A Retrospective Study of Mucopolysaccharidosis Type II in Brazil – Data from Brazilian Health System (DATASUS)

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Abstract

Data on Mucopolysaccharidosis type II (MPS II) in Latin America are scarce. This retrospective database study, using data from the Informatics Department of the Brazilian Health System (DATASUS), aimed to estimate the prevalence of MPSII in Brazil from 2008 to 2020 and to describe demographic and clinical profiles from patients under treatment. The study population was derived from DATASUS records of MPS II (ICD-10 E76.1) diagnosed in Brazil. Initially 455 patients were found, but only 181 patients who were receiving idursulfase treatment were included in this study. Among these cases, as expected in a X-linked disease, all were males and 40% of the cases were recorded in the Southeast region, and another 34% in the Northeast region. The biggest proportion of patients (39%) were diagnosed when they were 10-19 years old. There are 212 clinical conditions associated with MPS II, although the main comorbidities related to MPSII include: abdominal/inguinal hernia, respiratory complications, and carpal tunnel syndrome. Respiratory disorders were the fifth most frequent comorbidity recorded in these patients. The healthcare professionals in Brazil more involved in the diagnosis of MPS II were radiologists, followed by geneticists and cardiologists. Despite some limitations, DATASUS is a relevant database to provide information on rare diseases such as MPS II. Most cases were reported in southeast and northeast regions, respectively. This information is crucial to help design targeted public policies.

Keywords

Mucopolysaccharidosis Type II, SUS, ICD-10 E76.1, Idursulfase, Hunter Syndrome.

Introduction

Mucopolysaccharidoses (MPS) are a group of rare metabolic disorders, accounting for less than 0.1% of all genetic diseases [1]. Worldwide, the various types of MPS occur with a very low individual incidence. MPS are caused by the deficiency or lack of lysosomal enzymes required for the degradation of glycosaminoglycans (GAGs; formerly known as mucopolysaccharides), the key component of the connective tissue matrix [2,3]. The deficient activity of these enzymes leads to intra-lysosomal accumulation of GAGs, which characterizes MPS. The seven types of MPS are classified based on the deficiency in one of the 11 specific lysosomal enzymes and designated as MPS I to MPS IX (excluding MPS V and VIII, which are no longer recognized) [3].

MPS II (or Hunter syndrome) is characterized by a deficiency in the enzymatic activity of iduronate-2-sulfatase (IDS) encoded by the IDS gene [1]. The IDS gene has over 739 known variants [4]; this wide range of genetic variation reflects the diversity of symptoms and impairments presented by the affected patients [5,6]. MPS II is a multisystemic and progressive disorder with a broad phenotypical variability mainly classified into two main phenotypes: neuropathic and non-neuronopathic [7]. The neuronopathic phenotype is characterized by the involvement of the central nervous system (difficulty in maintaining attention, speech delay, cognitive impairment and epileptic seizures are commonly reported), but all patients with MPS II (neuropathic and non-neuropathic) present with substantial somatic disease burden with issues in multiple other systems or organs [3]. MPS

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II has an estimated incidence of 1 in 162,000 live male births [4] and accounts for nearly 50% of all cases of MPS [1].

Respiratory symptoms and inguinal or umbilical hernias are frequent and present as one of the first symptoms early in life. The growth pattern in patients with MPS II is usually characterized by overgrowth, although growth velocity falls below that of healthy individuals after one year of age. In addition, coarse facial features, macroglossia, and gingival hyperplasia are clinical manifestations that arise relatively early (first years of life) [2]. Upper respiratory tract disorders leading to recurrent respiratory infections are common [8,9]. Skeletal involvement can occur early in the in the first months of life with the appearance of hip dysplasia, and in the first 12–18 month those abnormalities are usually characterized by dysostosis multiplex, macrocephaly, abnormal first or second lumbar vertebra with kyphosis, broad chest, and thickening of the diaphysis of long bones. Progressive arthropathy leads to stiffness and contracture of large and small joints, with typical claw hands and carpal tunnel syndrome is a frequently described complication reported in infantile to juvenile patients. Hepatosplenomegaly could also occur and results in a prominent abdomen [8,9].

