Clinical Profile Among Brazilian Mucopolysaccharidosis type II Patients: Subgroup Analysis from the Hunter Outcome Survey

Journal of Inborn Errors
of Metabolism & Screening
2023, Volume 11: e20230002
DOI: https://doi.org/10.1590/2326-4594-JIEMS-2023-0002

Dafne D G Horovitz[1], Márcia G Ribeiro[2], Angelina X Acosta[3], Ana C Monteiro[4], Jaco Botha[5] and Roberto Giugliani[6]

Abstract

Mucopolysaccharidosis type II (MPS II) is a rare genetic, multiorgan disease. Little information about the Brazilian context is available to date; thus, this descriptive subgroup analysis was conducted on Brazilian data from the Hunter Outcome Survey (HOS), including clinical characteristics among MPS II patients from Brazil. HOS is a global, multi-center, long-term, observational registry of patients with MPS II (NCT03292887). Variables related to organ system involvement, signs and symptoms, surgical procedures and survival among Brazilian patients were extracted from HOS database. Data from 153 Brazilian patients with MPS II were analyzed. Musculoskeletal (96.6%), abdomen/gastrointestinal (95.2%), neurological (88.7%), pulmonary (86.2%), and ear (81.3%) were the most frequently observed organ/systems involved. Regarding signs and symptoms, the most prevalent symptom was coarse facial features consistent with the disease (94.6%), followed by joint stiffness and limited function (89.3%), hernia (84.2%) and hepatomegaly (82.2%). Median survival time was 22.0 years, and the major cause of death was respiratory failure (31.8%). These data may be helpful to understand disease characteristics and to help improve the quality of MPS II patient care in Brazil.

Keywords

Mucopolysaccharidosis II, Lysosomal Storage Diseases, Survival, Signs and Symptom.

Introduction

There are several types of mucopolysaccharidoses (MPS), caused by deficiencies in one of the enzymes involved in the degradation pathway of glycosaminoglycans (GAGs). It is estimated that the prevalence of MPS ranges from 1.8 in Poland to 16.9 per 100,000 live births in Saudi Arabia. Regarding MPS II, the prevalence ranges from 0.1 in British Columbia to 2.16 per 100,000 live births in Estonia [1].

Mucopolysaccharidosis type II (MPS II) is a genetic condition, also known as Hunter syndrome. It is an X-linked disorder, that mainly affects hemizygous males and is caused by mutations in the lysosomal iduronate-2-sulfatase (*IDS)* gene [2,3].

MPS II is a multiorgan disease that shows variable age of onset and rate of progression. Most common signs and symptoms are related to recurrent respiratory infections, coarse facial features, joint stiffness, otitis media, hearing loss, umbilical/inguinal hernias, and hepatosplenomegaly, emerging most frequently within the first years of life [4,5]. There is few information about MPS II patients' survival in the current literature, however available estimates range from 11.43 to 33.0 years, depending on the characteristics of the studied population [6–9].

[1] Fundação Oswaldo Cruz, Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira, Rio de Janeiro, RJ, Brazil.

[2] Universidade Federal do Rio de Janeiro, Instituto de Puericultura e Pediatria Martagão Gesteira, Rio de Janeiro, RJ, Brazil.

[3] Universidade Federal da Bahia, Faculdade de Medicina da Bahia Departamento de Pediatria, Salvador, BA, Brazil.

[4] Takeda, Departamento de Assuntos Médicos, São Paulo, SP. Brazil.

[5] Takeda Pharmaceuticals International AG, Opfikon, Zürich, Switzerland.

[6] Universidade Federal do Rio Grande do Sul, Serviço de Genética Médica, Programa de Pós-Graduação em Genética e Biologia Molecular, Porto Alegre, RS, Brazil.

Received February 17, 2023. Accepted for publication July 05, 2023.

Corresponding Author:
Ana Cristina Monteiro, E-mail: ana-cristina.monteiro@takeda.com

Enzyme replacement therapy is the current standard of care [10]. A curative alternative is not available to date. Disease management may also involve the use of hematopoietic stem cell transplantation (HSCT) or palliative care with symptomatic surgeries, and anti-inflammatory treatment [10,11]. Brazilian Clinical Protocol and Therapeutic Guidelines establishes the use of enzyme replacement therapy with intravenous idursulfase as a specific therapy and HSCT, with a multidisciplinary approach [10].

In Brazil, three studies have previously reported the birth prevalence and data ranges from 1.04 to 1.57 per 100,000 live births for all mucopolysaccharidoses and 0.37 to 1.32 per 100,000 live births for only MPS II [1,12,13]. The majority of MPS cases in the country are characterized as MPS II [1].

The Hunter Outcome Survey (HOS) is a global, observational registry of patients diagnosed with MPS II (NCT03292887). The registry was stablished in 2005 and have included more than a thousand MPS II patients, from 29 countries in 4 continents, 153 from Brazil until April, 2021 [14,15].

Data from several countries included in the HOS were previously published, however there have not been any publications focused only on Brazilian data to date [7,8,16–34]. Thus, this subgroup analysis was conducted aiming to describe Brazilian data from the HOS, including those related to the occurrence of different signs and symptoms, performance of surgical procedures and MPS II survival in the country.

