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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.