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Morquio B patient/caregiver survey: First insight into the natural course of a rare GLB1 related condition☆

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ABSTRACT

Morquio B disease (MBD) or Mucopolysaccharidosis type IV B (MPS IV B) is caused by particular GLB1 mutations specifically affecting the affinity of beta-galactosidase to keratan sulphate, resulting in dysostosis multiplex resembling Morquio A (MPS IV A) disease (GALNS deficiency). Additional neuronopathic features of GM1 II/III (juvenile/adult) gangliosidosis have been reported in some patients. Our patient/caregiver online survey was aimed at elucidating the clinical manifestations of this ultra-rare condition.

Comparing to previously published data on MPS IV A, the 30 respondents in our MBD group presented with greater growth chart values (weight and height) and with lesser effects of odontoid hypoplasia. The most common concerns are: (1) mobility issues - 84% having difficulty walking; (2) chronic pain - 96%; (3) surgeries - average 3 per person, 80% for hip problems; (4) hip dysplasia, knee/ankle concerns, and scoliosis. Approximately 50% of MBD participants live independently and actively contributing to society.

Evidence from our survey results supports the notion that skeletal manifestations in MBD are milder than in the majority of patients with MPS IV A. The data collected will help with the establishment of clinically meaningful outcomes for future therapeutic trials, and with the counseling of newly diagnosed patients about their health expectations.

1. Introduction

Morquio B Disease (MBD) (Ch. 151 OMMBID) is an autosomal recessive disorder caused by particular mutations in the *GLB1* gene coding for the lysosomal acid ß-galactosidase [22]. Patients with a *GLB1* related disorder can present within a broad clinical spectrum including infantile (OMIM #230500), juvenile (OMIM #230600), and adult (OMIM#230650) forms of GM1 gangliosidosis, manifesting with a range of rapidly progressive to attenuated course of neurodegeneration, visceral and skeletal involvement [4]. Onset beyond infancy is associated with a milder/less rapidly progressive course often referred to as Type II and Type III (juvenile/adult) GM1 gangliosidosis [17]. MBD (OMIM #253010) is a particular subtype of GLB1 related conditions presenting with a distinct type of dysostosis multiplex [22] initially described as Morquio Syndrome [3, 13].

GLB1 related conditions are all extremely rare with an overall estimated prevalence of 1: 100,000 to 300,000 [22].The prevalence of Morquio B specifically has been reported as 1:250,000 to 1,000,000 live births [2, 7].

GLB1 related MBD is one of two genetic conditions presenting with the Morquio type of dysostosis. GALNS related enzyme deficiency (Mucopolysaccharidosis type IV A, MPS IV A) was identified as the first genetic cause of Morquio syndrome [11]. A few years later, β-galactosidase (GLB1) deficiency was recognized as a second genetic cause for Morquio syndrome [1, 14]. Hence, GLB1 related Morquio syndrome has been referenced as Morquio B disease (MBD) or mucopolysaccharidosis type IV B (MPS IV B).

The dysostosis in MBD, similar to Morquio A disease, mainly affects the trabecular bone and ligament stability. Patients have a unique appearance caused by short stature with disproportionally short trunk with variable degree of kyphoscoliosis, pigeon chest (pectus carinatum), short neck, large appearing head with midface hypoplasia and mandibular protrusion, large appearing joints (elbows, wrists, knees, ankles), coxa and genua valga, and flat feet and hyperextensible joints.

☆ This international online patient survey enabled us to collect clinical data in the largest-ever reported cohort of people with Morquio B Disease.

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Characteristic radiological findings are platyspondyly and vertebral beaking involving all segments of the spine, odontoid hypoplasia, epi- and metaphyseal dysplasia of long bones, hip dysplasia, and dysplasia of carpal and tarsal bones. Spinal cord compression may cause neurological symptoms (spasticity, pain, bladder dysfunction) in advanced stages. Corneal clouding and cardiac valve disease are additional findings shared by those with Morquio A and B syndromes.