Methods

Design

This is a subgroup analysis, assessing data from Brazilian patients enrolled in HOS. The HOS is a global, multicenter, long-term, noninterventional observational registry, designed to acquire real-world data from patients with MPS II obtained in their usual medical care environment. The HOS registry included patients that received or are receiving treatment with idursulfase as prescribed by their physician following locally approved prescribing information or those receiving no treatment. Participants enrolled in an interventional clinical trial and those receiving treatment for MPS II with an enzyme replacement therapy product other than idursulfase were excluded. Information about idursulfase safety and effectiveness have been collected, beyond secondary endpoints such as the disease natural history, dosing of idursulfase, scoring in five domains in the patient- and parent-reported versions of the HS-FOCUS questionnaire [35]. Participants who were alive at the time of enrollment in HOS ("Prospective patients") and deceased participants ("Retrospective patients") were eligible to be enrolled in HOS, and for this analysis, both cohorts were considered. The analysis fulfilled ethical standards and was conducted in accordance with local applicable regulations. In Brazil, Research Ethics Committee approved the study, and all participants signed an informed consent before assignment. HOS is registered in ClinicalTrials.gov (NCT03292887).

Data Sources

Data collected in HOS include patient information extracted retrospectively from previous and current hospital records as well as patient information collected prospectively during follow-up assessments. Data entry is voluntary and at the discretion of the investigator. The analysis of data from center, regional, and global cohorts of patients is performed under the supervision of scientific boards representing participating HOS physicians. The HOS database, initiated in 2005, is the only global outcome survey of the natural history of the disease and the long-term idursulfase safety and effectiveness. A computer-based application is used to collect data and connects via the Internet to the database server using the Secure Socket Layer protocol. Data can therefore be entered remotely, at hospital/physician centers, through secured connections. The processing of data in the HOS database has been adapted to comply with the Swedish Personal Data Act (1998:204) and the EU Directive 2002/58/EC (July 12, 2002) on the processing of personal data and the protection of privacy in the electronic communication sector [19,20].

Population

For the present analysis, all Brazilian patients meeting the following eligibility criteria were included: confirmed diagnosis of MPS II (biochemically and/or genetically) and signed and dated written informed consent from the participant or parent and/or participant's legally authorized representative or assent of the minor, where applicable.

Variables

Variables related to organ system involvement, signs and symptoms, surgical procedures and survival were extracted from HOS database. General characteristics were also collected in order to characterize the sample.

Statistical Analysis

A descriptive analysis of the data using patient counts, percentages and measures of central tendency and dispersion was used to analyze sociodemographic data, family history, treatment information, cognitive impairment data, cause of death, organ involvement, signs/symptoms and surgeries performed. Measures of central tendency (mean and median) and dispersion (minimum, maximum and 10th, 25th, 75th and 90th percentiles) were used to analyze the length of time on treatment and the patient's age at HOS entry, at onset of symptoms/signs, at diagnosis, at treatment start, age at last visit in HOS and age at death. Graphical analyses were performed showing the median and percentiles (10th and 90th) of age at onset of signs and symptoms and age at first surgical procedures. In addition, Kaplan-Meier survival curves were plotted for the overall survival of the general population and stratified by different clinical characteristics.

Results

General Characteristics

The analyzed sample comprises 153 patients: 145 patients (94.8%) with prospective data and 8 patients (5.2%) with retrospective data. Table 1 shows general characteristics of the included sample, considering both prospective and retrospective cohorts.

Overall, 151 (98.7%) were men, 71 (57.3%) were white and 79 (56.4%) reported a positive family history. The median age was 8.7 years (P10: 2.5; P90: 19.2) at HOS entry, 1.8 years (P10: 0.2; P90: 4.5) at symptoms onset and 4.0 years (P10: 1.0; P90: 10.9) at diagnosis. In addition, of the total sample, 62.0% (88/142) of patients reported cognitive problems at any time, 63.7% (86/135) among those with prospective data and 28.6% (2/7) with retrospective data (Table 1).

Table 1. Demographics and baseline characteristics of patients included in this analysis.

Characteristic	Statistics	Prospective (n=145)	Retrospective (n=8)	Overall (n=153)
Gender	n total (n missing)	145 (0)	8 (0)	153 (0)
	Female (%)	2 (1.4)	0 (0.0)	2 (1.3)
	Male (%)	143 (98.6)	8 (100)	151 (98.7)
Race	n total (n missing)	117 (28)	7 (1)	124 (29)
	White (%)	67 (57.3)	4 (57.1)	71 (57.3)
	Other (%)	50 (42.7)	3 (42.9)	53 (42.7)
Family History	n total (n missing)	134 (11)	6 (2)	140 (13)
	Yes (%)	73 (54.5)	6 (100)	79 (56.4)
	No (%)	61 (45.5)	0 (0.0)	61 (43.6)
Age at HOS entry (years)	n total (n missing)	145 (0)	8 (0)	153 (0)
	Mean (SD)	9.9 (6.95)	16.1 (4.93)	10.2 (6.99)
	Median	8.3	14.6	8.7
	Q1; Q3	5.2; 13.3	12.5; 20.6	5.2; 14.1
	P10; P90	2.5; 18.8	9.8; 23.6	2.5; 19.2
	Min; Max	0.0; 34.0	9.8; 23.6	0.0; 34.0
Age at onset of symptoms (years)	n total (n missing)	131 (14)	7 (1)	138 (15)
	Mean (SD)	2.0 (1.70)	1.9 (0.91)	2.0 (1.67)
	Median	1.8	2.0	1.8
	Q1; Q3	0.6; 3.0	1.0; 3.0	0.7; 3.0
	P10; P90	0.2; 4.5	1.0; 3.0	0.2; 4.5
	Min; Max	0.0; 7.5	1.0; 3.0	0.0; 7.5
Age at diagnosis (years)	n total (n missing)	139 (6)	8 (0)	147 (6)
	Mean (SD)	5.2 (5.35)	8.4 (5.19)	5.4 (5.37)
	Median	4.0	7.8	4.0
	Q1; Q3	2.0; 6.0	5.7; 9.0	2.0; 6.0
	P10; P90	0.6; 10.9	2.5; 20.0	1.0; 10.9
	Min; Max	0.0; 33.0	2.5; 20.0	0.0; 33.0
Treated at any time	n total (n missing)	132 (13)	6 (2)	138 (15)
	No (%)	29 (22.0)	4 (66.7)	33 (23.9)
	Yes (%)	103 (78.0)	2 (33.3)	105 (76.1)
Age at treatment start (years)	n total (n missing)	103 (42)	2 (6)	105 (48)
	Mean (SD)	9.2 (6.24)	10.8 (0.56)	9.2 (6.18)
	Median	7.7	10.8	7.8
	Q1; Q3	5.2; 12.4	10.5; 11.2	5.3; 11.5
	P10; P90	3.0; 17.2	10.5; 11.2	3.0; 17.2
	Min; Max	0.0; 32.2	10.5; 11.2	0.0; 32.2

