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The Morquio A Clinical Assessment Program: Baseline results illustrating progressive, multisystemic clinical impairments in Morquio A subjects

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ABSTRACT

Objectives: The objectives of this study are to quantify endurance and respiratory function and better characterize spectrum of symptoms and biochemical abnormalities in mucopolysaccharidosis IVA subjects.
Methods: MorCAP was a multicenter, multinational, cross sectional study amended to be longitudinal in 2011. Each study visit required collection of medical history, clinical assessments, and keratan sulfate (KS) levels.
Results: Data from the first visit of 325 subjects (53% female) were available. Mean age was 14.5 years. Mean ± SD height z-scores were −5.6 ± 3.1 as determined by the CDC growth charts. Mean ± SD from the 6-minute-walk-test was 212.6 ± 152.2 m, revealing limitations in functional endurance testing, and 30.0 ± 24.0 stairs/min for the 3-minute-stair-climb test. Respiratory function showed limitations comparable to MPS VI patients; mean ± SD was 1.2 ± 0.9 l based on forced vital capacity and 34.8 ± 25.5 l/min based on maximum voluntary ventilation. Mean urinary keratan sulfate (uKS) was elevated for all ages, and negatively correlated with age. Higher uKS correlated with greater clinical impairment based on height z-scores, endurance and respiratory function tests. The MPS Health Assessment Questionnaire reveals impairments in mobility and activities of daily living in comparison to an age-matched control population.
Conclusions: MPS IVA is a multisystem disorder with a continuum of clinical presentation. All affected individuals experience significant functional limitations and reduced quality of life. Older patients have more severe exercise and respiratory capacity limitations, and more frequent cardiac pathology illustrating the progressive nature of disease.

1. Introduction

The mucopolysaccharidosis are a group of lysosomal storage disorders (LSDs) in which deficient enzyme activity results in impairment of the degradation of glycosaminoglycans (GAGs) which, in turn, accumulate in various tissues and organs. Morquio syndrome, including both MPS IVA (Morquio A syndrome; OMIM 253000) and MPS IVB (Morquio B syndrome; OMIM 253010), was first described in 1929 [1]. Although MPS IVB was originally thought to be the milder form of MPS IVA, these were later demonstrated to be genetically distinct disorders each with a different deficient enzyme [2]. MPS IVA is characterized by deficiency of N-acetylgalactosamine-6-sulfatase (GALNS), resulting in accumulation of the GAGs keratan sulfate (KS) and chondroitin-6-sulfate (CS) in various

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tissues and organs [3–5]. Accumulation of KS leads to multi-systemic impairments [5].

Information characterizing disease progression in MPS IVA is limited. The progression of symptoms is variable, likely due to known genetic heterogeneity [5–8] with over 175 identified mutations in the GALNS gene [9]. Life expectancy in patients with the rapidly progressing phenotype ranges from the second to the third decade [10,11]. Rarely patients with a more slowly progressing phenotype survive beyond 60 years. Mortality is commonly due to cardiorespiratory or neurologic complications [10,12–16]. To date, the management of MPS IVA has focused primarily on palliative care to manage pain, infection and respiratory disease [14], as well as on corrective orthopedic surgeries [17].

The wide phenotypic spectrum of MPS IVA [7,18,19] and limitations in current urinary GAG (uGAG) testing make it a challenging disorder to diagnose [9,20]. Clinical suspicion is usually based on skeletal radiographs revealing characteristic platyspondyly often with associated thoracolumbar gibbus, cox valga with flaring of the iliac wings, genu valgum and dysplastic capital femoral epiphyses, failure to ossify the lateral side of the upper tibial epiphysis and proximal pointing of the metacarpals [6]. Suspicion of MPS IVA may be supported by quantitative and/or qualitative testing of uGAG levels demonstrating increased levels and presence of KS, but diagnosis requires confirmation of GALNS deficiency in WBC or fibroblasts, or mutation analysis showing the presence of pathogenic mutations in both alleles [9,21]. However, patients with more slowly progressing disease may not present with these obvious physical or radiologic manifestations and diagnosis may not occur until later in life [4,6,22–25].

The Morquio A Clinical Assessment Program (MorCAP) is the first longitudinal study involving direct assessments of MPS IVA patients. This multicenter, multinational, prospective study was initiated in 2008 to assess and describe the spectrum of symptoms in this disorder including growth, endurance, respiratory function, cardiac function, medical and surgical history, as well as to measure select biochemical abnormalities such as GAG levels, and inflammatory markers in MPS IVA patients. This first report will describe the design and methodology of this clinical study as well as the cross-sectional baseline results of the first 325 patients enrolled.