MBD is caused by a limited number of GLB1 mutations [20] which particularly impact the catalytic effect of β-galactosidase on the degradation of keratan sulphate bound oligosaccharides, as opposed to other forms of GM1gangliosidosis where the degradation of gangliosides and non-keratan sulphate bound oligosaccharides is mostly impacted [15, 18]. As a consequence, a characteristic biomarker for MBD is an accumulation of keratan sulfate, which is predominantly found in cartilage [21].

The W273 L variant has been claimed as the classical MBD allele as homozygous patients consistently have been free of primary neurologic/neurodegenerative manifestations [5, 8, 9, 16]. Other alleles have been reported both with GM1 II/III gangliosidosis and MBD phenotypes. For example the R201H allele when in homozygosity was reported in association with the MBD phenotype [18], However when in compound heterozygosity with other GLB alleles, it has been reported in association with juvenile/adult GM1 gangliosidosis allele [19].This can lead to a blended phenotype, exhibiting both features of dysostosis type Morquio and at the same time neuronopathic features as seen in GM1-gangliosidosis. Patients with such blended phenotypes have been reported as atypical MBD or combined MBD/GM1 II/III [10].

While the W273 L variant causes a decreased hydrolytic activity due to its lower affinity towards keratan sulphate [6], the majority of additional variants observed in patients with the MBD/GM1 II/III are missense mutations resulting in instability and premature degradation of an enzyme protein with otherwise intact catalytic sites.

Given the extreme rarity of MBD, the knowledge of the clinical spectrum (age of onset, range of disease severity and progression) is quite limited. At the same time, there is an urgent need for a better understanding of the natural history of MBD, to identify clinical endpoints or comparative data needed for properly designed clinical trials for future treatments as was done in Montano et al.'s study to address the clinical needs of Morquio A patients (2007). The aim of this study was to describe the clinical spectrum of MBD. In order to reach out globally, we used a survey link which was directly accessible to patients outside clinical centres.

2. Methods

We developed a survey questionnaire to collect cross-sectional patient self-reported data. The survey was performed by a study team based at British Columbia Children's Hospital/Department of Pediatrics, University of British Columbia, Vancouver, Canada. The study was approved by the University of British Columbia Research Ethics Board (UBC REB, *H16-00192*). Data was gathered over a one year-period between March 2016 and May 2017.

The survey questions were inspired by published case reports and by our own experience achieved through study of the literature and clinical work with affected patients and their families. The survey consisted of 72 questions which were organized into 7 sections: (1) Demographics (2) Patient Health (3) Quality of Life (4) Access to Healthcare (5) Diagnostic History (6) Lifestyle and (7) willingness to volunteer in future clinical trials. The survey was translated from English into 8 languages: Dutch, French, German, Italian, Macedonian, Polish, Portuguese and Spanish. Translations were provided by certified interpreters (ABC Language Solutions). This was done to ensure that all patients could participate regardless of their proficiency level in the English language. The choice of language translations was informed by the social media contacts of one coauthor (TP).

Data was collected using REDCap, which is an online software platform capable of gathering various forms of clinical data safely and securely. The particular digital database used for this study is hosted by the Women & Children's Health Research Institute (WCHRI)'s Clinical Informatics Core (CRIC) in Edmonton, Alberta as part of the NeuroDevNet/Kid's Brain Health Network research initiatives (www.neurodevnet.ca). The study files were encrypted according to policies required by the University of British Columbia. De-identified, study-related electronic data was stored both on the REDCap database and on a secure password-protected, limited-accessed computer at BC Children's hospital. Every participant was provided with a study ID and no personal identifiers were collected, apart from e-mail addresses which were voluntarily provided by the participants at the end of the survey in case they wished to be contacted in relation to future clinical studies.

The survey was advertised to Morquio B communities through patient support group websites and through private Facebook groups, all of which were patient motivated. The survey links were hosted on two patient support group websites: www.MorquioB.com and National Organization for Rare Diseases or NORD (www.rarediseases.org).

