose and throat; ERT, enzyme replacement therapy; EU, Europe; GAG, glycosaminoglycan; Gen Pract, general practitioner; Gen/Met Dis, geneticist/metabolic disease specialist; HSCT, hematopoietic stem cell transplant; IDUA, α-L-iduronidase; LA, Latin America; MPS I, mucopolysaccharidosis Type I; Neuro, neurologist; Ophth, ophthalmologist; Ortho, orthopedist; Ped or P, pediatrician; Pulm, pulmonologist; Rheum or R, rheumatologist; US, United States.

* Corresponding author at: Strada Scaglia Est 136, 41126 Modena, Italy.
E-mail addresses: stefano.bruni@genzyme.com (S. Bruni), C.Lavery@mpssociety.org.uk (C. Lavery), Alexander.Broomfield@cmft.nhs.uk (A. Broomfield).

chart review was conducted. Surveys were available in English, French (Canadian and France), Brazilian Portuguese, Mexican Spanish, German, and Italian (Italian for physician surveys only).

2.1. Patient participants

Surveys were distributed to patients/caregivers with confirmed MPS I from 2009 through 2013 by direct mail/email via local MPS patient advocacy/support organizations in Europe, North America, Central America, and Latin America. Participation was not limited by patient age, duration of MPS I diagnosis, or MPS I treatment. All participants were informed of study aims and confidentiality, and gave consent upon survey submission.

The survey consisted of 17 open- and close-ended questions related to:

— Symptoms prompting physician visits
— History and pattern of referrals to specialists
— Diagnosing physician
— Time to diagnosis
— Alternate diagnoses
— Time to and type of treatment

2.2. Physician participants

Eligible board certified rheumatologists and pediatricians in Europe, North America, Central America, and Latin America identified from WorldOne database (SERMO, Charlotte, NC) were in practice between 3 and 30 years with direct patient care at least 75% of the time. Government employees or paid advisors to pharmaceutical companies were ineligible.

Physicians reviewed an unidentified case of attenuated MPS I and were asked a series of guided open- and close-ended questions in an online survey between 2012 and 2014.

Case Information:

Initial Information: 8 year old female presenting with slow progressive stiffness of joints, particularly of hands and fingers, has impaired fine motor skills, and limited range of motion in shoulders. No clinically apparent signs of inflammation. Past medical history is significant for surgical repair of umbilical hernia and two recent tympanostomy tube placements. Additional information: Patient has not responded to prior courses of steroid therapy, and is negative for rheumatoid factor.

Questions:

– Number of patients similar to the case study seen in the last year
– Possible diagnoses
– Diagnostic tests they would perform
– Specialty of physicians they would refer the patient to
– Experience with seeing and treating patients with MPS I

Physicians assessed the number of currently suspected patients with MPS I and the number of patients they would test for MPS I prior to and after reviewing educational materials.

Table 1
Patient characteristics and physician profiles.

Patient characteristics	All	Phenotype			Region		
	N = 168	Attenuated N = 60	Severe N = 93	Other N = 15	US N = 24	LA N = 58	EU N = 86
Gender (% pts)	n = 142	n = 53	n = 89			n = 56	n = 86
Male, female	49, 51	47, 53	53, 47			52, 48	48, 52
Age (% pts)	n = 165				n = 24	n = 57	n = 84
0–2 yr.	2				0	2	4
>2–11 yr	44				0	67	40
>11–18 yr	19				0	16	26
>18 yr	35				100	16	30
Age at presentation, yr	n = 157	n = 54	n = 88	n = 15			
Mean	2.9	5.5	1.2	3.9			
Range	<1mo–39 yr	<1mo–39 yr	<mo–8 yr	<1mo–20 yr			
Age at diagnosis, yr	n = 162	n = 56	n = 91	n = 15			
Mean	4.4	8.2	1.7	6.2			
Range	<1mo–48 yr	<1mo–48 yr	<mo–8.5 yr	<1mo–21 yr			
Treatment history, % pt	n = 110	n = 51	n = 59		n = 24		n = 86
ERT	64	82	47		71		62
HSCT							56
Both ERT and HSCT							22

Physician profile	North America		Latin America		Europe	
	Rheum N = 60	Ped N = 90	Rheum N = 60	Ped N = 81	Rheum N = 90	Ped N = 201
Years in practice	17.1	18.5	12.5	15.4	15.8	16.6
% of time in direct patient care	94	94	91	92	91	89
% of time in hospital setting	23	28	45	48	60	64
% of physicians						
>70% time hospital-based	8	16	18	26	56	62
30–70% time hospital-based	23	22	55	43	11	9
<30% time hospital-based	68	62	27	31	33	29
% physicians who have seen a confirmed MPS patient in past 5 years	18	14	15	26	19	25
% physicians						
Somewhat familiar with MPS I	30	31	30	30	47	46
Heard of, but not familiar with MPS I	52	63	65	63	42	46
Never heard of MPS I	15	6	5	4	8	3
Very familiar with MPS I	3	0	0	4	3	5
If at least somewhat familiar with MPS I, % of physicians very comfortable with diagnosing MPS I	15	0	6	15	7	7

ERT = enzyme replacement therapy; EU = Europe; HSCT = hematopoietic stem cell transplant; LA = Latin America; US = United States.