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Cervical cord compression in mucopolysaccharidosis VI (MPS VI): Findings from the MPS VI Clinical Surveillance Program (CSP)

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ABSTRACT

Objectives: To gain insight into the frequency, age of onset, and management of cervical cord compression in mucopolysaccharidosis VI (MPS VI).

Methods: Cervical spine magnetic resonance imaging (MRI) data and/or cervical decompression surgery data collected between 30 June 2005 and 1 September 2015 were analyzed from subjects enrolled in the MPS VI Clinical Surveillance Program (CSP) (ClinicalTrials.gov: NCT00214773), an ongoing multicenter, observational, retrospective and prospective registry.

Results: Of 213 subjects enrolled in the CSP, 134 (62.9%) had at least one documented cervical spine MRI assessment. An additional four subjects were identified through surgery records alone to yield a study population comprising 138 subjects (mean age at enrollment = 15.1 years; age range = 0.80–65.0 years). Cervical cord compression was documented in 101 (75.4%) of the 134 subjects with ≥1 MRI assessment, the majority (95.0%) by the time of the first recorded MRI. In general, subjects with cervical cord compression had significantly lower height *Z*-scores compared to those without cervical cord compression ($p < 0.0001$); nevertheless, a few subjects of taller stature had documented cervical cord compression at a young age. Most subjects >20 years of age (31/33, 93.9%) presented with cervical cord compression. There was an insufficient number of subjects with both pre- and post-enzyme replacement therapy (ERT) MRI data to determine any association between ERT and cervical cord compression. Surgical decompression was performed on 58 subjects (42.0%), with mean age at first surgery of 13.1 years. Decompression plus stabilization procedures accounted for 12.1% of surgeries. Eight subjects (13.8%) underwent reoperation. Complications during or following surgery were reported in 3 subjects, with anesthesia-related complications resulting in two deaths.

Conclusions: All individuals with MPS VI are at high risk of developing cervical cord compression at an early age. Routine MRI assessments should be initiated from the time of MPS VI diagnosis. The perioperative management of MPS VI patients can be challenging. This study contributes to the understanding of the natural history of MPS VI.

1. Introduction

Mucopolysaccharidosis VI (MPS VI, or Maroteaux-Lamy syndrome; OMIM 253200) is an autosomal recessive lysosomal storage disorder caused by deficient activity of *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B or ASB; EC 3.1.6.12), the enzyme that catabolizes the glycosaminoglycan (GAG) dermatan sulfate [1,2]. Progressive intracellular GAG accumulation leads to the development of multisystem complications and significant functional impairments. Characteristic clinical manifestations include short stature, skeletal deformities, joint abnormalities, respiratory complications, cardiac disease, corneal clouding, hearing loss and reduced physical endurance; however, there is wide variability in phenotypic presentation [1,2]. Rapidly progressing disease,

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characterized by early and rapid symptom onset and early death, is generally associated with urinary GAG (uGAG) levels >200 μg/mg creatinine, whereas a slower disease course and longer survival are associated with uGAG levels ≤200 μg/mg creatinine [3–5]. Age-adjusted height also provides an estimate of the degree of disease severity, as higher uGAG values have been shown to correspond to lower height values [3–5]. Regardless of the rate of disease progression, all patients have or are at risk of developing serious and debilitating morbidities [6]. Enzyme replacement therapy (ERT) with galsulfase is the recommended first-line therapy for treatment of MPS VI [7].

Spinal cord compression is a serious complication of MPS VI and typically arises from spinal canal stenosis secondary to malformations of the spine and skull base and/or to GAG accumulation in the soft tissues surrounding the spinal cord. Cord compression usually occurs in the cervical region, may involve multiple levels, and can lead to compressive myelopathy or myelomalacia. Cervical cord compression is potentially debilitating and life-threatening and has been reported to affect patients as young as 1 year of age [8] as well as those with slowly progressing disease [6,9]. Detailed recommendations for the diagnosis and management of cervical cord compression in individuals with MPS VI were published in 2012 [10]. Magnetic resonance imaging (MRI) is currently considered the gold standard for diagnosing spinal cord compression. Early signs of myelopathy can be detected by functional assessments and clinical neurological examinations. Surgical intervention generally involves decompression with or without stabilization; however, the airway and anesthetic management of these patients is challenging [11].

