Carpal tunnel syndrome in mucopolysaccharidosis I: a registry-based cohort study

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AIM To characterize carpal tunnel syndrome (CTS) in patients with mucopolysaccharidosis I (MPS I).

METHOD Data were included for patients with MPS I who had either nerve conduction examination that included a diagnosis of CTS or who had CTS release surgery. Although this represented a subset of patients with CTS in the MPS I Registry, the criteria were considered the most objective for data analysis.

RESULTS As of March 2016, 994 patients were categorized with either severe (Hurler syndrome) or attenuated (Hurler–Scheie or Scheie syndromes) MPS I. Among these, 291 had a CTS diagnosis based on abnormal nerve conduction (n=54) or release surgery (n=237). Median ages (minimum, maximum) at first CTS diagnosis were 5 years 2 months (10mo, 16y 2mo) and 9y 11mo (1y 8mo, 44y 1mo) for patients with severe and attenuated MPS I respectively. Most patients had their first CTS diagnosis after MPS I diagnosis (94%) and treatment (hematopoietic stem cell transplant and/or enzyme replacement therapy) (74%). For 11% of patients with attenuated disease, CTS diagnosis preceded MPS I diagnosis by a mean of 7 years 6 months.

INTERPRETATION CTS is a rare complication in pediatric patients and should alert medical care providers to the potential diagnosis of MPS I. Significant delays exist between diagnosis of CTS and MPS I for patients with attenuated disease.

Mucopolysaccharidosis I (MPS I) is a life-threatening disorder resulting from deficiency of α-1-iduronidase, a lysosomal enzyme required in the catabolism of the glycosaminoglycans (GAG) dermatan and heparan sulfate.1 MPS I is a pan-ethnic, autosomal recessive disorder with an estimated prevalence of 1 in 100 000 live births.2 MPS I ranges from severe (Hurler syndrome) to attenuated (Hurler–Scheie and Scheie syndromes) phenotypes that vary in the extent of neurocognitive involvement and the rate of disease progression. Treatment options include hematopoietic stem cell transplant (HSCT) (recommended before 2y of age) for patients with severe MPS I, and enzyme replacement therapy (ERT) with laronidase (recombinant human α-1-iduronidase; Aldurazyme) for the treatment of non-neurological manifestations of MPS I.3,4

The most severe form of MPS I, Hurler syndrome, has onset before 1 year of age and is associated with significant neurocognitive disability and developmental delay.5 Regardless of MPS I phenotype, patients with MPS I display a broad range of clinical manifestations, including hepatosplenomegaly, recurrent otitis media, hearing loss, obstructive sleep apnea, cardiac valve dysfunction, umbilical and inguinal hernias, recurrent respiratory infections, and corneal clouding.4 Progressive and pervasive musculoskeletal manifestations are a hallmark of MPS I resulting from accumulation of GAG in cartilage, tendon, and joint capsule tissue.6 Musculoskeletal defects including occipital cervical instability, spinal stenosis, thoracolumbar kyphosis, hip dysplasia, femoral head osteonecrosis, progressive genu valgum, joint stiffness and immobility, carpal tunnel syndrome (CTS), and trigger digits lead to significant joint pain, discomfort and disability, and often require surgical intervention.7 Joint stiffness and contractures, with or without pain, are early and prominent signs of MPS I, and for patients with attenuated MPS I are among the earliest manifestations.8

There is a high prevalence of CTS in MPS I, and, collectively, MPS disorders are the most common cause of CTS in children.9,10 In patients with mild, attenuated MPS I, CTS may be a presenting symptom.11 Symptoms of CTS are often subtle owing to the patient’s age and/or are masked by developmental delays in patients with severe disease.
Patients with MPS I typically have minimal complaints of pain, tingling, or numbness, but caregivers may observe difficulties with fine motor tasks and soft signs such as slapping hands, chewing and sucking on fingers, and hand rubbing.9,10 A diagnosis of CTS is often not made until thenar wasting and loss of function are apparent.12

