Threshold Effect of Urinary Glycosaminoglycans and the Walk Test as Indicators of Disease Progression in a Survey of Subjects With Mucopolysaccharidosis VI (Maroteaux–Lamy Syndrome)

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A cross-sectional survey in individuals affected with the lysosomal storage disease Mucopolysaccharidosis VI (MPS VI) was conducted to establish demographics, urinary glycosaminoglycan (GAG) levels, and clinical progression of the disease. The survey evaluated 121 bona fide MPS VI-affected individuals over the age of 4 years from 15 countries across the Americas, Europe, and Australia representing greater than 10% of the estimated world prevalence of the disease. A medical history, complete physical exam, urinary GAG determination, and assessment of several clinical measures related to physical endurance, pulmonary function, joint range of motion, strength, and quality of life were completed for each participant. Although a wide variation in clinical presentation was observed, several general findings were obtained reflecting progression of the disease. Impaired physical endurance, as measured by the distance achieved in a 6-min walk, could be demonstrated across all age groups of MPS VI-affected individuals. High urinary GAG values (>200 μg/g creatinine) were associated with an accelerated clinical course comprised of age-adjusted short stature and low body weight, impaired endurance, compromised pulmonary function, and reduced joint range of motion. An unexpected result was the predominance of urinary GAG values <100 μg/g creatinine for those participants over the age of 20 years. Pending the collection of longitudinal data, these results suggest that urinary GAG levels predict clinical morbidity, and longer-term survival is associated with urinary GAG levels below a threshold of 100 μg/g creatinine. © 2005 Wiley-Liss, Inc.

KEY WORDS: Mucopolysaccharidosis VI; MPS VI; urinary glycosaminoglycan; walk test; clinical survey

INTRODUCTION

Mucopolysaccharidosis VI (MPS VI) or Maroteaux–Lamy syndrome is a lysosomal storage disease resulting from a deficiency in the enzyme N-acetylgalactosamine 4-sulfatase (also known as arylsulfatase B, or ASB; E.C # 3.1.6.12) reviewed in (Whitely, 1993; Neufeld and Muenzer, 2001). This enzyme is responsible for the hydrolysis of the sulfate moieties of the glycosaminoglycan (GAG) dermatan sulfate during the stepwise degradation of this polymer. When insufficient enzyme activity is available, dermatan sulfate degradation is blocked, resulting in the intracellular accumulation of this substrate in the lysosomes of a wide range of tissues. The accumulation causes a progressive disorder with multiple organ and tissue involvement. The disease is inherited in an autosomal-recessive fashion, and carriers of mutated genes do not exhibit any evidence of lysosomal storage.

As with all the MPS disorders, MPS VI is a clinically heterogeneous disease in terms of the extent and rate of progression of organ impairment in affected individuals (Springer et al., 1970). Case studies reported in the literature have identified subjects presenting with marked physical changes and cardiovascular disease in the first year of life (Fong et al., 1987; Hayflick et al., 1992), whereas others have slowly advancing disease progressing over many decades (Pilz et al., 1979; Torneesen et al., 1991). Typically, the most rapidly advancing form presents with progressive deceleration of growth, skeletal deformities, coarse facial features, upper airway obstruction, recurrent airway and ear infections, and joint deformities. Affected individuals progress over years, and ultimately become wheelchair bound or bedridden secondary to skeletal deformities, joint disease, cardiopulmonary disease, blindness, and spinal cord compression. Usually, they eventually succumb to either infection, complications secondary to Naglazyme (galactosamine) is indicated for patients with mucopolysaccharidosis VI (MPS VI). Naglazyme has been shown to improve walking and stair-climbing capacity. This reprint contains information for Naglazyme that has not been approved by the Food and Drug Administration.

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surgery, or cardiopulmonary failure. MPS VI is not typically associated with progressive impairment of mental status, although physical limitations may impact learning and development.