2. Methods

Originally, MorCAP was a single visit, cross sectional study of MPS IVA patients without limitations on age or symptom severity with the first patient enrolling in 2008. To gain more detailed insight into the natural history of MPS IVA, the study was amended to be longitudinal and was approved as such at all sites in 2011. For inclusion to the study, individuals had a confirmed diagnosis of MPS IVA as documented by either molecular genetic testing or reduced GALNS activity as compared to the laboratory-reported normal enzyme activity range for GALNS. Not all individuals provided genetic diagnosis and consequently, this information is not reported or analyzed. Exclusion criteria included previous HSCT or a concurrent disease or condition that would interfere with participation in the study. Subjects remain in the study for up to 10 years unless the subject enrolls in an interventional trial or the study is discontinued for clinical or administrative reasons.

At the time of publication, baseline data from 325 patients were available. At each study visit, a detailed medical history, selected clinical assessments, and physical examination are completed. The 6-minute walk test (6-MWT) [26], 3-minute-stair-climb-test (3-MSCT) [27] and respiratory function tests are performed according to published guidelines. Sites were provided with scheduling recommendations to allow for adequate rest between effort-based procedures. The investigator may opt to forgo assessments if clinically contraindicated. Additional details of the schedule of assessments for the MorCAP study are available online in Supplemental Table 1.

The MPS Health Assessment Questionnaire (MPS HAQ) is a comprehensive clinical assessment instrument originally developed for MPS I patients, adapted for use in MPS VI patients [28] and now used to evaluate MPS IVA patients. Caregivers of patients <14 years of age complete the MPS HAQ patient questions until the patient reaches 14 years; at 14 years of age, the patient completes the questionnaire independently. Translations of the questionnaire have been provided to patients/caregivers in their native language.

Urine KS and creatinine are measured from a first morning void and uKS values are normalized to creatinine levels. Measurements of uKS are determined by a validated LC–MS/MS assay in which uKS measurements are a measure of the sum of mono- and di-sulfated galactoseβ1 N-acetyl-D-glucosamine disaccharides (Galβ1–4GlcNAc(6S) and Gal(6S) β1–4GlcNAc(6S)) generated after keratanase II digestion of KS in urine with values normalized to creatinine excretion [29–32]. Biochemical markers of bone and cartilage metabolism are collected from all subjects, and will be measured in a random subset with other samples stored for future analysis.

2.1. Statistical analysis

Baseline data from study visit 1 collected from clinical assessments were summarized descriptively and graphically, including demographics, medical history, growth history, medications, vital signs and findings from physical examinations. For 6-MWT, 3-MSCT, FVC and MVV, p-values were calculated using an analysis of variance (ANOVA) to compare low uKS versus high uKS groups, controlled for age group. For each age group, p-values were also calculated to test equality of low versus high uKS group.

Continuous variables were summarized using descriptive statistics for mean, median, standard deviation, minimum, and maximum. For subjects who were physically unable to perform the 6-MWT or the 3-MSCT, a value of zero was assigned. Count and percent were used to summarize categorical variables.

3. Results

3.1. Demographics

Complete baseline results are currently available from 325 subjects with MPS IVA representing a global sample including 10 countries. Genders were nearly evenly distributed. The majority (79%) of subjects were in the pediatric age group (18 years and younger); mean and median ages were 14.5 years and 11.6 years (Table 1). Short stature was apparent in the study population and affected male and female patients to approximately an equal degree (Figs. 1A and B) with mean ± SD (median; min, max) height z-score for ≤18 years population of −5.10 ± 2.85 (−5.23; −11.75, 1.93) and −7.59 ± 3.04 (−8.94; −11.37, 0.50) for >18 years population. The mean ± SD (median; min, max) for height is 101.2 ± 15.8 (97.4; 77.8, 163.0) cm and length is 104.2 ± 15.7 (101.0; 53.2, 156.5) cm (Table 1). Relative to previously reported height data in MPS IVA patients [11], the range of subject heights in the current study was generally similar, with the exception that many female subjects had heights >90th percentile when measured against curves derived from previously published data [11] (Figs. 1A and B).

Detailed medical histories, including chart review, were taken from all patients. Reported complications impacted multiple systems including musculoskeletal, nervous, respiratory, gastrointestinal, visual and auditory systems, with all subjects reporting at least one medical event, regardless of age. Musculoskeletal diagnoses were the most common category reported, with >90% of subjects reporting abnormal gait, genu valgum, short stature, and/or short neck. Other common features included joint laxity with stiffness and/or pain in >80% of subjects, and joint contractures and subluxation in 52% and 47%, respectively. Spinal abnormalities were commonly reported including kyphoscoliosis (85%), odontoid dysplasia (65%), lumbar lordosis (56%), cervical spinal instability (49%), and spinal disc disease (23%). Pectus carinatum was a near