Table 1. Cont.

Characteristic	Statistics	Prospective (n=145)	Retrospective (n=8)	Overall (n=153)
Length of Time on Treatment (Months)	n total (n missing)	103 (42)	0 (8)	103 (50)
	Mean (SD)	68.9 (47.00)		68.9 (47.00)
	Median	67.2		67.2
	Q1; Q3	30.5; 111.0		30.5; 111.0
	P10; P90	10.2; 132.4		10.2; 132.4
	Min; Max	0.0; 164.1		0.0; 164.1
Cognitive problem at any time	n total (n missing)	135 (10)	7 (1)	142 (11)
	Yes (%)	86 (63.7)	2 (28.6)	88 (62.0)
	No (%)	49 (36.3)	5 (71.4)	54 (38.0)
Age at last visit in HOS (years)	n total (n missing)	145 (0)	0 (8)	145 (8)
	Mean (SD)	13.5 (7.90)		13.5 (7.90)
	Median	12.1		12.1
	Q1; Q3	8.0; 17.9		8.0; 17.9
	P10; P90	4.5; 24.4		4.5; 24.4
	Min; Max	0.1; 37.1		0.1; 37.1
Deceased	n total (n missing)	145 (0)	8 (0)	153 (0)
	No (%)	109 (75.2)	0 (0.0)	109 (71.2)
	Yes (%)	36 (24.8)	8 (100)	44 (28.8)
Age at Death (Years)	n total (n missing)	36 (109)	8 (0)	44 (109)
	Mean (SD)	16.1 (7.85)	16.1 (4.93)	16.1 (7.36)
	Median	15.4	14.6	15.2
	Q1; Q3	10.4; 19.8	12.5; 20.6	10.6; 19.8
	P10; P90	8.1; 25.3	9.8; 23.6	8.8; 23.6
	Min; Max	3.1; 37.1	9.8; 23.6	3.1; 37.1

Among patients with prospective data, median age at diagnosis were similar when comparing patients with and without a family history, 4.0 (P10: 0.3; P90: 16.8) and 3.9 years (P10: 1.5; P90: 8.0), respectively. Among patients with retrospective data, 6 patients had a family history (median age at diagnosis was 7.8, P10: 2.5 and P90: 20.0) and data was missing for 2 patients (Table 1).

When treatment characteristics were assessed, 105 (76.1%) patients were treated at any time (prospective: 78.0%; retrospective: 33.3%), starting treatment at the median age of 7.8 years (P10: 3.0; P90: 17.2). The treatment duration had a median of 67.2 months (P10: 10.2; P90: 132.4). The median age at the last visit in HOS was 12.1 years (P10: 4.5; P90: 24.4). Additionally, 44 patients (28.8% - including all 8 patients with retrospective data) died at a median age of 15.2 years (P10: 8.8; P90: 23.6) (Table 1).

Organ System Involvement and Signs and Symptoms

The most involved organs and systems were musculoskeletal (96.6%; 144/149), abdomen/gastrointestinal (95.2%; 139/146), neurological (88.7%, including cognitive problems; 126/142), pulmonary (86.2%; 125/145), and ear (81.3%; 117/144). The median age at onset for the above organs and systems were 2.5, 1.0, 3.9, 3.2 and 3.2 years, respectively. The most prevalent specific symptom/sign was facial features consistent with Hunter syndrome, observed in 94.6% (141/149) of patients with median age at onset of symptom/sign of 2.8 years, followed by joint stiffness and limited function (89.3%; 133/149), hernia (84.2%; 123/146) and hepatomegaly (82.2%; 120/146). Median ages of symptoms onset are shown in Figure 1 and Table S1.

Surgical Procedures

At least one surgery occurred at any point in time in 65.4% of the patients (100/153). Median age at first surgical procedure was 3.0 years (P10: 0.2; P90: 11.4). Most frequently reported surgeries were hernia repair (45.8%; 70/153), adenoidectomy (26.1%; 40/153) and tonsillectomy (20.3%; 31/153). The median ages at the first surgery were 3.2, 3.7 and 4.2 years for hernia repair, adenoidectomy, and tonsillectomy, respectively (Figure 2).