As MPS II is a rare condition, therefore retrospective studies using large databases can provide unique perspectives on patient profiles, diagnostic processes, as well as the management options, and treatment patterns.

In this study, we conducted a retrospective study with Brazilian MPSII patients' records that were under treatment with enzyme replace therapy (ERT) in Brazil between 2008 and 2020.

We aim to detail manifestations and outcomes of MPS II to inform about disease epidemiology, treatment, diagnosis and comorbidities in Brazilian patients to enhance disease understanding.

Methods

The study´s data source is the Informatics Department of the Brazilian Health System (DATASUS – Departamento de Informações do Sistema Único de Saúde). DATASUS is a large secondary database comprising data from several health databases in Brazil and was established in 2008 [17]. DATASUS is responsible for providing the Brazilian Healthcare System (SUS) entities with information systems and informatics support necessary for the planning, operation and control process by the Ministry of Health. The structure from DATASUS allows to store healthcare data from all the Brazilian population. In addition, it provides links spread across several Brazilian regions with connections to all states within the country.

Within the DATASUS the data of interest can be extracted from two information systems: Outpatient Procedures Information Systems (SIA), and Hospital Admissions Information System (SIH). SIA processes all outpatient production information from the SUS Basic and Specialized Care. This system consolidates outpatient information for later dissemination by DATASUS, in addition to generating value for payment of outpatient production. On the other hand, SIH records hospital admissions and inpatient events that were financed by SUS, and it generates reports for managers enabling them to make payments to the health facilities.

SIA has three databases:

1. Individualized patient care – provides individual information about the patient (i.e. registration number, name, birth date, International Classification of Disease [ICD], type of consultation, gender, and place of residence).
2. Miscellaneous procedures – Outpatient procedures; it provides the patient's age in the moment of procedure.
3. Drugs – it identifies the drugs used for treatment.

Data of interest were provided by a platform called *Techtrials data warehouse (TT RWD Platform*). TT RWD Platform does not belong to DATASUS; however, it automatically obtains new data from DATASUS that becomes available every month. Therefore, in this study, the TT RWD Platform vendor performed the data extraction, applying relevant filters to obtain the data of interest.

The study population included MPS II cases (International Classification of Disease, 10th Revision [ICD-10] E76.1) reported in Brazil. Initially, the study sample included all MPS II records from January 1st, 2008, to September 30th, 2020. However, these entries could include false positive cases, as some of these entries would not have a confirmed diagnosis, but only a clinical suspicion. In order to include only patients with a confirmed diagnosis, we decided to use the data of patients under treatment with Idursulfase enzyme replacement therapy (ERT) because these patients receive the medication based on the diagnosis confirmation. Therefore, the final study sample was comprised entirely of records from all MPS II patients of any age and both genders who received Idursulfase at least once, as reported in DATASUS from January 1st, 2008, to September 30th, 2020 (date on which the syndrome was included in DATASUS databank and date close to the start of the study, respectively). Cases of MPS II reported outside this period were excluded. Demographic and clinical data were extracted for this database, however the age at diagnosis was not available as this information is not required for treatment enrollment. Table 1 describes the variables of interest.

The primary outcomes included the number of subjects diagnosed with MPS II and the comorbidities associated with the syndrome. Secondary outcomes included the geographic distribution of cases and the age when this ICD (E76.1) was first reported in the system.

Ethics approval was not required due to the nature of the study (retrospective/database study based on secondary use of data). The contract between the sponsor and the database vendor adheres to privacy and protection data requirements of Brazil.

Table 1. Demographic and clinical variables extracted from DATASUS.