CTS is present across the spectrum of MPS I phenotypes.10 Excessive tissue GAG leads to thickening of the flexor retinaculum as well as the tenosynovium,8 resulting in impaired tendon excursion and the typical ‘claw’ deformity with flexed distal interphalangeal joints.12,14 If untreated, severe median nerve compression can result in irreversible damage.10 Given the often subtle symptomatology in patients with MPS I, nerve conduction studies are recommended to confirm diagnosis.15 CTS diagnosis in patients with MPS I usually results in carpal tunnel release surgery.9,10,16 Early diagnosis and treatment is important since nerve recovery is associated with early intervention.10

Because CTS is a common manifestation of MPS I that can significantly affect patients’ quality of life, we sought to better characterize CTS in patients with both severe and attenuated forms of MPS I to facilitate early intervention.

METHOD
The MPS I Registry (https://clinicaltrials.gov, NCT00144794) is a voluntary, observational database designed to track the clinical progression and management in patients with MPS I throughout the world, regardless of treatment status or treatment choice.17 The MPS I Registry is the largest cohort of patients with MPS I worldwide. Patient information collected in it is submitted voluntarily by physicians after obtaining approval from their institutional investigational review board or ethics committee and written informed consent from patients or their parents/guardians. All patient data are de-identified and entered by physicians after obtaining approval from their institutional review board or ethics committee and written informed consent from patients or their parents/guardians. Sites selected from a list of 60 different surgical procedures and provided the date of surgery and where applicable, side of surgery. Carpal tunnel release data were captured on the case report form as ‘carpal tunnel surgery’. All analyses were stratified by MPS I phenotype. Data were analyzed by timing of MPS I diagnosis and by treatment type. Descriptive analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS
Patients
As of 4 March 2016, 994 patients with known MPS I phenotype were enrolled in the registry and categorized with either severe MPS I (Hurler syndrome, n=641) or attenuated MPS I (Hurler–Scheie or Scheie syndromes, n=353). Among the 994 patients, 291 were included in the analyses. Information about corrective surgery for CTS was available for 237 patients. Results of nerve conduction examinations were unavailable for these patients; however, it is presumed that preoperative diagnostics indicated potential benefits from surgical intervention. Sixty-seven patients had available data for nerve conduction assessments, of which 54 were abnormal: 14 out of 54 patients had abnormal nerve conduction examinations only, and 40 out of the 54 patients had both abnormal nerve conduction examinations and CTS surgery. Of the patients diagnosed with CTS using these criteria, 138 had attenuated MPS I and 153 had severe MPS I.

Demographic data for the 291 patients in the MPS I Registry with a diagnosis of CTS are presented in Table I.
There were similar percentages of male and female patients overall and within phenotypes. Patients with severe MPS I were diagnosed at a younger age (median 1y) than patients with attenuated disease (median 5y 2mo). Almost all patients (282 out of 291, 97%) received HSCT and/or ERT as their primary treatment for MPS I. Patients with attenuated disease primarily received ERT only, whereas patients with severe MPS I received either HSCT alone or in combination with ERT.

Characteristics of patients’ CTS diagnoses (based on abnormal nerve conduction tests or surgery) and timing relative to diagnosis of MPS I are shown in Table II and Figure 1a. The median (minimum, maximum) ages at first CTS diagnosis were 5 years 2 months (10mo, 16y 2mo) and 9 years 11 months (1y 8mo, 4y 1mo) for patients with severe and attenuated MPS I respectively. Among patients with a known date of CTS diagnosis (287 out of 291, 99%), most (152 out of 153 patients with severe MPS I and 119 out of 134 patients with attenuated MPS I; 271 out of 287, 94% total) had the first CTS diagnosis after their diagnosis of MPS I (Fig. 1a).