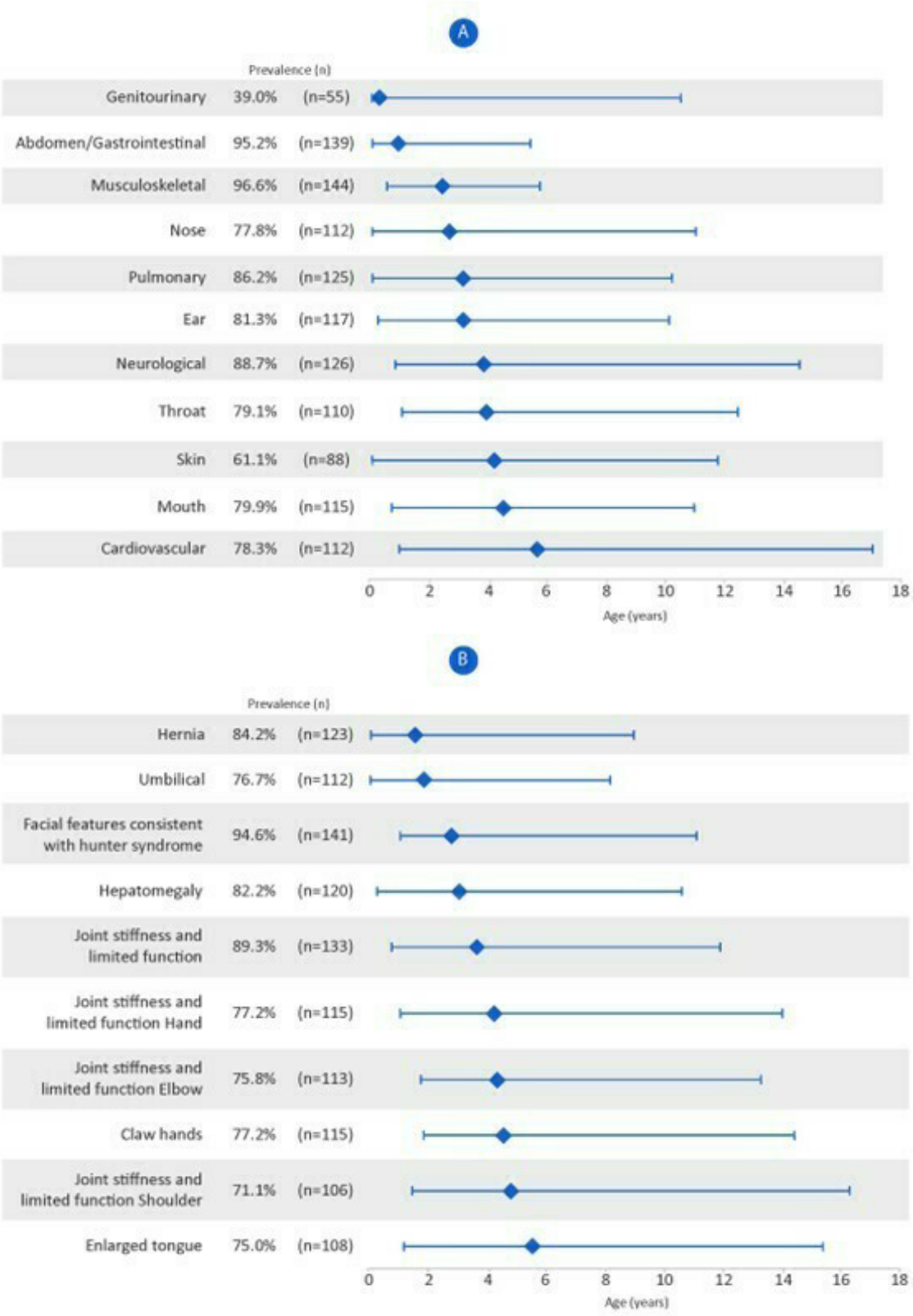

Figure 1. Disease manifestations and signs and symptoms in the overall HOS population. Prevalence and median age at onset of (a) organ system involvement and (b) signs and symptoms present in more than 70% of patients in the overall HOS population. Diamonds represent the median age of onset (years) and error bars indicate the 10th and 90th percentiles.