Variable	Description
Patients with MPS II diagnosis	All cases of MPS II reported in the period of interest
Current age	0-3 years, 4-6 years, 7-9 years, 10-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, over 60 years, or unknown
Gender	Male, female, or unknown
MPS II record location (by month/year and geographic region)	Health care unit where MPS II patient was reported – one of five Brazilian geographic regions (Northeast, Southeast, South, North, and Midwest) or unknown. Home address is not available in DATASUS
MPS II first issued date	The first time that ICD code E76.1 was reported in the system (from the first time it was recorded as an ambulatory service or drug dispensation with the MPS II ICD code)
Age when the MPS II keyword was entered *	Age when the ICD code E76.11 was first reported in the system for that specific case
Associated comorbidities	Clinical conditions diagnosed before and after MPS II that may be related to the syndrome
Ambulatory procedures	Entry of any procedure assigned to the ICD code E76.1
Drug dispensation	Entry of medication use assigned to the ICD code E76.1
Hospitalization and associated procedures	Entry of hospitalization (Hospital Inpatient Authorization) assigned to the ICD code E76.1
Treatment before and after the MPS II diagnosis	Any record of treatment associated with the ICD code E76.1. The proportion of patients who used at least one medication type and the absolute number of times each drug was used is also described
Start date of treatment	The first time the ICD code E76.1 is assigned to a treatment. It represents the physician`s entries in the dataset mentioning that the patient should start treatment. But it does not guarantee that the patient started the medication
Patients diagnosed with MPS II who did not receive treatment	The proportion of patients with MPS II who do not have a treatment record (do not have any registration of treatment-associated with ICD code E76.1)
Time between the diagnosis of MPS II and the start of treatment	The average or median time between the diagnosis of MPS II and the start of treatment
Time from first SUS consultation until an MPS II diagnosis	Aims to estimate the average or median time between the first SUS consultation and the MPS II diagnosis
Medical specialist who diagnosed MPS II	Aims to know which medical specialists have diagnosed the disease
Medical specialist visited until the MPS II diagnosis	Aims to know which medical specialists were consulted before the diagnosis of MPS II

Race is not available in DATASUS.
* Age at diagnosis was not available.
Legends: ICD, International Classification of Diseases; MPS II, mucopolysaccharidosis type II.

Results

From January 1st, 2008, to September 30th, 2020, 455 unique MPS II records were identified in the SIA, 251 from the outpatient individualized database, 23 from miscellaneous procedures, and 181 from the drugs database. As 40 records were duplicated (between outpatient individualized and drugs) the initial study sample comprised of 415 patients with MPS II. However, 234 patients were not under treatment so there was not a confirmed diagnosis, or it was not available. We then decide to perform a new search in the drugs database in which we identified 181 treated MPS II patients (ERT with Idursulfase) with clinical and laboratory diagnosis confirmed, who were considered as a sample for this study (Figure 1).

After careful data curation, 40 duplicated records were found (the databases are not integrated with each other). Moreover, some patients did not have a confirmed diagnosis (clinical suspicion), and several female patients were included (in this initial assessment, about 30% of the patient records were from females which is highly unlikely due to the X-linked inheritance of this disorder).

As expected for an X-linked disorder none of the confirmed cases reported here were females. The highest region with cases was the Southeast region (40%) followed by the Northeast region (34%) (Figure 2). Among the states, São Paulo had the greatest number of cases (n=49), followed by Rio de Janeiro, Paraná, and Ceará (n=12 each). All patient characteristics are summarized in Table 2. It was not possible to identify whether there is consanguinity or affected relatives.

The most common clinical conditions (212 comorbidities) or procedures that were associated with MPS II in our cohort, were hernia (ICD 10: K40), sensorineural hearing loss – bilateral (ICD-10 H903), and spastic quadriplegic cerebral palsy (ICD-10 G800). Although, in the literature, the main comorbidities related to MPSII include abdominal/inguinal hernia, sensorineural hearing loss – bilateral, respiratory complications, and carpal tunnel syndrome. Respiratory disorders were the fifth most frequent comorbidity recorded in these patients. As expected, genetic counseling (ICD-10 Z315) was also frequently performed. A list of the 13 most prevalent ICD codes associated with the syndrome is shown in Table 3.