The following information was provided to participants within the consent form: (1) the purpose of the study, (2) the type of data we were gathering, as well as the manner in which the data was stored and used safely during publication, (3) criteria for patient inclusion in this study, and (4) mention of any potential harms or concerns that may occur. All participants were required to read and confirm their understanding of our study and were prompted to provide their consent prior to gaining access to the online survey. Particular emphasis was placed on asking patients to clearly confirm that they have bone disease and have been diagnosed with MBD (MPS IVB) and not with MPS IVA. Patients with a MBD phenotype blended with neuronopathic features of GM1 gangliosidosis were given the option to click both Morquio B and GM1 gangliosidosis. Those patients were then categorized as MBD/ LO-GM1.

Completeness of the survey was judged to be a time stamped official submission of the REDCap survey online, with participants answering “yes” to reading the consent form. The participants were able to submit the survey even if not all questions were answered.

3. Results

3.1. Demographics

We were able to collect survey data from 30 patients: n = 11, 37% male; n = 19, 63% female (Table 1); n = 9 (30%) residing in Northern America (USA and Canada), n = 21 (70%) residing in greater Europe including Austria, Germany, Belgium, Italy, Ireland, Macedonia, Netherlands, Poland, Portugal and Spain, as well as UK. 25 participants (83%) reported themselves as having MBD. We assigned the remaining 5 participants to the MBD/GM1 II/III group. Since our sample of patients with assumed MBD/GM1 II/III was so small (n = 5), and also because there is no possible way for us to ascertain which genetic subtypes these 5 participants may have based on our methods, we have excluded any results from this group in the remaining sections.

Table 1
Type and frequency of skeletal involvement for MBD participants.

Musculoskeletal issues	MBD participants (n = 23) (n = 25)*
Hip dysplasia	12 (52%)
Knee/ankle problems	11 (48%)
Scoliosis	10 (43%)
Odontoid/dens hypoplasia	3 (13%)
Carpel tunnel	1 (4%)
Bone fractures (Hip, femur)	8 (32%)*

* Bone fractures (Hip, femur), there were n = 25 (8/25) respondents. All of the previous musculoskeletal issue categories outlined in the table had only n = 23 respondents.

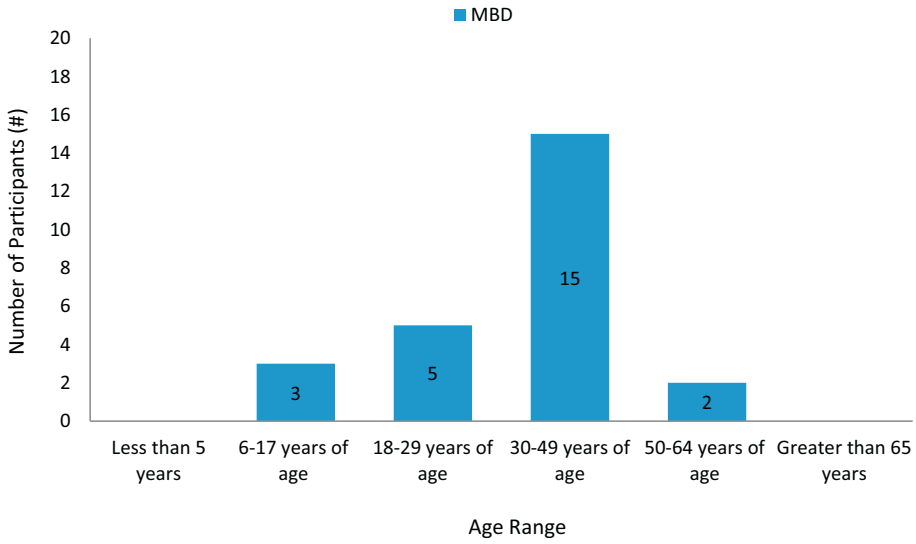

Fig. 1. Age range of participants with MBD (n = 25).