Among patients with attenuated MPS I who were diagnosed with CTS before their MPS I diagnosis (15 patients), the median (minimum, maximum) number of years preceding the MPS I diagnosis was 2 years 8 months (0, 35y 6mo) and median age at MPS I diagnosis was 19 years 6 months (3y 6mo, 41y 8mo), suggesting that most of these patients had the most attenuated form of MPS I (Scheie syndrome) (Table II).
For patients with MPS I who had CTS and who received treatment (278 out of 291, 96%), treatment was initiated before receiving the first CTS diagnosis in most cases (207 out of 278, 74%) (Fig. 1a), particularly in the group with severe MPS I (89%). Among the 994 patients with known phenotype, 397 received HSCT, 30% (119 out of 397) of whom had their first CTS diagnosis after receiving HSCT. Median age (25th, 75th centiles) at HSCT was 1 year 5 months (1y 1mo, 1y 11mo) and median age at CTS diagnosis was 5 years 4 months (3y 11mo, 8y 4mo). In patients with attenuated MPS I, 43% \( (n=55) \) initiated MPS I treatment after receiving a CTS diagnosis (Table II). For patients who had CTS diagnosis before receiving treatment, the number of years preceding treatment is indicated in Table II (3.5mo for severe MPS I and 7y 5mo for attenuated MPS I).

Among the 291 patients with CTS included in the analyses, 277 (95%) had surgery to correct CTS (Fig. 1b and Table III). Most of these had surgery after their diagnosis of MPS I and after initiating MPS I treatment. Multiple CTS surgeries were reported for 47 out of 277 patients (17%), most of which were in patients with attenuated disease (35 out of 47, 74%).

**DISCUSSION**

While it may be recognized among geneticists and specialists in metabolic disease that patients with MPS disorders have a high likelihood of developing CTS, pediatricians and general practitioners may be less aware of the association. In addition, the initial assessment of pediatric patients with CTS and undiagnosed MPS I is likely to be made by hand surgeons and/or orthopedists.

The patients in the MPS I Registry included in the analyses were diagnosed with CTS relatively young and, for most, after receiving an MPS I diagnosis and initiating MPS I treatment. Early diagnosis of CTS in patients with MPS I is important as it is associated with better functional and neurophysiological outcomes after surgery.\(^{10,16}\)

However, a proportion (11%) of patients with attenuated disease were diagnosed with CTS before receiving their MPS I diagnosis. These patients had a median of almost 3 years between their diagnoses of CTS and MPS I, indicating that CTS can be a presenting manifestation of attenuated MPS I and that there is the need for increased awareness of the association between childhood CTS and MPS disorder. Increased awareness of the need to screen for MPS I in pediatric and adolescent cases of CTS can have a significant impact for patients, since early ERT initiation can improve clinical outcomes in patients with attenuated disease.\(^{19}\)

For the analyses in this study, patients in the registry population were included if they had either electrophysiological data to support a CTS diagnosis (with or without surgery) or release surgery for CTS (electrophysiology data unavailable). These criteria were selected to ensure the most objective set of patients for the analyses. We realize, however, that these 291 patients represented only a subset of all 994 patients in the registry and that additional patients may have been diagnosed with CTS on the basis of their clinical records and medical history. Therefore, we do not discuss information on CTS prevalence for patients.
Table III: Patients diagnosed with carpal tunnel syndrome and with information on surgery, mucopolysaccharidosis I (MPS I) diagnosis dates, and MPS I treatment dates

|                                | Severe (n=153) | Attenuated (n=138) | Total (n=291) |
|--------------------------------|---------------|--------------------|---------------|
| Ever had carpal tunnel surgery, n (%) | 146 (95%) | 131 (95%) | 277 (95%) |
| Age at first carpal tunnel surgery (y:mo) | 5:5 (3:7, 7:5) | 10:0 (6:8, 14:11) | 6:9 (4:9, 10:7) |
| Minimum, maximum | 1:2, 16:2 | 1:8, 44:1 | 1:2, 44:1 |
| Patients with more than one surgery, n (%) | 12 (8%) | 35 (27%) | 47 (17%) |
| Age at second surgery (y:mo) | 8:2 (6:0, 10:3) | 16:5 (9:7, 25:5) | 12:5 (7:10, 19:6) |
| Minimum, maximum | 4:2, 15:4 | 3:8, 48:7 | 3:8, 48:7 |
| Patients with surgery before MPS I diagnosis, n (%) | NA | 5:76 (1:57, 13:00) | 4:21 (0:67, 13:00) |
| Number of years before MPS I diagnosis | NA | 0:0, 35:5 | 0:0, 35:5 |
| Minimum, maximum | 13 (9%) | 53 (44%) | 66 (25%) |
| Patients with surgery before MPS I treatment (ERT, HSCT, or both), n (%) | 0.35 (0:10,0,50) | 5:87 (2:28, 11:75) | 3:50 (0:64, 9:60) |
| Number of years before treatment | 0:1, 0:9 | 0:0, 35:9 | 0:0, 35:9 |