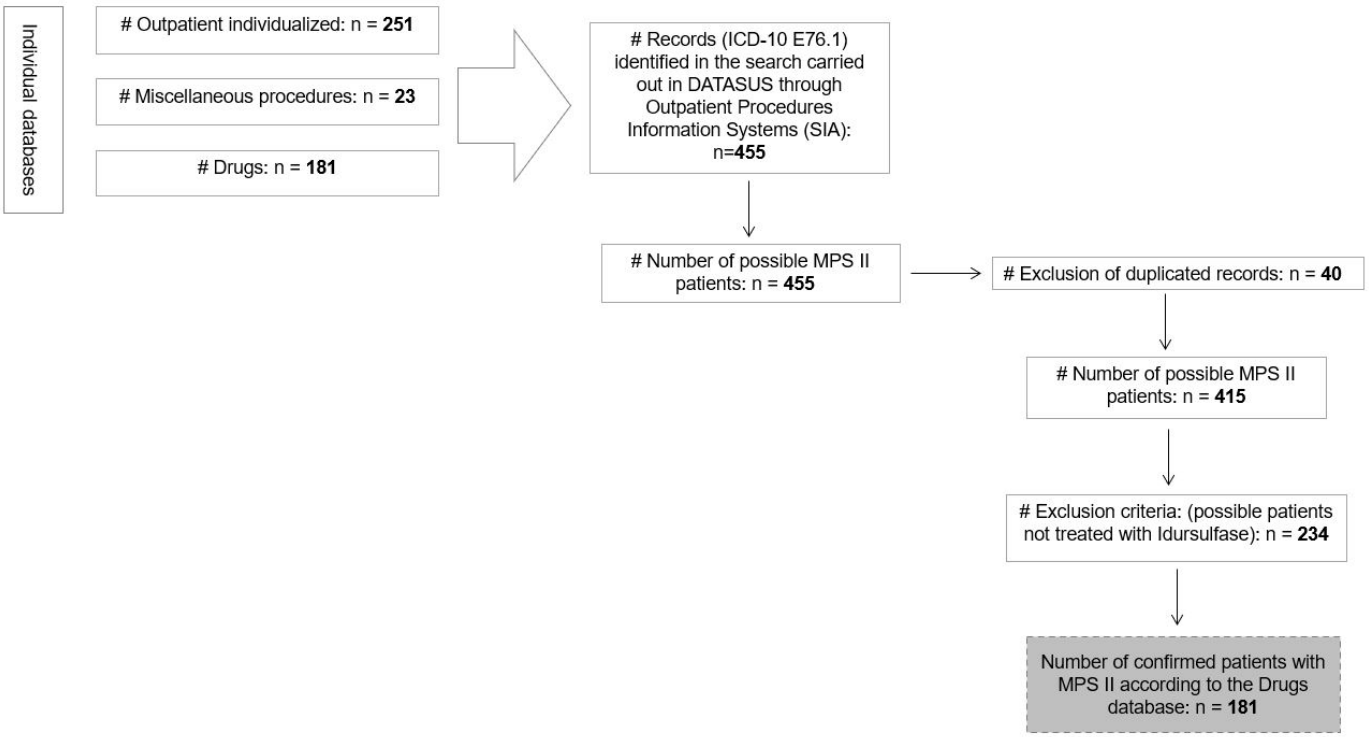

Figure 1. Record selection flowchart. ICD-10, International Classification of Diseases, Tenth Revision; MPS II, mucopolysaccharidosis type II.

Figure 2. Incidence of MPS II (patients taking idursulfase) in Brazil by geographic regions. MPS II, mucopolysaccharidosis type II.

Table 2. Characteristics of confirmed MPS II patients registered in the DATASUS.

Characteristic	Number of Patients	Frequency
	181	
GENDER		
Male	181	100%
Female	0	-
AGE GROUP* (YEARS)		
0-3	6	3.3%
4-6	21	11.6%
7-9	40	22.1%
10-14	45	24.9%
15-19	31	17.1%
20-29	28	15.5%
30-39	8	4.4%
40-49	2	1.1%
≥50	0	-
Unknown	0	-
Average	13.6	

*Age of the patients in 2020.

Table 3. Most frequent comorbidities associated with MPS II patients.

ICD Codes	Clinical Conditions and Procedures	Number of Patients
E76.3	Mucopolysaccharidosis, unspecified	9
F70.0	Mild mental retardation with the statement of no or minimal impairment of behavior	5
F83	Mixed specific developmental disorder	7
F84.9	Pervasive developmental disorder, unspecified	7
G80.0	Spastic quadriplegic cerebral palsy	11
G80.8	Other cerebral palsy	7
G80.9	Cerebral palsy, unspecified	8
H90.3	Sensorineural hearing loss, bilateral	13
H90.6	Mixed conductive and sensorineural hearing loss, bilateral	5
H91.9	Unspecified hearing loss	6
H93.2	Other abnormal auditory perceptions	6
J98.9	Respiratory disorder, unspecified	9
Q89.9	Congenital malformation, unspecified	6

Legends: ICD, International Classification of Diseases; MPS II, mucopolysaccharidosis type II.