In defining the age categories of our respondents, we have determined that three of the 25 participants with MBD were within the pediatric age range 6–17 years, and 22 of the 25 participants were within the adult age range 18–64 years (Fig. 1).

3.2. General medical information

The mean weight for male (n = 9) and female (n = 13) MBD participants over 19 years of age was 60.7 kg and 46.1 kg respectively, while the mean height was 151.6 cm for males and 136.9 cm for females.

Fig. 2b shows that the mean heights of all males and all females with MBD over 19 years of age were below the 15th percentile (WHO growth charts for Canada https://www.dietitians.ca/Dietitians-Views/Prenatal-and-Infant/WHO-Growth-Charts/WHO-Growth-Charts-Set-1.aspx, 2014). Compared to the average heights of patients with Morquio A disease ([12], average weight and height in Morquio A patients is marked as "X" in Fig. 2a, b), our MBD participants were considerably taller.

The median age of onset was 5.5 y (range 3–11). Among the 24 respondents, 70.8% (n = 17) had their diagnosis confirmed enzymatically which overlapped with 62.5% (n = 15) of diagnoses being confirmed via gene testing.

The most common first signs and symptoms described by participants (n = 17 respondents) were irregular gait/walking (n = 7, 41%) and pain in joints/limbs (n = 6, 35%) as shown in Fig. 3.

3.3. Functional concerns

3.3.1. Mobility

All MBD participants reported having difficulty with walking. 84% (n = 21) were using a walking aid. Of those who responded positively to using walking aids, only 15 participants reported the age of first use. The vast majority (14/15) started using walking aids in the 10 to 20 years age range and beyond (Fig. 4). The most popular walking aid was the wheelchair, with n = 10 (66.7%) participants using this type of aid. Other walking aids mentioned by respondents were the use of a cane (13.3%, n = 2), crutches (20.0%, n = 3) or walker (13.3%, n = 2).

3.3.2. Pain

Pain was reported as a health issue by a vast majority of respondents (n = 24/25). Typical locations were spine, head, chest, hip, and ankle. Most participants reported experiencing minor (16.7%) to moderate (62.5%) degrees of pain throughout the one year prior to their participation in our survey. Activities that were reported by our participants to cause the most pain were walking (83%) and physical activities (71%).

3.3.3. Sleep concerns

The measure for sleep quality in our survey was informal, and we assumed the presence of poor sleep quality if participants responded with having insomnia as well as subjectively rating their quality of sleep as poor or very poor. In our sample, 7/24 (29%) of participants had trouble falling asleep (insomnia), and 3/24 (12.5%) thought they had poor/very poor sleep quality.

3.3.4. Pulmonary function

15/25 respondents had pulmonary function tests done, and the results were reported to be abnormal in 40% (n = 6/15), with assessments done later in life at a mean age of 20.4 years. To address some of their respiratory issues, around 20% (n = 5/25) of our cohort collectively had adenoidectomy and tonsillectomy surgeries between 4 and 5 years of age.

3.4. MBD related bone disease

3.4.1. Skeletal problems

Table 1 shows the type and frequency of skeletal involvement. Hip dysplasia, knee/ankle problems, and scoliosis were the most frequently reported concerns. Odontoid/dens hypoplasia, which is frequently found in Morquio A disease, was mentioned as a concern only by a minority 13% (n = 3/23). One third of participants reported bone fractures, particularly in the hip and the femur. In terms of hip involvement, no information was available on whether the participants suffered from a true fracture or from subluxation.

3.5. Surgeries

The distribution of surgical operations, their frequency, and the mean age for each operation are outlined in Fig. 5. MBD participants had an average of 3 surgeries per person. The mean age was 22.5 years for hip surgery and 20.1 years for knee surgery.