Based on the known genetic defect, the expression of functional ASB is the crucial determinant influencing the clinical phenotype. Although the key structural features of the ASB glycoprotein have been characterized, the identification of over 45 different genetic mutations has hindered establishing a genotype-phenotype correlation [Litjens and Hopwood, 2001]. The majority of these mutant alleles are either unique or present in a small number of subjects, and unlike other MPS disorders, common mutations have not been identified. Biochemical heterogeneity resulting from the combination of two different mutant alleles also contributes to the clinical heterogeneity. The finding that subjects along the entire spectrum of slowly to rapidly advancing disease were similarly deficient in endogenous enzyme activity [Brooks et al., 1991] makes it challenging to predict clinical outcomes based on residual enzyme levels.

There is no effective treatment for this disease, although bone marrow transplantation (BMT) has provided clinical benefit based on published case studies or series [Krivit, 1992; Hoogerbrugge et al., 1995; Herskovicz et al., 1999]. With the recent introduction of an enzyme replacement therapy (ERT) for MPS VI into human clinical studies [Harmatz et al., 2004], there is greater interest in understanding the evolution of this disease, however, there are no published studies describing the natural history of MPS VI-affected subjects. The clinical reports that have been published have not been based on a large cross section of the population, and have not included quantitative measurements of clinical disease. The primary purpose of the present study was to provide several quantitative measures of clinical disease across a wide demographic of MPS VI-affected individuals.

SUBJECTS AND METHODS

Subjects

This was a multicenter, multinational study that evaluated clinical and biochemical parameters known to be involved in MPS VI subjects. The study enrolled 125 individuals older than 4 years at seven centers with expertise in evaluating and treating subjects with MPS VI. Although clinical history and physical exam were sufficient to gain entry into the study, inclusion in the data analyses required confirmation of the diagnosis of MPS VI. This was accomplished by biochemical demonstration by an accredited clinical laboratory of (1) a reduction of leukocyte or fibroblast ASB levels, and (2) elevated urinary GAG levels. Two siblings with questionable diagnostic results from the medical record were excluded because they were determined to have a disorder other than MPS VI based on normal urinary GAG values and normal ASB levels for one sample obtained. The protocol and subject informed consent form were approved by each center's IRB or IEC. Thirteen subjects were enrolled in the study despite not meeting one or more of the original inclusion or exclusion criteria; nine subjects were enrolled who were between the ages of 4 and 5 years, two subjects were enrolled who had undergone BMT, which failed in both cases, and two subjects were enrolled who had only one of the two measures of biochemical confirmation of MPS VI disease.

Methods

The evaluations conducted in this study were previously applied to an ongoing Phase 1 Study evaluating ERT with recombinant human ASB for MPS VI subjects [Harmatz et al., 2004].

RESULTS

Demographics

The 121 individuals with MPS VI in this study were derived from 15 countries, primarily from North America, South America, Europe, and Australasia. There was a similar
distribution of males and females ranging from 4 to 56 years of age, with 75% between 4 and 18 years of age (Table I). Large differences between the mean and median values for height and weight reflected the contribution of a minority of larger subjects with slowly advancing disease who lived beyond the second decade. The mean height was 115.2 ± 29.1 cm (Table I) with a range of 80.0–169 cm and a median value of 103.7 cm, while the mean weight was 30.47 ± 18.0 kg (range of 12.1–84 kg) with a median value of 20.8 kg.

From the perspective of clinical presentation, the subjects represented a broad spectrum of MPS VI disease. Many subjects had extensive medical complications, including multiple surgeries for problems ranging from hernias to carpal tunnel syndrome to elevated intracraniapressure. The common features in these subjects obtained from clinical history and physical evaluation were short stature, large head with coarse facies, flat nasal bridge, enlarged tongue, joint contractures, scoliosis, pectus carinatum, valvular cardiac disease, corneal clouding, hernias, weakness in grip, chronic ear infections, hepatosplenomegaly, airway obstruction, recurrent sinopulmonary infections, carpal tunnel syndrome, skeletal abnormalities (dysostosis multiplex), and blindness or visual acuity ≥20/200.