Most cases of MPS II were reported in 2019. However, this information does not mean that the cases were necessarily diagnosed in that year as this was the first time that ICD-10 E76.1 was reported in the system. This is probably because in that year idursulfase was incorporated into the SUS in Brazil and many patients previously diagnosed could have access to medication. The age at diagnosis was not available, but we were able to recover the age at the beginning of treatment with ERT with Idursulfase (Figure 3).

Table 4 summarizes the most common outpatient procedures associated with the MPS II patients.

During the study period, 16 hospital procedures were associated with patients with MPS II during the study period. Metabolic disorders treatment and diagnostic and/or emergency

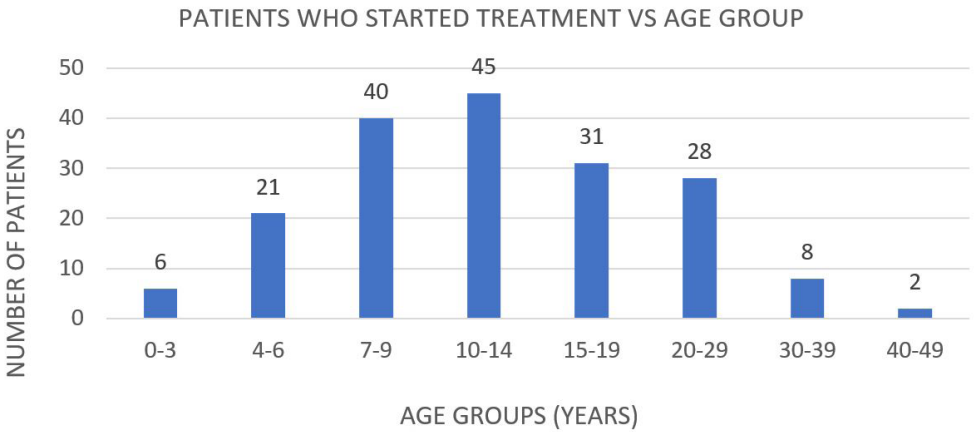

Figure 3. Age at the start of treatment with enzyme replacement therapy. MPS II, mucopolysaccharidosis type II.

Table 4. Most common outpatient procedures associated with MPS II patients. *

ICD Codes	Clinical Conditions and Procedures	Number of Patients
000	Procedures without specific ICD code	121
Z31.5	Consultation genetic counseling	12
Z00.0	Consultation for general adult medical examination	10
Z006	Consultation for examination for normal comparison and control in clinical research program	9
Z00.8	Consultation for other general examination	6
Z00.1	Consultation for newborn, infant, and child health examinations	5
Z00.2	Consultation for examination for period of rapid growth in childhood	0
Z00.3	Consultation for examination for adolescent development state	0
Z00.4	General psychiatric examination, not elsewhere classified	0
Z00.5	Consultation for examination of potential donor of organ and tissue	0
Z006	Consultation for examination for normal comparison and control in clinical research program	9
Z00.8	Consultation for other general examination	6

ICD, International Classification of Diseases; MPS II, mucopolysaccharidosis type II.

call in pediatric clinic were the most common hospital procedures (Table 5).

Data on health care specialists visited were available for 22% of the patients (Figure 4). In this subgroup, radiologists had made the greatest number of MPS II entries, followed by geneticists and cardiologists. Radiologists were also the most visited specialty by patients before diagnosis, followed by cardiologists.

As expected, consultations for clinical examinations were the most common outpatient procedure followed by control examinations or other examinations (Table 4). Treatment for common medical complications such as airway infections was the main hospitalization procedure followed by diagnostic/emergency call in pediatric clinic and treatment for inflammatory polyarthropathies (Table 5). A list of medications used by the patients is described in detail in Table 6.

It´s important to note the fact that this study did not include patients treated with other therapies, such as gene therapy and bone marrow transplantation and also did not include patients for whom the healthcare professional did not prescribe treatment, such as patients with the neuropathic neurological form. In addition, DATASUS is a database for administrative purposes and, in many cases, the person responsible for the data entry is not a healthcare professional limiting the quality of clinical information added in the database.