The literature on cervical cord compression in MPS VI is currently limited [8,9,12–15] and based primarily on studies comprising small patient series and single case reports. While surveys involving larger patient cohorts have provided better insight into the natural history of MPS VI [3,4], these studies did not collect or examine data on spinal canal stenosis, spinal cord compression or spinal surgery. Consequently, little is known about the age of onset and prevalence of cervical cord compression and the outcomes of cervical decompression surgery in MPS VI patients. The MPS VI Clinical Surveillance Program (CSP) was established in 2005 to collect observational data from routine clinical and laboratory assessments of patients with MPS VI over a period of at least 15 years [16]. Data for up to 5 years on 132 subjects enrolled in the CSP were published and revealed that individuals with MPS VI experience multiple comorbidities, but data on spinal anomalies, spinal cord compression, and spinal surgery were not analyzed as part of this report [16]. The objectives of this current study are to examine collective data from the CSP to estimate the frequency and age of onset of cervical cord compression in MPS VI, and to gain insight into the clinical management and surgical outcomes of MPS VI patients with cervical cord compression.

2. Methods

2.1. MPS VI Clinical Surveillance Program (CSP) design

The MPS VI CSP is a voluntary, ongoing, multicenter, multinational observational program designed to further characterize the natural history of MPS VI and to evaluate the long-term efficacy and safety of ERT with galsulfase. Retrospective and prospective data are collected in the CSP. It is being conducted in accordance with post-marketing commitments to the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for galsulfase. Individuals with documented reduced ARSB enzyme activity and/or molecular testing confirming a diagnosis of MPS VI are eligible to participate. Treatment with galsulfase is not a requirement for eligibility. The CSP was approved by all local institutional review boards and ethics committees. Subjects gave written informed consent, or, in the case of subjects aged <18 years, written consent was obtained from a legally authorized representative.

2.2. Data collection

Submission of data by participating sites is voluntary. Data are collected using an electronic database and include patient demographics, medical history, results of recommended assessments, and adverse events. Participating investigators are encouraged to collect and enter longitudinal data from recommended assessments, including radiological examinations of the spine, and are directed to report all severe and serious adverse events. The data are managed by BioMarin Pharmaceutical Inc. using a webhosted electronic data capture system.

2.3. Subject selection

For the purposes of the present study, only subjects with data pertaining to the cervical spine, cervical cord compression, and/or cervical spine surgery were considered for inclusion. Since most available information about spinal stenosis, spinal cord compression, and spinal decompression surgery was not reported in a standardized manner, keyword searches as well as manual review were conducted to identify eligible subjects and to retrieve relevant data from medical histories, radiological assessments, surgical records, and adverse events. Keyword search terms used were “spine”, “spinal”, “cervical”, “compress”, and “decompress”. Only subjects with evaluable MRI assessments of the cervical spine and/or subjects with documented cervical decompression surgery were included in this study.

2.4. Statistical analysis

All analyses were performed using SAS® 9.4 software (SAS Institute, Cary, NC). Categorical data variables were summarized using frequencies and percentages. Continuous data variables were summarized by the number of subjects (n), mean, standard deviation, median, minimum, and maximum values. A general linear model was used to compare height *Z*-scores and pre-ERT uGAG measurements between subjects with cervical cord compression and subjects without cervical cord compression; these analyses were performed only on subjects ≥3 years of age at the time of assessment since it is recognized that height (length) for MPS VI individuals is typically within normal range in the first two years of life [5,17,18] and infants have naturally high uGAG levels [19]. Height for age *Z*-scores were calculated for all subjects who had height information and are based on Centers for Disease Control (CDC) reference data for the normal population [20]; subjects who were 20 years of age or older at the time of height assessment were imputed as 19.5 years for height *Z*-score determination. Height assessments closest to the date of enrollment (i.e. date of CSP entry) were used for calculating height *Z*-scores. Pre-ERT uGAG assessments were the most recent assessments within 180 days prior to first ERT date, or if no assessment was recorded prior to ERT, the earliest assessment within 30 days after first ERT date.