Forty-four of the 121 subjects (36%) were not taking any medications at the time of the survey. Concomitant medication use by indication was highest in 30 subjects (25%) taking medications for cardiac disorders, including angiotensin-converting enzyme (ACE) inhibitors (15 subjects), diuretics (10 subjects), sulfonamides (4 subjects), aldosterone antagonists (3 subjects), and various medications for tachycardia (3 subjects). Twenty-nine subjects (24%) were taking medications for respiratory/pulmonary disorders. The most frequently prescribed classes of these medications were beta-2 agonists (18 subjects), corticosteroids (10 subjects), antihistamines (6 subjects), mucolytics (4 subjects), and sympathomimetics (3 subjects). Nineteen subjects (15%) were taking one or more medications for joint pain, including analgesics (7 subjects), acetic acid derivatives (7 subjects), and propionic acid derivatives (7 subjects). Twelve subjects (10%) were taking one or more medications for glaucoma, and an equal number were taking one or more medications for non-joint (headache, ear ache) pain. Several other medications were used by a small number of subjects for a variety of gastrointestinal disorders and neurological disorders.

### Clinical Assessments

To provide indicators of the degree of disease symptomatology, the severity of excretory dyspepsia and orthopenia was assessed for each subject. Excretory dyspepsia was observed in 36 of the 118 subjects assessed, while only 5 in this group were felt to have orthopenia. Nine subjects presented with tachycardia, 7 with tachypnea, and 6 with a combination of both.

Sixteen subjects across all age groups required ventilatory assistance in which 7 subjects had tracheotomies, 5 required CPAP or BiPAP during sleep, 1 used a ventilatory mask, 1 was on a ventilator 24 hr per day, and 2 used O2 nasal prongs.

Cardiac function was assessed using a 12-lead ECG, and 59 of 120 (49%) had some evidence of abnormality. The most common abnormalities were sinus tachycardia (n = 17), right or left axis deviation (n = 17), and atrial enlargement (n = 14). Nine subjects had right or left ventricular hypertrophy, 4 had sinus arrhythmia, and 6 had nonspecific T-wave abnormalities. Eight subjects had a conduction block including 3 with incomplete right bundle branch block, 2 with first degree AV block, 2 with fascicular block, and 1 with sinus arrest and transient AV block. Echocardiograms were performed on a subset of 68 subjects. Mitral, aortic, pulmonary, and tricuspid valves were evaluated for stenosis and regurgitation. Nearly all of these subjects (96%) had evidence of stenosis and/or regurgitation. Twenty-four subjects had evidence of stenosis and regurgitation in one or more valves, 36 with regurgitation only, and 5 with stenosis only.

Evidence for severe limitations in endurances, pulmonary function, joint range of motion, and strength were captured in several ways. For the 6-min walk, 54 of the 117 subjects with test results (46%) walked between 5 and 270 m. Unlike height or weight, subjects walking distances that were below the mean or median were found in all age groups, and the overall group exhibited nearly coincident values for the median (268.0 m) and mean (275.1 ± 137.0 m) distance walked (Fig. 1). Lung volumes were determined for 108 subjects able to perform spirometry with mean values (in liters) for FVC and FEV₁ as 1.16 ± 1.03 and 1.06 ± 0.91, respectively, and median values of 0.6 for both, which reflect the contribution of a minority of larger subjects with slowly advancing disease. With two exceptions, all of the FVC values were less than normal for males and females relative to age (Fig. 2). Flexion and extension in the shoulder, knee, and elbow were assessed using a goniometer, and a wide range of joint restriction was observed for all the joints surveyed (Table II). Impairment was most evident in shoulder flexion where the combined mean value for

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**TABLE I. Summary of Subject Demographics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>N</th>
<th>Height (cm)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>63</td>
<td>111.8 ± 24.8</td>
<td>52.1</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>58</td>
<td>120.6 ± 29.6</td>
<td>47.9</td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4–12</td>
<td>70</td>
<td>98.4 ± 10.1</td>
<td>57.9</td>
</tr>
<tr>
<td></td>
<td>13–18</td>
<td>22</td>
<td>125.6 ± 25.1</td>
<td>18.2</td>
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<tr>
<td></td>
<td>19–24</td>
<td>15</td>
<td>142.7 ± 20.1</td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td>25–50</td>
<td>14</td>
<td>157.0 ± 8.5</td>
<td>11.6</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>99</td>
<td>81.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>3</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>19</td>
<td>15.7</td>
<td></td>
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</table>
both shoulders was $97.2 \pm 28.4$ degrees versus a maximum range of 180 degrees (Fig. 3). However, the finding of values between 21 and 176 degrees in these individuals exemplified the large range of values across this population.