Table 5. Main hospital (AIH principal) and assorted procedures.

Procedure	Number	Frequency
Metabolic disorders treatment	3,731	83.2%
Diagnostic and/or emergency call in a pediatric clinic	616	13.7%
Treatment of inflammatory polyarthropathies	77	1.7%
Diagnostic and/or emergency call in a medical clinic	43	1%
Diagnostic and/or emergency care in a surgical clinic	3	0.07%
Allogeneic transplantation of bone marrow hematopoietic stem cells – unrelated	3	0.07%
Neurodegenerative diseases treatment	2	0.04%
Treatment of stroke (acute ischemic or hemorrhagic)	1	0.02%
Treatment of complications of surgical or clinical procedures	1	0.02%
Treatment of complications after organ/hematopoietic stem cells transplant	1	0.02%
Allogeneic transplantation of bone marrow hematopoietic stem cells – related	1	0.02%
Implantation of semi or fully implantable long stay catheter (main procedure)	1	0.02%
Treatment of other diseases of the respiratory tract	1	0.02%
Treatment of patients under long-term care for neurological disease	1	0.02%
Umbilical hernia repair	1	0.02%
Ventricular peritoneum – atrium – pleura – spinal derivation	1	0.02%

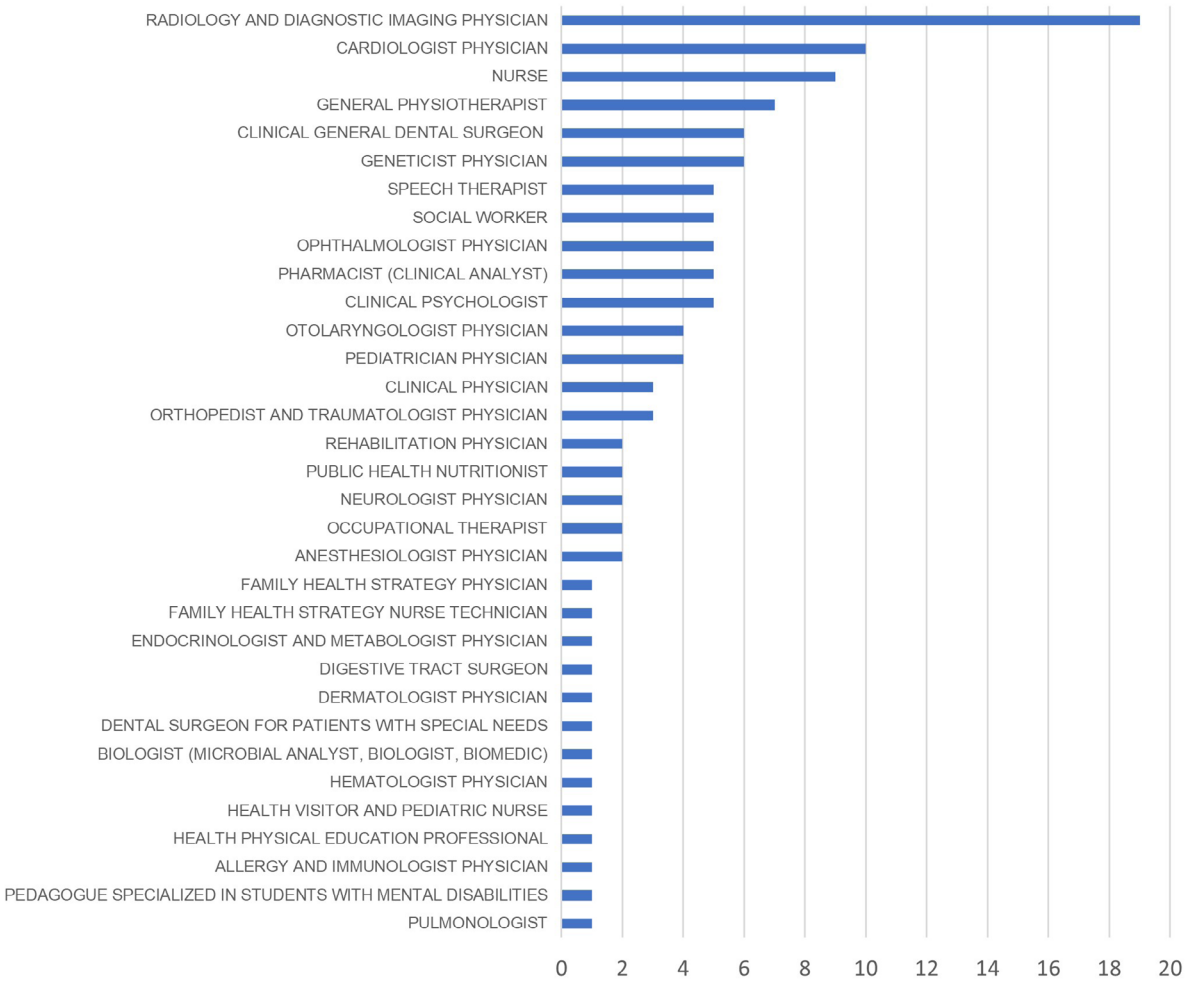

Figure 4. Health care professionals visited by patients before MPS II diagnosis. MPS II, mucopolysaccharidosis type II.

Table 6. Medications used by patients with MPS II.

Medication	Number Of Patients
Idursulfase	181
Painkillers	
Codeine	1
Morphine	1
Gabapentin	1
Neurological Drugs	
Botulinum toxin	6
Risperidone	8
Clobazam	4
Levetiracetam	3
Quetiapine	2
Topiramate	3
Clobazam	1
Vigabatrin	1
Olanzapine	3
Lamotrigine	3
Drugs for Growth	
Somatropin	2
Others	
Formoterol + budesonide	6
Cyclosporine	4
Budesonide	2
Salbutamol	2

Other medications were found in the database but used by less than two patients.

Discussion

Mucopolysaccharidosis type II (MPS II) is a rare X-linked lysosomal disorder caused by the deficiency of IDS enzyme that leads to the accumulation of dermatan and heparan sulfate. Patients with MPS II have a progressive disease with irreversible organ damage and in patients with the neuropathic phenotype irreversible neurological impairment when untreated [2]. If patients are not identified correctly, the recorded prevalence rates will be extremely low [3]. Therefore, this study highlights the importance of disease/health databases as resourceful option to estimate disease prevalence and the patient`s profile.