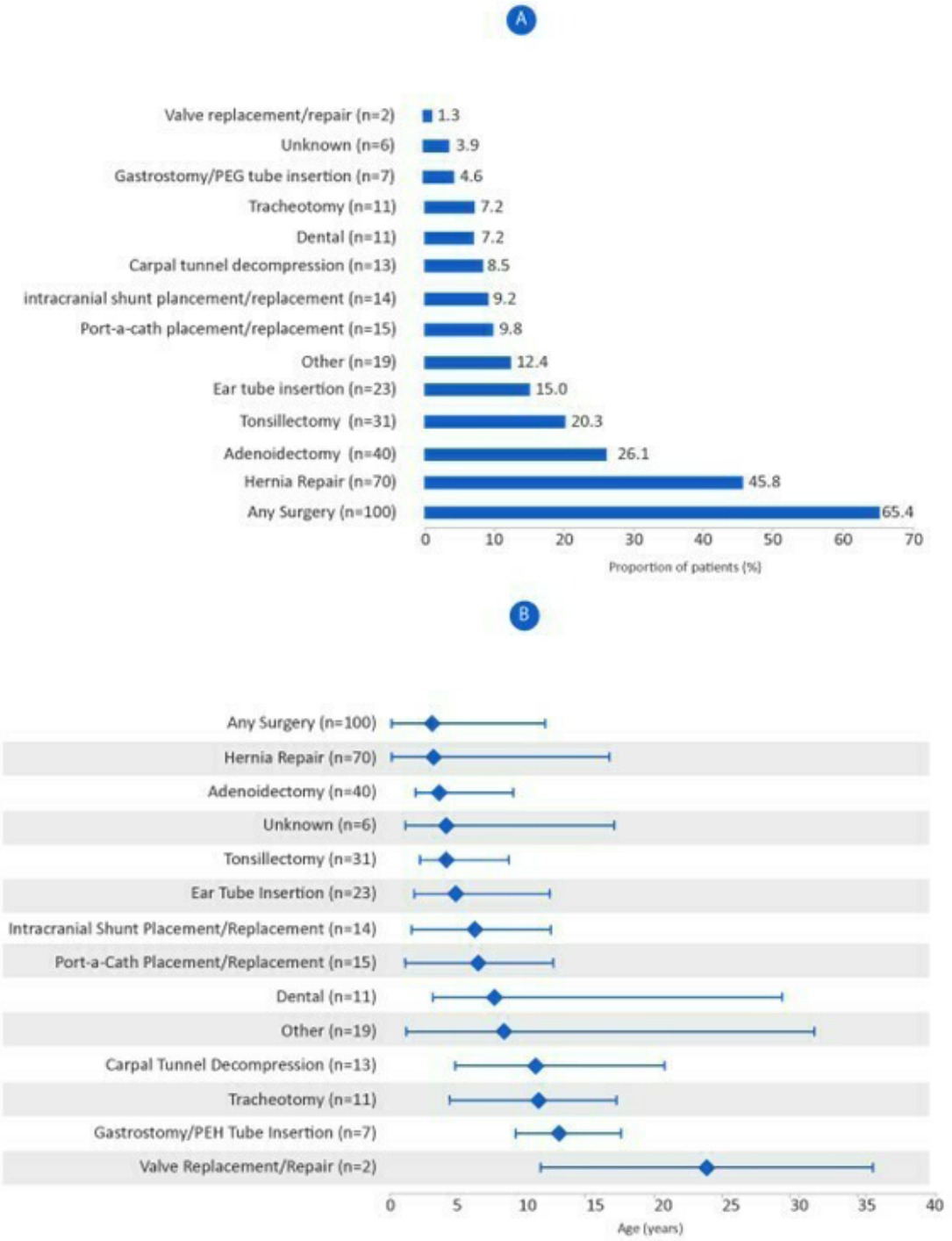

Figure 2. Surgical procedures in the overall HOS population, where >1 patient underwent surgery. (a) Percentage of patients in the overall population undergoing surgical procedures at any time (N = 100). (b) Median age at first surgical procedure for surgeries performed in the overall population. In part (b), diamonds indicate the median age of onset (years) and bars indicate the 10th and 90th percentiles.

Survival Analysis

A total of 44 patients died (28.8%; 44/153). The main cause of death was respiratory failure (31.8%; 14/44). Causes of death in prospective and retrospective patients are shown in Figure S1.

The overall survival is presented with a Kaplan-Meier curve and can be seen in Figure 3. The median survival was 22.0 (95% CI: 19.4; 30.4) years for the overall group. Table 2 shows information about median survival according to different clinical characteristics.

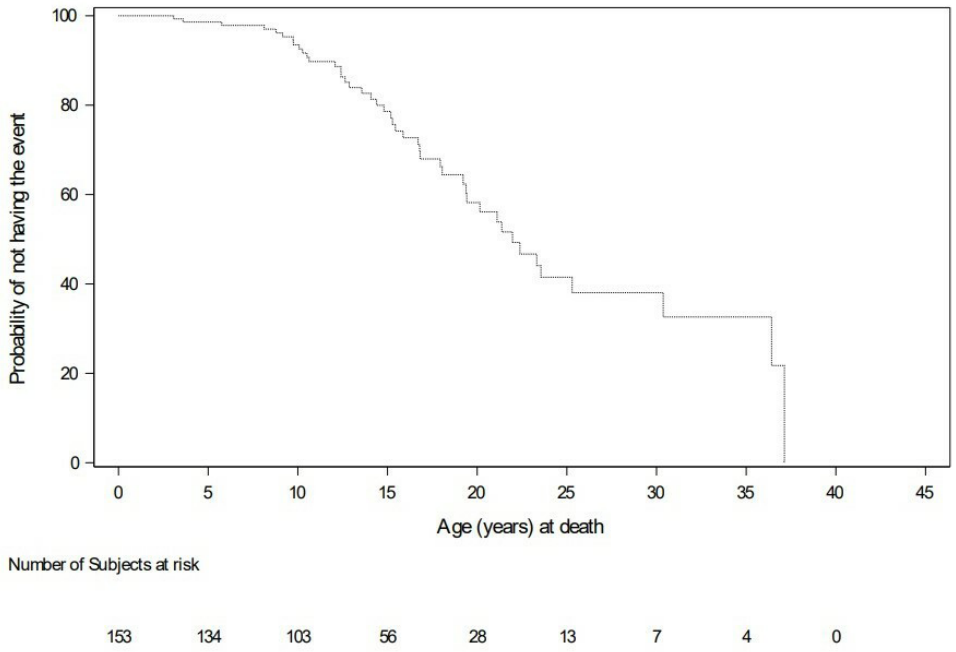

Figure 3. Median survival in the overall population.

Table 2. Median survival estimates according to different clinical characteristics of the sample.

Characteristic	Group	At least one event		Median survival (95%CI)
		N (%)	95%CI	
Total sample	–	44 (28.8)	21.6; 35.9	22.0 (19.4; 30.4)
Treatment	Treated (N=103)	29 (28.2)	19.5; 36.8	23.3 (20.2; 36.4)
	Untreated (N=42)	7 (16.7)	5.4; 27.9	19.4 (15.4; Not estimable)
Any surgical intervention	Yes (N=71)	19 (26.8)	16.5; 37.1	30.4 (17.9; Not estimable)
	No (N=32)	10 (31.3)	15.2; 47.3	20.2 (15.2; Not estimable)
Age at diagnosis (years)	<5 (N=22)	2 (9.1)	0.0; 21.1	–
	≥5 (N=81)	27 (33.3)	23.1; 43.6	23.3 (20.2; 36.4)
Cognitive impairment	Yes (N=88)	28 (31.8)	22.1; 41.5	18.1 (15.4; 20.2)
	No (N=54)	14 (25.9)	14.2; 37.6	30.4 (23.3; Not estimable)