Grip and pinch scores indicated severe limitation in the majority of individuals, with scores generally tracking with age (data not shown). Twenty-two subjects were unable to perform the grip test. Of the 95 subjects tested, 53 had grip strengths of 5 pounds or less in both hands, while some had values up to the normal range of 85 pounds [Matliowetz et al., 1984]. Eleven

<table>
<thead>
<tr>
<th>TABLE II. Mean Joint Range of Motion</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Right shoulder flexion</td>
</tr>
<tr>
<td>Left shoulder flexion</td>
</tr>
<tr>
<td>Right shoulder extension</td>
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<tr>
<td>Left shoulder extension</td>
</tr>
<tr>
<td>Right elbow flexion</td>
</tr>
<tr>
<td>Left elbow flexion</td>
</tr>
<tr>
<td>Right knee flexion</td>
</tr>
<tr>
<td>Left knee flexion</td>
</tr>
</tbody>
</table>

![Fig. 2. FVC versus age as stratified by urinary GAG in MPS VI subjects.](image)

![Fig. 3. Urinary GAG versus mean shoulder flexion as stratified by age in MPS VI subjects.](image)

...subjects were unable to perform the tip-to-tip pinch test and two subjects were unable to perform the key pinch (tip-to-lateral) test. Sixty-eight subjects had tip-to-tip pinch tests and 56 had tip-to-lateral pinch tests of 5 pounds or less in both hands. The ranges observed for these tests were 0.3–25.3 pounds for the tip-to-tip test, and 0.7–34.3 pounds for the tip-to-lateral test.

Visual acuity was evaluated using standard Snellen eye chart testing. Visual acuity was reported as two sequential numbers reflecting the smallest size letters that a subject could read at 20 feet (first number) relative to the distance that an individual with normal vision could read the same size letters (second number). Normal visual acuity is 20/20, and subjects with acuity less than 20/200 are considered legally blind. Of the 113 subjects, 21 subjects were legally blind in both eyes, and an additional 3 subjects had acuity of 20/200 or worse in only one eye.

The results for the CHAQ/HAQ scores are summarized in Table III. Twenty-seven of the 120 subjects (23%) with results on the CHAQ/HAQ questionnaire used one or more devices as an aid for walking, with 23 using a wheelchair, 8 using a

<table>
<thead>
<tr>
<th>TABLE III. CHAQ/HAQ Pain and Arthritis Scores and Disability Index*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter by age</td>
</tr>
<tr>
<td>Pain score^a</td>
</tr>
<tr>
<td>≤18 years</td>
</tr>
<tr>
<td>&gt;18 years</td>
</tr>
<tr>
<td>Arthritis score^b</td>
</tr>
<tr>
<td>≤18 years</td>
</tr>
<tr>
<td>&gt;18 years</td>
</tr>
</tbody>
</table>

*Based on the Health Assessment Questionnaire (HAQ) for subjects older than 18 years of age, or Childhood Health Assessment Questionnaire (CHAQ) for the younger group.

*Pain and arthritis during the past week were rated on a scale of 0–100, with 0 = no pain or no effect of arthritis to 100 = severe pain or severe effect of arthritis.

*Disability index ranges from 0 to 3, with 0 = no disability and 3 = severe disability.
Urinary GAGs and the Association of Other Clinical Outcomes

Skeletal disease represents the most intractable component of MPS VI to treat based on the inability of BMT to reverse established skeletal dysplasia or promote growth in those individuals treated after growth has stopped [Heartiowitz et al., 1999]. Height, as an indicator of skeletal development and dysplasia, was examined as a function of age and stratified by urinary GAG levels and gender (Fig. 5). High urinary GAG values corresponded to low height values at all ages, while individuals with GAG levels of <100 μg/mg creatinine approached or were within the lower end of the normal range for height. Similar results were obtained when the analysis was applied to weight (data not shown). Also of interest was the identification of only two subjects under the age of 10 with GAG values <100. Based on Figure 5, these individuals were in the normal range for height. This may indicate the rare frequency of these individuals, or suggest that they do not come to medical attention or are misdiagnosed within the first decade due to the mild features of slowly advancing disease. The relationship of urinary GAG to FVC produced similar findings to those for height (Fig. 2); the higher the GAG, the worse the pulmonary function.