3.6. Other health concerns

Participants' health concerns were broadly determined by

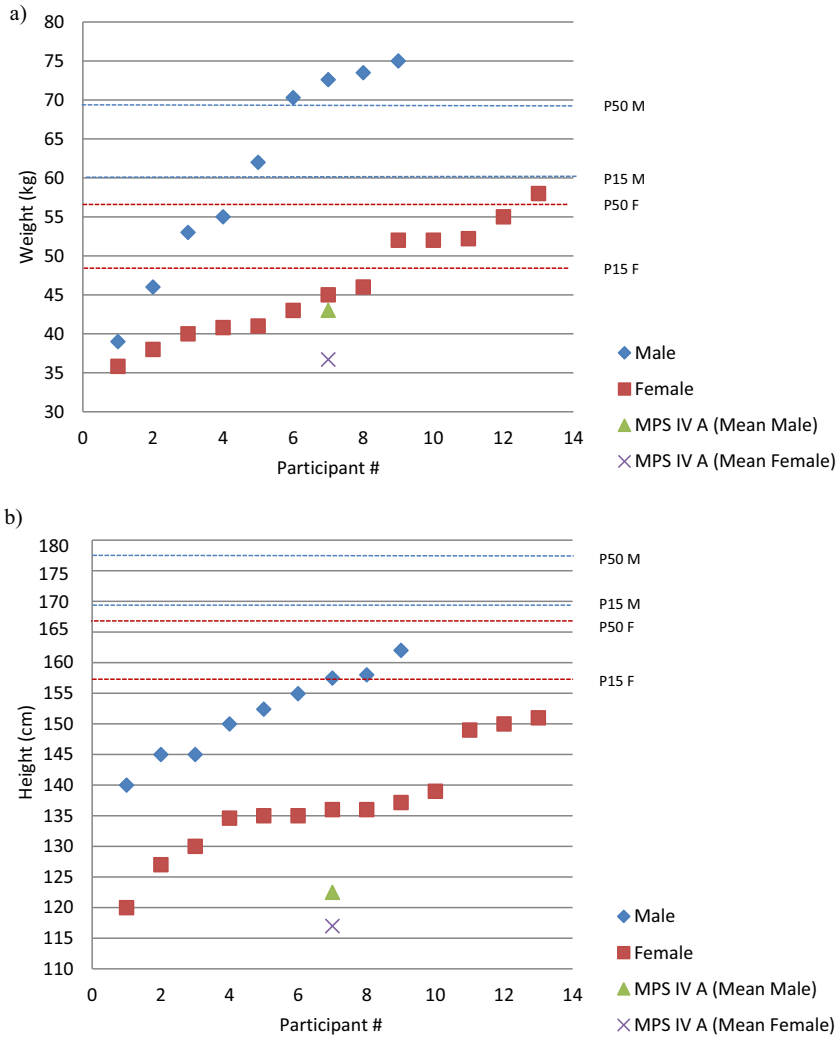

Fig. 2. a) Weight (kg) and b) height (cm) values reported by MBD patients at ages > 19 yrs. showing individual values for female participant (squares) and male participants (diamonds). The 15th and 50th weight percentile values for male (M) and female (F) (WHO growth charts for Canada) were included. The value for mean a) weights (kg) and b) heights of male (green triangle) and female (grey X) MPS IV A patients were included [12]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