ERT, enzyme replacement therapy; HSCT, human stem cell transplant.

in the MPS I Registry. In a recent retrospective analysis of CTS in 74 patients with severe MPS I who had undergone HSCT, approximately 50% had developed CTS by 5 years of age regardless of ERT administration in the peri-transplant period.20 All children with severe MPS I undergoing HSCT at the study center had screening CTS and assessments by hand surgeons, which may have contributed to the heightened detection of CTS in their institution.

There are currently no accepted standard procedures for diagnosing CTS in MPS I.12 Given the lack of standard guidelines, some clinicians may use only clinical history and physical examinations to assess CTS; however, this approach may result in delays in both diagnosis and corrective surgery for patients with MPS I. Waiting for symptoms to develop, especially in patients with severe disease where communication is impaired, may result in irreversible nerve damage.9 Routine electrophysiological testing for patients with MPS I is controversial because the sensitivities identified in adult populations without MPS I (ranging between 49% and 84%) may not be transferrable to pediatric populations, and are associated with false-positive and false-negative results.12 Electrophysiological assessments in pediatric patients with MPS I, which must be performed by experienced neurologists, can be difficult to perform and may require anesthesia because of lack of cooperation from patients.9,10 Physicians may make a diagnosis of CTS on the basis of symptoms alone and proceed directly to surgery, or conduct electrophysiological tests immediately preceding surgery when the patient is already sedated. A recent report suggests that ultrasound testing (which is faster than electromyography and painless) performs as well as, or better than, nerve conduction/electromyography for screening patients with MPS I for CTS, which may facilitate CTS diagnoses in the future.21

Among patients who had multiple surgeries for CTS, most had attenuated MPS I. Although the reasons for this are unknown, contributing factors may include the better ability of patients with attenuated MPS I to communicate symptoms, as well as their longer medical histories than patients with the severe phenotype.

In most cases, first CTS diagnosis as well as multiple release surgeries occurred after patients were receiving treatment for MPS I. These data are consistent with case reports and retrospective studies indicating that neither HSCT nor ERT can prevent development or recurrence of CTS.20,22–24 Early intervention may be associated with better outcomes.24 Khanna et al. retrospectively assessed characteristics that predicted CTS development in patients with severe MPS I and concluded that HSCT by 2 years of age as well as higher enzyme levels after transplantation were significant factors in reducing risk of CTS.23 However, routine monitoring was still required as all patients remained at risk regardless of treatment.23 In another study, however, CTS prevalence was similar in patients with severe MPS I who received HSCT before and after 2 years of age.20 In our study, approximately one-third of all patients who received HSCT had a CTS diagnosis after transplantation, and typical time between HSCT and post-HSCT CTS diagnosis was 2 years or more.

Certain limitations are inherent to data analyses from observational databases, including incomplete and missing data that limited our ability to truly examine repeated CTS surgeries in the same wrist, as well as inconsistencies in data collection from sites around the world. Typically, patients with MPS I may be managed by multiple physicians, and this multidisciplinary approach to patient care can result in incomplete accounting and transfer of patient records, and incomplete information during data collection for the registry. On a technical note, analysis of the MPS I Registry for discrepancy in data collection identified a small (<4%) rate of source-to-database error and no systematic errors.25 On the basis of the clinical experience of the authors, one of the limitations of the present study was the likely under-enrollment of patients with CTS from the registry. There are a few potential reasons for this: (1) the exclusion from analyses of patients in the registry with a
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