Shoulder flexion showed significant overlap across all GAG levels, although higher GAG values were clearly associated with more restrictive (flexion <90°) function across all individuals.

![Fig. 4. Urinary GAG versus age in MPS VI subjects and normal individuals. Urinary GAG values adjusted for creatinine for normals (open triangle, n = 46), MPS VI females (open squares, n = 63), and male MPS VI males (gray circles, n = 56) were determined and assessed versus age in years.](image)

![Fig. 5. Height versus age as stratified by urinary GAG in MPS VI subjects. Standing height was determined and assessed versus age in years for females and males and stratified for urinary GAG (<100 μg/mg creatinine, open triangles; 100–200 μg/mg creatinine, filled squares; >200 μg/mg creatinine, dotted circle). The growth curves represent the 3rd percentile (broken lines) and 50th percentile (solid lines) and were obtained from the CDC (http://www.cdc.gov/growth).](image)
ages (Fig. 3). Likewise, impaired endurance based on a 6-min walk was evident across all GAG levels independent of age (Fig. 1). Younger individuals with higher urinary GAGs and rapidly advancing disease had already experienced a significant decline in distance walked, whereas half of those individuals age 25 and older with lower GAG levels and more slowly advancing disease nevertheless experienced impaired walking ability and a decrease in their overall functional status.

**DISCUSSION**

The natural history of MPS VI has not been defined. This multicenter, multinational cross-sectional survey in subjects with MPS VI disease was designed to establish a large database on demographics, urinary GAG levels, and the severity of disease as determined by clinical testing. Information was collected for 121 bona fide MPS VI-affected individuals over the age of 4 years identified by seven centers and representing 15 countries. Several publications provide estimates of MPS VI incidence from 1,248,900 to as low as 1,100,000 (Lowry et al., 1990; Nelson, 1997; M€ollke et al., 1999; Poorthuis et al., 1999; Nelson et al., 2003). Based on these surveys, an estimate of 1,100 MPS affected individuals in the world is obtained, indicating that the current effort has evaluated more than 10% of those individuals.

Although variation in the clinical presentation of the subjects of this survey confirms that MPS VI is a heterogeneous disorder, some key general conclusions can be drawn. High urinary GAG values correlated with age-adjusted short stature and lower body weight, and with clinical parameters indicating more rapidly progressing disease. Impaired endurance, as measured by a 6-min walk, was found to be present across all age groups. Subjects with a very high urinary GAG might have an impaired ability to walk prior to age 10, while those with a GAG just above the normal range might require three to four decades to reach an equivalent level of impairment. Nevertheless, as a general clinical tool, the walk test appears to be an appropriate measure to evaluate endurance in the entire MPS VI population. The majority of studies in the literature employing a walk test have been performed in adults (Solway et al., 2001), and no normative data exist for children. The lower limit of normal for healthy adult women has been reported to be 310 m (Enright and Sherrill, 1998) and the lower limit of normal for routine efforts such as crossing the street, or, as it is termed, community ambulation, is 332 m at a near-normal velocity of approximately 80 m/min (Rabinett and Vondran, 1988; Memard-Roth et al., 1997). Considering the limitations in the comparison, the mean or median values obtained for the MPS VI population represent a significant level of impaired endurance.