This retrospective study, based in DATASUS from 2008 to 2020, aimed to describe demographic and clinical findings of the patients with MPS type II. There were 455 patients identified in DATASUS, but the analysis of this study was reduced to 181 patients due to some limitations described below.

To assess patients with a confirmed diagnosis of MPS II, we decided to include only patients treated with Idursulfase ERT. Surely, these patients had the clinical and laboratory diagnosis confirmed (enzyme activity measurement, glycosaminoglycan analysis, and molecular diagnosis). We were then able to identify 181 MPSII patients (Figure 1, Table 1).

No epidemiological studies have specifically assessed the prevalence of MPS II in Brazil to date. Although the prevalence of MPS II in Brazil is not well established, some studies on MPS have made estimates based on data from the MPS Brazil network. The MPS Brazil network is a network that aims to provide a diagnosis to MPS patients and to assist patients with MPS.

According to Bonmann et al. (2009), from 2004 to April 2009, the MPS Brazil network has diagnosed 161 cases of MPS II in the country (average 2.5 cases/month) [11]. Comparing this data with the cases in our study in proportion to the time period (1.2 cases/month), the MPS Brazil network would be able to detect twice as many diagnoses of MPS II. The estimates of cases indicated by Bonmann et al. (2009) is closer to that estimated by Giugliani et al. (2017), who found 343 confirmed cases of MPS II in Brazil. The difference in the number of cases could be due to different case definition criteria [11,12].

In our study only cases with idursulfase treatment were included, while the MPS Brazil network includes all patients with a confirmed diagnosis regardless of the treatment status and it also covers a larger period before the approval of ERT as a treatment option. This study was also limited by the fact that if patients are diagnosed in private clinics or by using

health insurance their information could not be accessed by DATASUS. Also, if another treatment approach is chosen, such as hematopoietic stem cell transplantation (HSCT), those patients would not be included and thus a true prevalence cannot be established with the current database [16].