Discussion

The analysis of Brazilian subgroup data from HOS database provided a better understanding of clinical profile, surgical procedures, and survival among MPS II patients in the country. Three previous analyses assessed similar parameters from the HOS registry. The first article described the initial study data (Wraith, 2008; first cut-off including baseline demographics and clinical characteristics), the second article included descriptive information from Taiwanese patients only (Lin, 2018) and lastly, the third article reported survival analyses (Burton, 2017) [7,8,26]. MPS II is a rare condition and such analyses are helpful to promote a proper care for Hunter patients. In addition, only publications reporting small MPS II samples in Brazil are available to date, reinforcing the relevance of the present analysis [36,37].

Organ system involvement was initially assessed to understand MPS II clinical profile. Musculoskeletal, abdomen/gastrointestinal, neurological, pulmonary, and ear were the most frequently observed organs/systems involved. Wraith et al. reported the initial HOS data in a 2008 publication in which the abdomen, head and neck and skeletal organ systems were those most frequently affected. Furthermore, musculoskeletal, abdomen/gastrointestinal, neurological, pulmonary, and ear involvement also had prevalence higher than 80% [26]. Taiwanese HOS cohort showed similar results, with musculoskeletal (100%), abdomen/gastrointestinal (98.2%), and pulmonary (98.2%) organ systems most frequently involved [8]. Individuals with MPS II may present with several ocular conditions, including retinopathy [38]. Lin et al. (2019) reported a prevalence of 50.0% of retinopathy among Taiwanese MPS II patients, however no ocular issues were reported in our subgroup [39].

Regarding signs and symptoms, the most prevalent symptom was coarse facial features consistent with the disease, followed by joint stiffness and limited function, hernia and hepatomegaly. Such signs and symptoms are consistent with HOS data from May 2007 (Wraith, 2008) and Taiwanese results (Lin, 2018) that reported facial features, claw hands, enlarged liver/spleen, and joint stiffness as main findings [8,26].

Most of the Brazilian MPS II patients underwent at least one surgical procedure; hernia repair, adenoidectomy and tonsillectomy were the most frequently observed. In comparison, most Taiwanese patients also had at least 1 surgical procedure performed, however in a higher proportion than Brazilian patients 65.4% vs. 78.7%). Hernia repair was also the most frequently reported surgical procedure in this analysis, however, a frequency of 27.9% of ear tube insertion was reported in Taiwan while in the Brazilian sample it was 15.0% [8].

Median age at death, and median survival, among Brazilian MPS II patients were also calculated. Median survival was 22.0 years, and the major cause of death was respiratory failure. Estimated survival in Brazil was higher than that reported in Taiwan, with median survival of 19.4 years [8]. Burton et al. (2017) reported survival data from HOS registry and described that median Kaplan–Meier survival estimates were 33.0 and 21.2 years among idursulfase treated and untreated patients, respectively [7]. Stratifying survival by treatment status, untreated individuals showed still lower survival rates (19.4 years) compared to treated individuals. Results highlights that survival estimates in Brazil are low, comparable to untreated patients from the whole HOS sample, but higher than the observed in other developing countries such as Taiwan. Further analyses are still needed to determine factors associated with decreased survival in the country.

Despite the important contribution of this analysis, some limitations need to be highlighted. HOS is a patient registry, and all data is dependent on quality of collection, which may vary across study sites. In addition, the retrospective nature of a part of the analysis may also impose some quality issues. Finally, a group of patients was treated with idursulfase, and the treatment impact was not assessed.

Conclusion

The subgroup analysis of HOS data for patients living in Brazil showed that patients with MPS II in the country have similar clinical profile when compared to previously published overall HOS data. Regarding survival rates, Brazilian estimates are still low, similar to those of untreated MPS II patients. Further information on the clinical profile of MPS II patients in Brazil will contribute to the wealth of data available and to an increased understanding of specific disease characteristics in the country which will ultimately serve as a basis to improve local healthcare.

Acknowledgements

We acknowledge ORIGIN Inteligência em Saúde S.A. for the support with statistical analysis and medical writing funded by Takeda Distribuidora Ltda., done under the direction of the authors, and was, provided by Fernando Alencar, Roberta Arinelli Fernandes and Ana Carolina Padula Ribeiro Pereira.

Funding

This analysis was funded by Takeda Distribuidora Ltda., Brazil

Authors' Contributions

Dafne D G Horovitz: data acquisition; data analysis and interpretation; manuscript writing; critical review; final approval. Márcia G Ribeiro: design; data acquisition; data analysis and interpretation; manuscript writing; critical review; final approval. Angelina X Acosta: data acquisition; data analysis and interpretation; manuscript writing; critical review; final approval. Ana C Monteiro: conception and design; data analysis and interpretation; manuscript writing; critical review; final approval. Jaco Botha: conception and design; data analysis and interpretation; manuscript writing; critical review; final approval. Roberto Giugliani: conception and design; data acquisition; data analysis and interpretation; critical review; final approval.

Declaration of Conflicting Interests

Ana C Monteiro is Takeda Distribuidora Ltda. employee. Jaco Botha is a full-time employee of Takeda and stockholder of Takeda Pharmaceuticals Company Limited. Dafne D G Horovitz, Márcia G Ribeiro, Angelina X Acosta and Roberto Giugliani declare no conflicts of interest.

Supplementary Material

The following online material is available for this article:

Table S1. Prevalence and median age at onset of organ system involvement and signs and symptoms present in more.
Figure S1. Causes of death observed in prospective and retrospective samples.