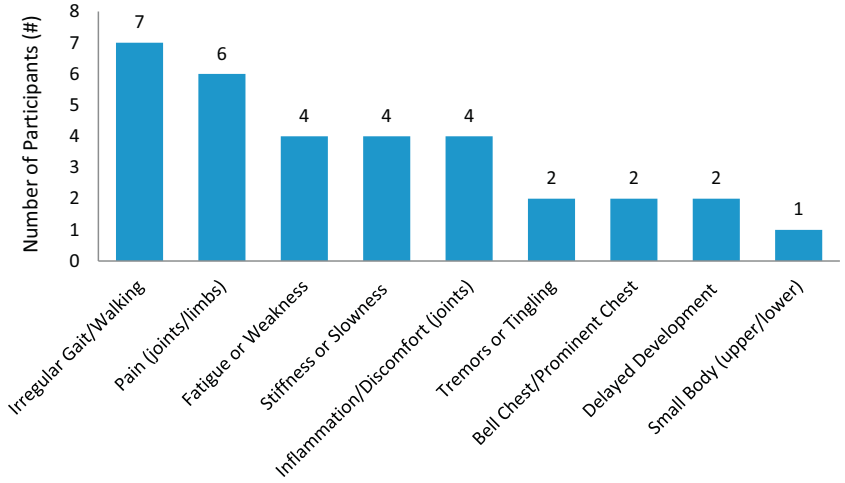

Fig. 3. Number of MBD participants (n = 17) who reported having each of the clinical symptoms as initial manifestation. Numbers at the top indicate number of participants who had each clinical symptom.

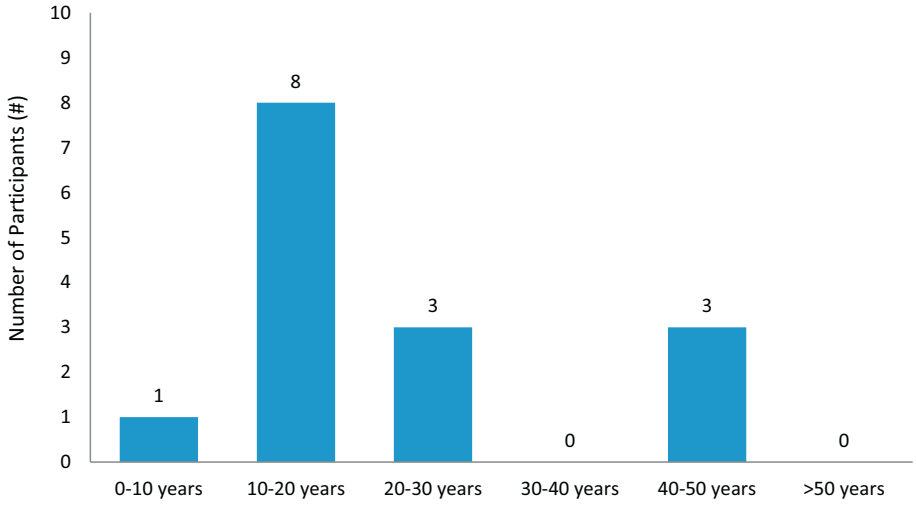

Fig. 4. Number of MBD participants (n = 15) who reported using walking aids, showing the age distribution of their first time use of walking aids. Numbers at the top indicate number of participants in each age range.

investigating the types of clinical assessments and results information provided by the patients. Apart from bone assessments (X-rays) which were done in 15/25 (60%) of participants, other common assessments were eye exams, which were abnormal in 11/23 (48%) respondents, dental exams, which were abnormal in 3/20 (15%), as well as heart assessments, which were abnormal in 14/20 (70%).

3.7. Lifestyle

To understand the degree of independence and level of mobility in our study participants, we inquired about their educational status, professional status, leisure, and daily living and self-care activities. The most common educational status reported by 7/30 (23%) participants was high school graduate, followed by several years of university or college where 5/30 (16.7%) participants had incomplete degrees. 4 participants reported obtaining post-graduate degree. In regards to professional activities, 37% (n = 11) of participants were employed/self-employed and 10% (n = 3) were retired or had unspecified disability benefits. Half of the MBD participants indicated that they engaged in physical activities such as swimming, cycling, and going on walks. Other reported leisure activities were professional development, reading, writing, as well as creative arts, dance, and music.

Slightly less than half (46%) of participants lived independently. More than half (59%) reported that they were able to drive independently while a few (18%) use public transportation. Respondents were capable of completing most of the activities from a list of activities of daily living (ADL) (Table 2). Only 2/27 individuals were not able to tackle any of these activities without assistance. None of the participants experienced consistent difficulties with swallowing, or the need to use a G-tube. 79% of respondents commonly identified their parents as their primary support, as well as their friends (70.8%) and their community (33.3%).