3. Results

3.1. Patient demographics

As of 1 September 2015, 213 individuals with MPS VI from 56 sites in the USA, Europe and Australia had enrolled in the Clinical Surveillance Program (CSP). Of the 138 subjects (64.8%) included in this study, 134 were identified through documented MRI assessments of the cervical spine, and an additional 4 subjects were identified through surgical records alone (documented cervical cord decompression). A total of 58 subjects had undergone cervical decompression surgery. Table 1 shows the demographic and clinical characteristics of these groups of subjects.

Table 1
Demographics and characteristics of subjects.

	All subjects	Subjects with ≥1 MRI of cervical spine	Subjects who underwent cervical decompression surgery
N	138	134	58
Female	62 (44.93%)	60 (44.78%)	31 (53.45%)
Ethnicity			
White	89 (64.49%)	85 (63.43%)	38 (65.52%)
Black	5 (3.62%)	5 (3.73%)	2 (3.45%)
Hispanic	18 (13.04%)	18 (13.43%)	8 (13.79%)
Asian	9 (6.52%)	9 (6.72%)	3 (5.17%)
Other	13 (9.42%)	13 (9.70%)	7 (12.07%)
Age at enrollment (years)			
n	138	134	58
Mean (SD)	15.14 (12.62)	15.12 (12.69)	15.58 (12.66)
Median	12.65	12.65	13.25
Min, max	0.80, 65.00	0.80, 65.00	1.30, 65.00
0–2	13 (9.42%)	13 (9.70%)	3 (5.17%)
3–5	24 (17.39%)	23 (17.16%)	9 (15.52%)
6–12	34 (24.64%)	33 (24.63%)	16 (27.59%)
13–18	27 (19.57%)	27 (20.15%)	14 (24.14%)
Over 18	40 (28.99%)	38 (28.36%)	16 (27.59%)
Height at enrollment (cm)			
n	137	133	58
Mean (SD)	113.77 (26.72)	113.61 (26.26)	110.45 (23.76)
Median	106.00	106.00	106.00
Min, max	71.40, 182.90	71.40, 182.90	77.00, 167.60
Height *Z*-score at enrollment			
n	137	133	58
Mean (SD)	−3.83 (2.95)	−3.85 (2.98)	−4.72 (2.85)
Median	−3.48	−3.51	−4.68
Min, max	−11.57, 1.75	−11.57, 1.75	−11.19, 1.18
Weight (kg) at enrollment			
n	137	133	58
Mean (SD)	29.68 (18.77)	29.62 (18.68)	27.92 (17.63)
Median	23.50	23.50	22.55
Min, max	7.00, 103.90	7.00, 103.90	9.00, 90.70
Pre-ERT uGAG (μg/mg creatinine)			
n	68	65	29
Mean (SD)	259.75 (287.65)	255.88 (277.54)	299.03 (263.35)
Median	138.30	144.00	186.52
Min, max	0.00, 1491.31	0.00, 1491.31	0.00, 971.50
ERT treated anytime			
n	130	126	56
On ERT at enrollment			
n	103	100	44
Age at first infusion (years)			
n	130	126	56
Mean (SD)	12.72 (12.23)	12.68 (12.26)	13.29 (12.42)
Median	9.74	9.74	10.32
Min, max	0.30, 63.34	0.30, 63.34	0.78, 63.34
ERT exposure time (years)			
n	129	125	56
Mean (SD)	8.08 (3.09)	8.08 (3.13)	8.92 (3.02)
Median	8.89	8.93	9.33
Min, max	0.54, 14.81	0.54, 14.81	0.54, 14.81

Enrollment is defined as CSP entry.
Abbreviations: uGAG = urinary GAG; ERT = enzyme replacement therapy.

3.2. Cervical cord compression

134 (62.9%) of the 213 MPS VI subjects enrolled in the CSP had at least one documented MRI assessment of the cervical spine. For this subset of subjects, the mean age at CSP enrollment was 15.12 years (median = 12.65 years; range = 0.80–65.00 years), and the mean age at the first documented MRI assessment was 15.24 years (median = 12.97 years; range = 0.51–64.82 years). 92 subjects (43.2%) had >1 cervical spine MRI assessment, with mean duration of follow-up of 47.55 months (median = 45.05 months, range = 4.00–123.13 months).