References

1. Çelik B, Tomatsu SC, Tomatsu S, Khan SA. Epidemiology of Mucopolysaccharidoses Update. *Diagnostics (Basel)*. 2021;11(2):S116. doi:10.3390/diagnostics11020273.
2. D'avanzo F, Rigon L, Zanetti A, Tomanin R. Mucopolysaccharidosis type II: One hundred years of research, diagnosis, and treatment. *Int J Mol Sci*. 2020;21(4):1258. doi:10.3390/ijms21041258.

3. Verma S, Pantoom S, Petters J, Pandey AK, Hermann A, Lukas J. A molecular genetics view on Mucopolysaccharidosis Type II. *Mutat Res Rev Mutat Res*. 2021;788:108392. doi:10.1016/j.mrrev.2021.108392.

4. Martin R, Beck M, Eng C, et al. Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). *Pediatrics*. 2008;121(2):e377-e386. doi:10.1542/peds.2007-1350.

5. Galimberti C, Madeo A, Di Rocco M, Fiumara A. Mucopolysaccharidoses: early diagnostic signs in infants and children. *Ital J Pediatr*. 2018;44(Suppl 2):133. doi:10.1186/s13052-018-0550-5.

6. Broomfield A, Davison J, Roberts J, et al. Ten years of enzyme replacement therapy in paediatric onset mucopolysaccharidosis II in England. *Mol Genet Metab*. 2020;129(2):98-105. doi:10.1016/j.ymgme.2019.07.016.

7. Burton BK, Jego V, Mikl J, Jones SA. Survival in idursulfase-treated and untreated patients with mucopolysaccharidosis type II: data from the Hunter Outcome Survey (HOS). *J Inherit Metab Dis*. 2017;40(6):867-874. doi:10.1007/s10545-017-0075-x.

8. Lin HY, Chuang CK, Chen MR, et al. Clinical characteristics and surgical history of Taiwanese patients with mucopolysaccharidosis type II: Data from the hunter outcome survey (HOS). *Orphanet J Rare Dis*. 2018;13(1):89. doi:10.1186/s13023-018-0827-1.

9. Sohn YB, Choi EW, Kim SJ, et al. Retrospective analysis of the clinical manifestations and survival of Korean patients with mucopolysaccharidosis type II: Emphasis on the cardiovascular complication and mortality cases. *Am J Med Genet Part A*. 2012;158A(1):90-96. doi:10.1002/ajmg.a.34371.

10. Ministério da Saúde. Secretária de Atenção à Saúde. Protocolo Clínico e Diretrizes Terapêuticas. Mucopolissacaridose do Tipo II. 2018. 23 p. http://conitec.gov.br/images/Protocolos/PCDT_MPS-II.pdf. Accesed March 16, 2022.

11. Stapleton M, Hoshina H, Sawamoto K, et al. Critical review of current MPS guidelines and management. *Mol Genet Metab*. 2019;126(3):238-245. doi:10.1016/j.ymgme.2018.07.001.

12. Federhen A, Pasqualim G, de Freitas TF, et al. Estimated birth prevalence of mucopolysaccharidoses in Brazil. *Am J Med Genet Part A*. 2020;182(3):469-483. doi:10.1002/ajmg.a.61456.

13. Josahkian JA, Trapp FB, Burin MG, et al. Updated birth prevalence and relative frequency of mucopolysaccharidoses across Brazilian regions. *Genet Mol Biol*. 2021;44(1):e20200138. doi:10.1590/1678-4685-GMB-2020-0138.

14. ClinicalTrials.gov. Hunter Outcome Survey (HOS). https://clinicaltrials.gov/ct2/show/NCT03292887. Accessed March 16, 2022.

15. Muenzer J, Jones SA, Tylki-Szymańska A, et al. Ten years of the Hunter Outcome Survey (HOS): insights, achievements, and lessons learned from a global patient registry. *Orphanet J Rare Dis*. 2017;12(1):82. doi:10.1186/s13023-017-0635-z.

16. Keilmann A, Nakarat T, Bruce IA, Molter D, Malm G. Hearing loss in patients with mucopolysaccharidosis II: data from HOS - The Hunter Outcome Survey. *J Inherit Metab Dis*. 2012;35(2):343-353. doi:10.1007/s10545-011-9378-5.

17. Kampmann C, Beck M, Morin I, Loehr JP. Prevalence and characterization of cardiac involvement in hunter syndrome. *J Pediatr*. 2011;159(2):327-331.e2. doi:10.1016/j.jpeds.2011.01.054.

18. Jones SA, Parini R, Harmatz P, Giugliani R, Fang J, Mendelsohn NJ. The effect of idursulfase on growth in patients with Hunter syndrome: data from the Hunter Outcome Survey (HOS). *Mol Genet Metab*. 2013;109(1):41-48. doi:10.1016/j.ymgme.2013.03.001.

19. Jones SA, Almássy Z, Beck M, et al. Mortality and cause of death in mucopolysaccharidosis type II - A historical review based on data from the Hunter Outcome Survey (HOS). *J Inherit Metab Dis*. 2009;32(4):534-543. doi:10.1007/s10545-009-1119-7.

20. Burton BK, Whiteman DAH. Incidence and timing of infusion-related reactions in patients with mucopolysaccharidosis type II (Hunter syndrome) on idursulfase therapy in the real-world setting: A perspective from the Hunter Outcome Survey (HOS). *Mol Genet Metab*. 2011;103(2):113-120. doi:10.1016/j.ymgme.2011.02.018.