In our study, the estimated prevalence of cases of MPS II across the five regions of the country was relatively similar to that reported by Josahkian et al. (2021), who reported 493 cases of MPS II in Brazil from 1982 to 2019, with the highest number of cases reported in the Southeast (42% vs 39% in our study) and followed by Northeast (30% vs 34% in our study); North was the region with the lowest number of cases (6% vs 7% in our study) [10]. Although the study periods are different, the geographic distribution of cases remains similar (Figure 2).

As expected, no female cases were identified (Table 2). In the study performed by Vieira et al. (2007) with 43 MPS II subjects, none were female [13].

Furthermore, the group of MPS II patients in that study had the most heterogeneous clinical manifestations [13]. In our study, while there were comorbidities identified in MPS II patients, it was not possible to determine some aspects such as age of onset of symptoms or age of diagnosis, and main clinical findings. The clinical manifestations associated with MPS II were also wide-ranging (13 patients had a sensorineural hearing loss – bilateral, 11 had spastic quadriplegic cerebral palsy, 9 had respiratory disorder, and 7 had pervasive developmental disorder) (Table 3). Respiratory disorders are common in patients with MPS II, and in our study, they represent the third most common comorbidity associated with the syndrome.

Nonetheless, we were still limited by the fact that sometimes it is a non-healthcare professional that enter the patient data and the information does not provide the whole clinical picture. The same is also true for the outpatient procedures (Table 4), hospital/assorted procedures (Table 5), and medications (Table 6).

Brazilian studies developed by Pinto et al. (2004) [14] and Schwartz et al. (2004) [15] reported approximately 71 months (about 6 years old) as the average age at MPS II diagnosis. In our study, we were unable to report age at the diagnosis, but we demonstrate the age at the start of ERT treatment (Figure 3). As DATASUS does not provide the date of the MPS II diagnosis, it is possible that the clinical manifestations of the syndrome had already started before diagnosis.

Regarding healthcare professionals, radiologists were the most frequently visited specialists involved in the MPS II diagnosis, followed by geneticists and cardiologists (Figure 4). While X-rays are requested by other specialists, and radiologists are not directly involved in the patient management, they are trained professionals able to recognize typical signs of MPS II. Additionally, the X-ray is a simpler, faster, and easier to access exam compared to enzyme and GAGs analysis.

Despite the important contribution of this study, we found some limitations. First, the cases were extracted from a secondary data source, and thus it was not possible to determine the exact age of diagnosis. Second, it is likely that true cases of the syndrome could have been missed as only those taking Idursulfase were included, thus underestimating the real number of cases. Similarly, additional analyses could not be performed due to this inclusion criteria. Most of the MPS II records included in this study (78%) came only from the DATASUS drug database. Since the drug database did not contain all data about the patients, some information could not be tracked (e.g., health care professionals visited by patients until the MPS II diagnosis nor who diagnosed MPS II, and ambulatory procedures).

Statistical analysis provides a relative characterization of the epidemiological profile of MPS II patients in Brazil and its variation across states and regions. Most cases of MPS II were from São Paulo, Rio de Janeiro, Paraná, and Ceará; this information can help to design targeted local public policies (Figure 2).

This is the first epidemiological study to assess exclusively MPS II in Brazil. Despite its limitations, DATASUS is a relevant database to provide data on the characteristics of patients with this syndrome. It is also extremely important to have concise and integrated databases now that rare diseases are being included in newborn screening, patients will be diagnosed earlier, treated, and the databases must be integrated to provide the best possible outcome to patients.

This paper highlights the limitations of databases such as DATASUS for rare diseases, nonetheless DATASUS has demonstrated to be a reasonable source to estimate disease prevalence in Brazil [2,10]. It is important to demonstrate the usefulness of these databases in a way that the developers can allow for data integration of disease and natural history assessments. This study supports other previous publications related to MPSII that shows the distribution of MPS II patients in different states in Brazil.

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Author contributions

FT Study Concept, analysis, and interpretation of results. CSMS Study Concept, analysis, and interpretation of results. All authors reviewed the results and approved the final version of the manuscript.

Declaration of Conflict of Interests

FT are current employee of Takeda Pharmaceuticals, Brazil. CFMS declare no conflicts of interest.

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