Of the 134 subjects with at least one documented cervical spine MRI, 101 (75.4%) were reported to have or have had cervical cord compression. Myelopathic symptoms, including weakness, numbness, paresthesia, gait difficulty, and abnormal evoked potentials, were documented in 26 of these subjects, and myelomalacia was noted in 14 subjects. Of the 33 subjects without MRI evidence of cord compression, 31 were documented to have abnormal MRI findings, with cervical canal stenosis reported in 21 subjects. Dysmorphic vertebrae and ligamentous hypertrophy were commonly reported cervical spine abnormalities observed on MRI. Less commonly reported abnormalities were dens hypoplasia (5 subjects), os odontoideum (2 subjects) and cervical subluxation (2 subjects). Flexion-extension MR imaging of the cervical spine was documented for 7 subjects, one of whom was reported to have cervical instability. No additional information regarding instability was available from the few cervical spine X-ray assessments reported (documented for only 7 subjects).

Table 2 summarizes the key characteristics of subjects with and without cervical cord compression. Compared to subjects without

Table 2
Characteristics of subjects with and without cervical cord compression. Only subjects with ≥1 MRI assessment of the cervical spine are included.

	Cervical cord compression	No cervical cord compression
N	101	33
Female	49 (48.51%)	11 (33.33%)
Ethnicity		
White	67 (66.34%)	18 (54.55%)
Black	3 (2.97%)	2 (6.06%)
Hispanic	13 (12.87%)	5 (15.15%)
Asian	7 (6.93%)	2 (6.06%)
Other	10 (9.90%)	3 (9.09%)
Age at enrollment (years)		
n	101	33
Mean (SD)	17.34 (13.54)	8.32 (5.81)
Median	13.90	6.60
Min, max	1.30, 65.00	0.80, 21.90
0–2	6 (5.94%)	7 (21.21%)
3–5	16 (15.84%)	7 (21.21%)
6–12	22 (21.78%)	11 (33.33%)
13–18	21 (20.79%)	6 (18.18%)
Over 18	36 (35.64%)	2 (6.06%)
Height at enrollment (cm)		
n	100	33
Mean (SD)	114.46 (25.53)	111.05 (28.64)
Median	106.80	102.00
Min, max	77.00, 180.00	71.40,182.90
Height *Z*-score at enrollment		
n	100	33
Mean (SD)	−4.50 (2.85)	−1.89 (2.49)
Median	−4.27	−1.28
Min, max	−11.57, 1.18	−9.86, 1.75
Pre-ERT uGAG (μg/mg creatinine)		
n	46	19
Mean (SD)	239.68 (245.11)	295.11 (348.40)
Median	138.30	193.60
Min, max	0.00, 1026.32	20.10, 1491.31
Age at first reported MRI (years)		
n	100	33
Mean (SD)	17.70 (13.39)	8.63 (5.99)
Median	14.77	7.77
Min, max	1.29, 64.82	0.51, 28.49
>1 MRI		
n	73	19
>1 MRI, time from first to last MRI (days)		
Mean (SD)	1452.04 (904.30)	1328.11 (786.69)
Median	1422.00	1226.00
Min, max	120.00, 3694.00	305.00. 3033.00
Abnormal MRI		
n	101	31
ERT treated anytime		
n	94	32
On ERT at enrollment		
n	76	24
Age at first infusion (years)		
n	94	32
Mean (SD)	14.55 (13.29)	7.17 (5.88)
Median	11.75	5.92
Min, max	0.78, 63.34	0.30, 21.94
ERT exposure time (years)		
n	94	31
Mean (SD)	8.55 (3.13)	6.68 (2.71)
Median	9.33	6.92
Min, max	0.54, 14.81	0.75, 11.46

Enrollment is defined as CSP entry.
Abbreviations: uGAG = urinary GAG; ERT = enzyme replacement therapy.