Definitive conclusions regarding the relationship of the variables studied in this survey and clinical outcomes will require a longitudinal study of several decades duration to assess the population at hand. Pending the collection of longitudinal data, these results raise the possibility that urinary GAG levels predict clinical morbidity, and longer-term survival is observed for subjects whose urinary GAG level is below the threshold of 100 μg/mg creatinine. The accumulated data suggest, but do not prove, the eventual plateaus or diminution of subject due to MPS VI disease, regardless of the rate of progression of disease. The relationship between urinary GAG level and age suggests that the majority of MPS VI individuals with urinary GAG levels >100 μg/mg creatinine do not survive beyond the age of 20 years. Those individuals examined over the age of 20 years had less significant elevations in urinary GAG levels and more slowly advancing disease. These individuals will eventually develop severe clinical manifestations, as these individuals reach their third or fourth decade of life. A related question is the ease to which these subjects are identified prior to puberty. Only two MPS VI-affected individuals under the age of 12 had a urinary GAG of <100 μg/mg creatinine, and these individuals were within normal limits for age-adjusted height and weight. While the basis for the rarity of this subgroup in the population may be based on allele frequencies, it is more likely that they escape medical attention or are not correctly diagnosed prior to puberty based on the slow progression of their physical deterioration.

In addition to the walk test and urinary GAG determinations, the clinical assessments obtained in this survey greatly expand our understanding of the clinical presentation of MPS VI. The finding of a median height of only 163.7 cm reinforces the view that MPS VI is primarily a disease of skeletal dysplasia and abnormal growth. Although the majority of subjects were not felt to have progressed to cardiac failure, the presence of cardiac abnormalities in 49% and valvular disease in nearly all of the 68 subjects evaluated by echocardiography suggests that the cardiac changes generally progress slowly over many years. This supports earlier studies employing color Doppler flow mapping showing the frequency of aortic and/or mitral regurgitation was 76% in all MPS subjects, and 100% in the 8 MPS VI subjects assessed (Wippermann et al., 1995). In addition, the strong correlation of a severity score for the valve regurgitation and age in that study is consistent with the findings in the present survey of less advanced valvular disease in the younger subjects.

The significantly low lung volumes based on FVC in the survey clearly reflected the skeletal disease in terms of the influence of height and the size of the thorax, as well as by the restrictive disease imparted by the dysplastic changes in the ribcage. There is no evidence from the literature that the storage in the lung actually interferes with the diffusion and exchange of gases in the lung. The absence of a standard curve for subjects with MPS VI that reflects their height and dysplastic bone changes to the thorax renders the calculation of % predicted FVC meaningless. This is not unlike the situation with achondroplasia, where percent predicted lung volumes were significantly miscalculated relative to the small stature and dysplastic changes exhibited in affected individuals (Stokes et al., 1988, 1990).

Several findings revealed the potential impact of the disease on activities of daily living. Shoulder flexion was the only consistently affected joint motion, consistent with the studies evaluating ERT for MPS I (Kakkis et al., 2001; Wraith et al., 2004) and in the initial ERT study for MPS VI (Harmatz et al., 2004). The profound weakness reflected in the low grip and pinch scores would be expected to limit multiple tasks. Approximately one-fifth of the participants had a visual acuity of 20/200 or worse, and over 20% of the subjects require one or more devices as an aid for walking. The CHAQ/HAQ scores revealed a large difference in the Disability Index between those above or below 18 years of age, consistent with the observation that subjects who live beyond 18 years have slowly advancing disease. Finally, the scores for pain and arthritis for all subjects indicated mild to moderate severity. Although possibly a shortcoming of the questionnaire, the fact that only 15% of the individuals were on medication for joint pain may indicate that pain tolerance in these individuals is high and reflects the slow progression of the joint disease. To put these scores in perspective, in a study of 136 children with rheumatoid arthritis, the median CHAQ scores corresponding to mild, mild-to-moderate, and moderate disability were 0.13, 0.63, and 1.75, respectively (Dempster et al., 2001). The minimal clinically important improvement was a reduction in score of 0.15. The minimal clinically important deterioration was a median change in score of 0.75.

A final observation relates to the use of the terms "severe" and "mild" forms of MPS VI in the medical genetics community. Although debilitating disease may not develop in some affected
individuals until they reach the third or fourth decades of life, all patients with MPS VI develop serious manifestation of the disease at some point. It would be more appropriate to refer to the rate of the advancement of the disease, designating each subject either as "rapidly" or "slowly" advancing. Further follow-up of the participants in the present survey will be necessary to provide validation of this concept.

In summary, the data from this survey study, representing a significant portion of the world population with MPS VI, provide biochemical and clinical parameters that have important implications for the evaluation of future treatment options for this disease.

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