Table 2
Activities of daily living (ADL) reported by 24 participants with MBD.

Activities of daily living completed by participants	MBD participants (n = 24)
Dressing	18 (67%)
Grooming	18 (67%)
Washing	20 (74%)
Toileting	21(78%)
Eating	21(78%)
Moving/walking	18 (67%)
House chores	13 (48%)
Leisure time	16 (59%)

For 75% of the participants the most important motivator in their lives was the option to set their own goals and the ability to work in order to achieve them. Two-thirds also reported that their hobbies are important, about a half listed their work and career, and around two-fifths said that pursuing physical activities was important. When asked about the most challenging aspects of living with MBD, participants

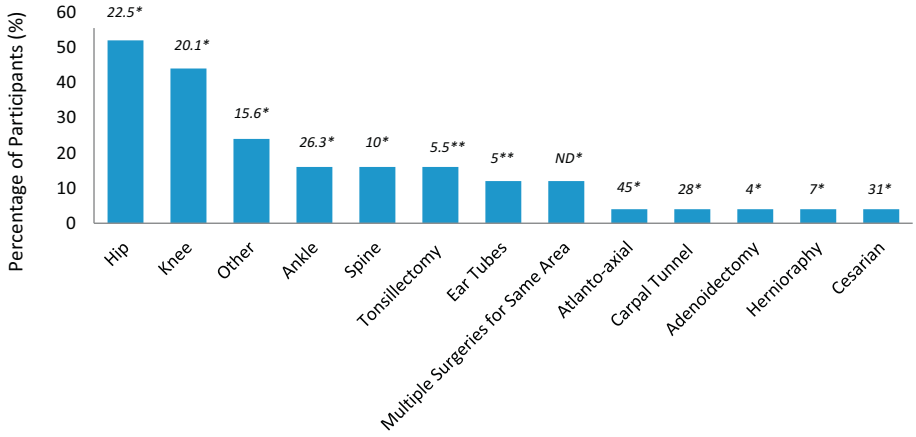

Fig. 5. Surgical operations performed on MBD patients n = 25.Values italicized above each bar depicts the mean age of the patients who underwent surgery*.

commented that having to "*deal with [their] pain… is the worst*". They also found it difficult to "*keep up with others*", and "*not being able to do activities that average people can do*". Participants, however, were encouraged by a positive outlook on their lives: "*maintaining [their] health [by] staying active*", "*having a good diet*", as well as "*having the* "*right medications and proper surgeries*". Around 40% of participants say they volunteer or are involved in their communities. Over 50% of the participants connected with the Morquio community through social media sites, such as Facebook groups. A few found the Research Foundation for Rare Disorders website, as well as personal blogs or advocacy websites, to be a useful means of connecting with other groups.

4. Discussion

This patient survey enabled us to collect cross-sectional disease specific data from 25 individuals with MDB. We were able to collect and analyze data on this extremely rare condition within a time frame as short as 2 years, through the support we received from the Morquio B community. A major advantage of this patient directed survey was that it allowed us to reach out globally and collect data from patients that are not exclusively seen in large clinical research centres. Seeing that 80% of our respondents accepted to be contacted for further research, our survey also provides a registry for potential participants in upcoming clinical trials.

Our survey findings allowed, for the first time, an understanding of the clinical severity, type, and progression of skeletal and organ involvement in MDB. 60% of our respondents were over 30 years of age, suggesting that MBD is mainly prevalent in adult patients and that life expectancy is at least into mid adulthood or beyond.