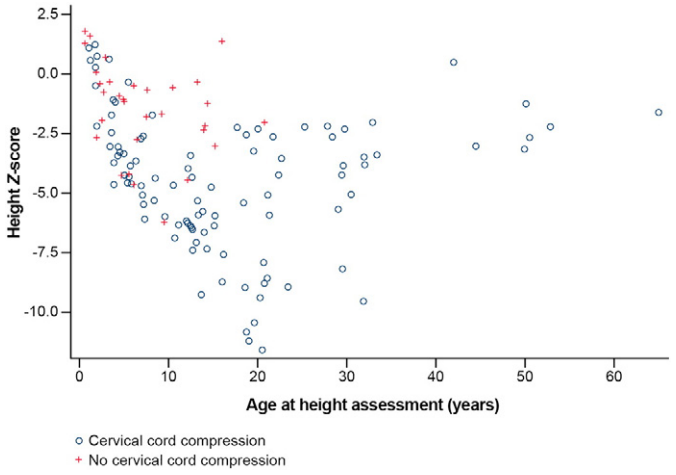

Fig. 1. Height *Z*-score versus age of subjects with and without cervical cord compression. Only subjects with ≥1 cervical spine MRI are included. Height *Z*-scores were calculated based on CDC data for normal population. For subjects ≥20 years of age, age was imputed as 19.5 years for height *Z*-score determination.

cervical cord compression, subjects with cervical cord compression had lower height for age *Z*-scores and were older. Further analysis revealed a statistically significant difference in height *Z*-scores between subjects with and without cord compression ($p < 0.0001$), with lower height values associated with cervical cord compression. Height *Z*-scores summarized by enrollment age groups (0–2 years, 3–5 years, 6–12 years, 13–18 years, and ≥19 years at enrollment) are presented in Supplemental Table 1. Nevertheless, cervical cord compression manifested in a few subjects of taller stature at a young age (Fig. 1). Most (31/33, 93.9%) subjects >20 years of age had cervical cord compression (Fig. 1).

While height data were available for 137 subjects, pre-ERT uGAG measurements were available for only 68 subjects (Supplemental Fig. 1). Collectively, no overall significant difference in pre-ERT uGAG was observed between subjects with and without cervical cord compression ($p = 0.6677$). However, in the 6–12 year enrollment age group, subjects with cervical cord compression had considerably higher pre-ERT uGAG values compared to those without cord compression (Supplemental Table 1).

3.3. Age of onset of cervical cord compression

It was not possible to obtain a precise estimate of the range of age of onset of cervical cord compression in this study population because the vast majority of affected subjects (96/101 subjects, 95.0%) had developed or had a documented history of cervical cord compression by the time of the first recorded MRI assessment. However, as shown in Fig. 2, cervical cord compression can develop at a young age: 4 children under 2 years of age (age range = 1.12–1.81 years) were reported to have cervical cord compression at the first MRI examination, and a total of 15 subjects (11.2%) assessed by MRI were documented with cervical cord compression before age 6 years. Of the 5 subjects who developed cervical cord compression after the first reported MRI, the mean age of onset was 8.50 years (median = 9.34 years; range = 2.27–13.04 years), the mean age at first MRI was 7.05 years (median = 8.87 years; range = 1.29–11.12 years), and the mean duration of MRI follow-up was 35.7 months (median = 37.8 months; range = 11.9–55.9 months).

3.4. ERT

A total of 126 (94.0%) of the 134 subjects with ≥1 cervical spine MRI had received or were receiving ERT at the time of data analysis. Since the majority of these subjects (96/126, 76.2%) started ERT prior to the time of the first reported MRI assessment, a documented pre-ERT MRI assessment was available for only 30 subjects. Of the 9 subjects who showed no MRI evidence of cervical cord compression prior to ERT initiation and who had at least one post-ERT MRI assessment, 2 (22.2%) were