21. Burton BK, Guffon N, Roberts J, van der Ploeg AT, Jones SA. Home treatment with intravenous enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II - data from the Hunter Outcome Survey. *Mol Genet Metab*. 2010;101(2-3):123-129. doi:10.1016/j.ymgme.2010.06.011.

22. Ficicioglu C, Giugliani R, Harmatz P, Mendelsohn NJ, Jego V, Parini R. Intrafamilial variability in the clinical manifestations of mucopolysaccharidosis type II: Data from the Hunter Outcome Survey (HOS). *Am J Med Genet Part A*. 2018;176(2):301-310. doi:10.1002/ajmg.a.38551.

23. Muenzer J, Botha J, Harmatz P, Giugliani R, Kampmann C, Burton BK. Evaluation of the long-term treatment effects of intravenous idursulfase in patients with mucopolysaccharidosis II (MPS II) using statistical modeling: data from the Hunter Outcome Survey (HOS). *Orphanet J Rare Dis*. 2021;16(1):456. doi:10.1186/s13023-021-02052-4.

24. Muenzer J, Giugliani R, Scarpa M, Tylki-Szymańska A, Jego V, Beck M. Clinical outcomes in idursulfase-treated patients with mucopolysaccharidosis type II: 3-year data from the hunter outcome survey (HOS). *Orphanet J Rare Dis*. 2017;12(1):161. doi:10.1186/s13023-017-0712-3.

25. Cohn GM, Morin I, Whiteman DAH. Development of a mnemonic screening tool for identifying subjects with Hunter syndrome. *Eur J Pediatr*. 2013;172(7):965-970. doi:10.1007/s00431-013-1967-x.

26. Wraith JE, Beck M, Giugliani R, Clarke J, Martin R, Muenzer J. Initial report from the Hunter Outcome Survey. *Genet Med*. 2008;10(7):508-516. doi:10.1097/GIM.0b013e31817701e6.

27. Alcalde-Martín C, Muro-Tudelilla JM, Cancho-Candela R, et al. First experience of enzyme replacement therapy with idursulfase in Spanish patients with Hunter syndrome under 5 years of age: case observations from the Hunter Outcome Survey (HOS). *Eur J Med Genet*. 2010;53(6):371-377. doi:10.1016/j.ejmg.2010.07.013.

28. Parini R, Jones SA, Harmatz PR, Giugliani R, Mendelsohn NJ. The natural history of growth in patients with Hunter syndrome: data from the Hunter Outcome Survey (HOS). *Mol Genet Metab*. 2016;117(4):438-446. doi:10.1016/j.ymgme.2016.01.009.

29. Link B, Lapagesse de Camargo Pinto L, Giugliani R, et al. Orthopedic manifestations in patients with mucopolysaccharidosis type II (Hunter syndrome) enrolled in the Hunter Outcome Survey. *Orthop Rev (Pavia)*. 2010;2(2):16. doi:10.4081/or.2010.e16.

30. Muenzer J, Beck M, Giugliani R, et al. Idursulfase treatment of Hunter syndrome in children younger than 6 years: results from the Hunter Outcome Survey. *Genet Med*. 2011;13(2):102-109. doi:10.1097/GIM.0b013e318206786f.

31. Tomanin R, Zanetti A, D'Avanzo F, et al. Clinical efficacy of enzyme replacement therapy in paediatric Hunter patients, an independent study of 3.5 years. *Orphanet J Rare Dis*. 2014;9:129. doi:10.1186/s13023-014-0129-1.

32. Mendelsohn NJ, Harmatz P, Bodamer O, et al. Importance of surgical history in diagnosing mucopolysaccharidosis type II (Hunter syndrome): data from the Hunter Outcome Survey. *Genet Med*. 2010;12(12):816-822. doi:10.1097/GIM.0b013e3181f6e74d.

33. Bodamer O, Scarpa M, Hung C, Pulles T, Giugliani R. Birth weight in patients with mucopolysaccharidosis type II: data from the Hunter Outcome Survey (HOS). *Mol Genet Metab Rep*. 2017;11:62-64. doi:10.1016/j.ymgmr.2017.02.004.

34. Giugliani R, Harmatz P, Jones SA, et al. Evaluation of impact of anti-idursulfase antibodies during long-term idursulfase enzyme replacement therapy in mucopolysaccharidosis II patients. *Mol Genet Metab Reports*. 2017;12:2-7. doi:10.1016/j.ymgmr.2017.01.014.

35. Wiklund I, Raluy-Callado M, Stull DE, Jangelind Y, Whiteman DAH, Chen WH. The Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS) Questionnaire: evaluation of measurement properties. *Qual Life Res*. 2013;22(4):875-884. doi:10.1007/s11136-012-0196-5.

36. Pinto LLC, Schwartz IVD, Puga ACS, et al. Prospective study of 11 Brazilian patients with mucopolysaccharidosis II. *J Pediatr (Rio J)*. 2006;82(4):273-278. doi:10.2223/JPED.1512.

37. Schwartz IV, Ribeiro MG, Mota JG, et al. A clinical study of 77 patients with mucopolysaccharidosis type II. *Acta Paediatr*. 2007;96(455):63-70. doi:10.1111/j.1651-2227.2007.00212.x.

38. Ashworth JL, Biswas S, Wraith E, Lloyd IC. Mucopolysaccharidoses and the eye. *Surv Ophthalmol*. 2006;51(1):1-17. doi:10.1016/j.survophthal.2005.11.007.

39. Lin H, Chan W, Chen L, et al. Ophthalmologic manifestations in Taiwanese patients with mucopolysaccharidoses. *Mol Genet Genomic Med*. 2019;7(5):e00617. doi:10.1002/mgg3.617.