MBD is often considered as a milder clinical variant of Morquio A disease (MPS IV A). A comparison of our data with a similar patient directed study for MPS IV A [12] supports this notion. Demographically, a significant portion of respondents in our MBD survey (77%) were older than 18 years of age, while only 36% respondents were 18 or older in the MPS IV A survey. There was also a difference in the age at diagnosis, with a mean of 6.3 years in the MBD sample compared to 3 years in the MPS IVA sample. Findings suggest that MBD's phenotypic manifestation is less severe permitting a longer life expectancy, and/or that it is more difficult to initially diagnose based on less pronounced early skeletal signs and symptoms. Indeed, bone deformities and short stature were not common initial descriptors made by our MBD participants, whereas bone deformity (knocked knee, backspine, bell chested or protruding chest), and short stature were reported as early clinical signs in the MPS IV A survey. Another indicator for the comparatively mild course of MBD is the later use of walking aids in MBD patients (22 years) compared to the respondents in the MPS IV A survey (14.2 years).

Surgical operations for our study population differed significantly from Montano et al.'s [12], both in regards to the most common types, as well as in the mean age at which these surgeries took place. In particular, the most predominant surgical operation types for MBD patients were for hip and knee problems. Atlanto-axial instability in our MBD respondents was quite rare, and only one patient had a corrective operation, which was performed at age 45. In contrast, data from Montano et al.'s [12] study shows that most surgeries were completed under the age of 12 (based on mean age values only), and that the most prevalent surgery was decompression/cervical fusion (mean age 9.9 years), and others such as leg and hip joint correction. Not only did the surgeries differ between these two study populations, but there were significant differences in adult weight and height between MPS IV A and MBD patients which were outlined in the results section. The patient profile of Morquio B participants demonstrates, once again, a decreased severity of phenotypic manifestations, particularly in terms of height, with all of our participants reporting higher values in comparison to the average adult height of MPS IV A patients.

Pulmonary function tests were reported abnormal both in our MBD pro-bands (40%; 6/15), as well as in Montano et al.'s [12] MPS IV A participants (24%). Pulmonary functioning has been used as primary outcome test in clinical trials for enzyme replacement therapies for MPS IV A, and this may also be a suitable endpoint in non-pediatric populations in future MBD treatment trials.

An important point to make is that participants maintained a high level of function in ADLs. Yasuda et al. [23] developed a patient self-administered ADL questionnaire for Morquio A disease. Given the similarity between Morquio A disease and MBD it will be interesting to administer this questionnaire to MBD patients and to evaluate its potential applicability in future clinical trials.

Furthermore, our data supports the claim that MBD participants were well-integrated in society, as they participated in social and community activities, and had the capacity to pursue higher levels of education or have an active professional role. The survey results also demonstrate higher functioning in terms of participating in a variety of outdoor and physical activities (particularly swimming), creative projects and hobbies, as well as reading and socializing. Development of causal treatments would enable patients to perform these activities more often, with fewer physical and mobile impairments, or health complications.

5. Limitations

Inherent to the type of survey and the extreme rarity of MBD, our study had several limitations. While we were able to collect data from a larger distribution of the MBD population we were not able to control whether patients self-reported their diagnoses accurately. We attempted to minimize self-reporting errors for diagnoses by providing clear survey instructions to participants in order to prevent those with MPS IV A to participate in the survey. We also distributed the survey directly to groups known to have MBD.

5.1. Summary and outlook

Overall the data obtained in this study indicate that MBD in most cases takes a milder clinical course compared to its phenocopy, MPS IV A. The data obtained in this study can be used to provide background information on useful clinical outcomes for upcoming clinical trials and to make suggestions for long-term outcome studies. Given enough time and outreach, an increased number of patients, as well as a yearly collection of data (survey or medical files), will provide a better framework and more accurate information regarding the progression of these disorders and the efficacy of treatments.

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Competing interests

None declared.

Contributions

Maria Bleier: Coordinated and carried out major parts of the projects, including set up of REDCap database, data analysis, manuscript writing.

Nataliya Yuskiv: Carried out ethics submissions; contributed to set up of REDCap database.

Tina Priest: Participated in design of patient/caregiver survey, distributed survey link on social media.

Marioara Angela Moisa Popurs: Contributed to design of survey and

development of REDCap database.

Sylvia Stockler-Ipsiroglu: Initiated the project, supervised progress of work, data analysis, and manuscript writing.

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