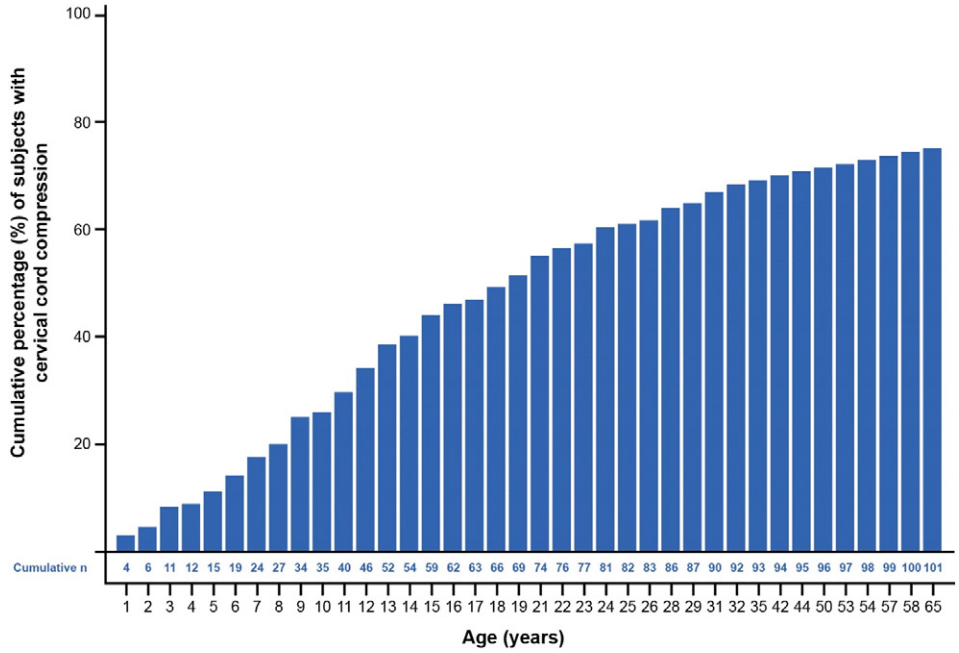

Fig. 2. Cumulative percentage of subjects with documented cervical cord compression by age. Only subjects with ≥1 cervical spine MRI are included. The number immediately below each bar represents the cumulative number of subjects with cervical cord compression at that age.

reported to have developed cervical cord compression at some point after starting ERT (Fig. 3).

3.5. Surgical intervention and outcomes

Table 1 summarizes the key characteristics of the 58 subjects who underwent cervical decompression surgery. These subjects had lower height *Z*-scores and higher uGAG levels compared to subjects with cervical cord compression who did not undergo decompression surgery (Supplemental Table 2), suggesting that surgical intervention is associated with patients with a more severe clinical phenotype. Fourteen subjects (24.1%) were reported to have myelopathic symptoms prior to surgery. Decompression alone was performed on 51 subjects, while combined decompression and stabilization procedures were performed on 7 subjects.

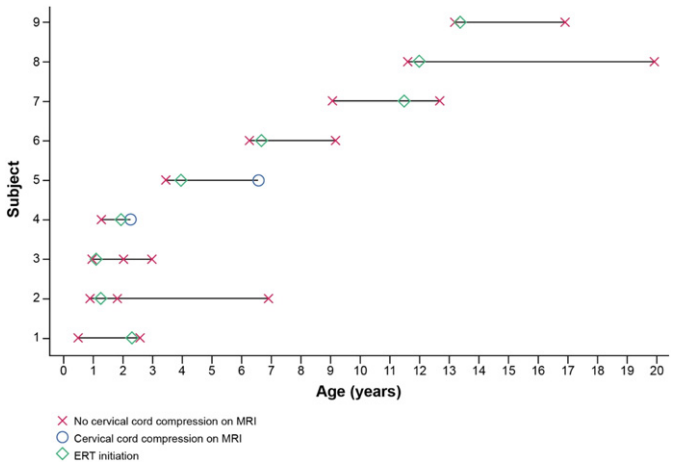

Fig. 3. Subjects with no MRI evidence of cervical cord compression prior to ERT and with post-ERT cervical spine MRI data. Cervical cord compression was reported 116 and 948 days after ERT initiation for Subjects 4 and 5, respectively. All other subjects showed no evidence of cervical cord compression based on the last documented post-ERT MRI.

The mean age at first surgery was 13.05 years ($n = 50$; median = 12.66 years; range = 1.13–66.42 years). Eleven subjects (19.0%) were reported to have undergone surgery before 6 years of age (Fig. 4).

Forty subjects (69.0%) had radiological (MRI, CT or X-ray) assessments following decompression surgery, with mean duration of follow-up of 55.60 months (median = 50.55 months; range = 0.07–256.5 months). A post-operative MRI assessment (obtained up to 6 months post-surgery) was documented for 13 subjects, with improvement noted in all but one subject. Improvement in clinical symptoms following surgery was documented for two individuals. Eight subjects (13.8%) underwent reoperation, one of whom was reported to have undergone a total of four decompression surgeries. Complications during or following surgery

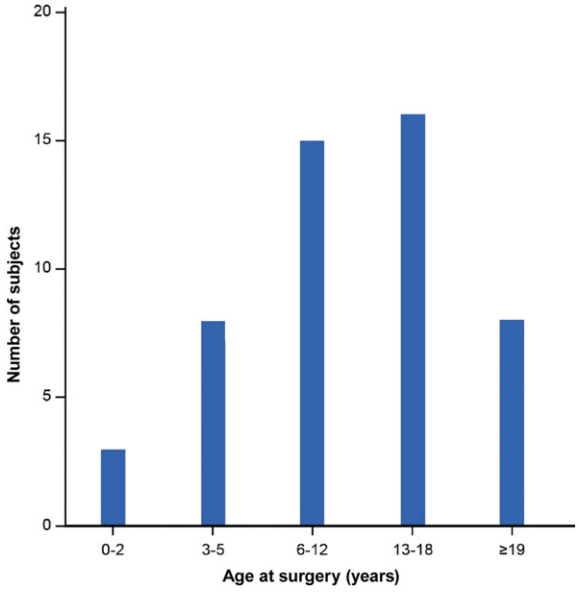

Fig. 4. Frequency of cervical decompression surgery by age group. Only first surgeries are included.

were reported in 3 subjects (5.2%): one subject contracted *Enterobacter aerogenes* meningitis that resolved with treatment after one month, and two (3.4%) subjects died as a result of anesthesia-related complications.

4. Discussion

This study, the largest to date to examine cervical cord compression and its management in MPS VI individuals, yielded several key findings. First, approximately 75% of subjects assessed by MRI in this study had documented cervical cord compression, indicating that the frequency of cervical cord compression in the general MPS VI patient population is high. Second, we found that the onset of cervical cord compression can occur at very young ages, including in children under 2 years of age, which is in line with prior observations by Horovitz et al. [8]. Third, while we found a statistically significant association between disease severity (based on height *Z*-scores) and cervical cord compression, a few subjects of taller stature, and with presumably slower progressing disease, had developed cervical cord compression at an early age. Fourth, even among those subjects without MRI evidence of cervical cord compression, almost all (>93.9%) had cervical spine abnormalities on MRI (e.g. stenosis, dysmorphic vertebrae, dens hypoplasia). Taken together, these specific findings suggest that all MPS VI patients are at significant risk of developing cervical cord compression at a young age and underscore the importance of routine MR imaging of the cervical spine beginning at the time of MPS VI diagnosis.

Cervical cord compression in MPS VI is mainly caused by bony stenosis, peri-odontoid soft tissue mass, hypertrophy of the posterior longitudinal ligament, and/or GAG-related dural thickening [10]. Less commonly, cervical subluxation and instability may also be contributing factors. Results from this study suggest that subjects with shorter stature are at increased risk of developing cervical cord compression at an early age, which is likely due to the greater degree of skeletal dysplasia and the more extensive GAG accumulation and tissue thickening associated with a more rapidly progressive disease course. However, our data demonstrate that subjects with less growth retardation can also develop cervical cord compression at a young age, reflecting the clinical heterogeneity of the MPS VI population. It should be noted that individuals with MPS VI are normal in height (length) during infancy and do not typically manifest growth failure until 2–3 years of age [5,17,18]. Notably, the majority of subjects who were >20 years of age were of taller stature but had documented cervical cord compression at the time of the first reported MRI assessment. Although age-adjusted height values have been demonstrated to inversely correlate with pre-ERT uGAG values [3–5], we did not observe an association between pre-ERT uGAG values and cervical cord compression, which is most likely attributable to incomplete and insufficient uGAG data as well as to analyses being performed by different laboratories.

Considerable insight into the surgical management and outcomes of MPS VI patients with cervical cord compression was also gained from this study. Surgical decompression was performed on 42.0% of the study population, and decompression plus stabilization procedures accounted for 12.1% of surgeries. The mean age at first decompression surgery was 13.05 years (median = 12.66 years), and 19.0% of subjects underwent surgery before age 6 years. Cervical decompression in MPS VI patients may be achieved by laminectomy or laminoplasty; in some cases, in situ duraplasty may also be required for the thickened compressive dural elements. Cervical subluxation or cervical instability was documented in 2 subjects who underwent decompression and stabilization procedures. While cervical instability is not thought to be common in MPS VI, its presence can exacerbate cord compression, cause cord injury, and prompt surgical intervention (Fig. 5). In this study population, only 7 subjects were reported to have undergone flexion/extension imaging of the cervical spine to assess for dynamic instability, and while only one subject was reported to have instability, it should be noted that the presence of cervical instability is not specifically queried in the CSP. Guidelines recommend that flexion/extension studies of the cervical spine be conducted every 3 years or more frequently if clinically indicated [10]; dynamic flexion-extension MRI may be particularly useful for assessment of cervical cord compression secondary to instability but should be performed carefully in young children under anesthesia or sedation [21]. Reasons for surgical intervention are not specifically sought in the CSP, but myelopathy was cited in several cases (Fig. 5 is an example). Specific indications for spinal decompression surgery in MPS VI have not been formally established. Treatment decisions and approaches vary and are dependent on the overall clinical picture, functional testing and radiological findings, as illustrated by the selected CSP cases depicted in Figs. 5-7; in practice, additional factors including institutional resources and treating physician experience play a significant role in determining time to surgery and how surgery is performed.

Less than 15% of subjects required reoperation, although one patient underwent four decompressive surgeries. While the overall complication rate was low (5.1% of subjects), 2 (3.4%) subjects died as a result of anesthesia-related complications during or following cervical decompression procedures. In one case involving a 12 year old patient, episodes of desaturation followed by cardiac arrest occurred 36 h after surgery. In the other case, failure to successfully intubate resulted in hypoxia and the death of a 13 year old subject. Both cases serve to illustrate the high anesthetic risk of individuals with MPS VI. Obstructive airways, restrictive pulmonary disease, cardiac problems, and cervical instability and myelopathy contribute to the increased risk of anesthesia-related complications in these patients. Careful preoperative assessments, anticipation of potential problems, and involvement of an anesthesiologist and support personnel experienced in managing MPS patients are essential for minimizing the risk of perioperative morbidity and mortality in individuals with MPS VI. Guidelines for anesthesia management in MPS patients have recently been published [11]. Cervical spinal surgery is a complex procedure and should only be performed in expert centers with experience in managing these complex patients. There are different modalities that can be used to ensure patient safety and these will be driven by local expertise and facilities. While data on how often continuous intra-operative electrophysiological neuromonitoring is used are not available, its inclusion, in the authors' experience, significantly adds to patient safety during surgery. We feel this measure should at least be considered in all cases of elective surgery; the local expert team should decide if this would be practical or if other measures are adequate to ensure the integrity of the spinal cord during surgery.

There was an insufficient number of subjects with both pre- and post-ERT MRI data to draw conclusions regarding an association between ERT and cervical cord compression. It is important to establish baseline MRI characteristics of the spine at the time of MPS VI diagnosis for patients 1 year of age or older in order to provide a metric to assess change over time and the impact of ERT.

Current management guidelines recommend frequent MRI assessments of the cervical spine in MPS VI patients [10]. Approximately 60% of all subjects in the CSP database had at least one MRI assessment of the cervical spine, and 43% had >1 cervical spine MRI with mean duration of follow-up of 47.5 months. This indicates that, at least in the regions represented in the CSP (Europe, USA, Australia), current clinical practices are reasonably aligned with the recommendations, pointing to growing recognition among clinicians of the high risk of cervical cord compression in this patient population and of the key role of MRI findings in guiding its management. This is in contrast to practices recently reported for MPS II, in which cervical cord compression is rare and MRI is typically not performed without clear neurological signs/symptoms: only 12% of MPS II subjects from the Hunter Outcome Survey were reported to have had at least one cervical spine MRI assessment [22].

There are several limitations associated with this study. Due to the voluntary nature of data collection and submission, incomplete and missing data are inherent, and the reported frequencies of cervical

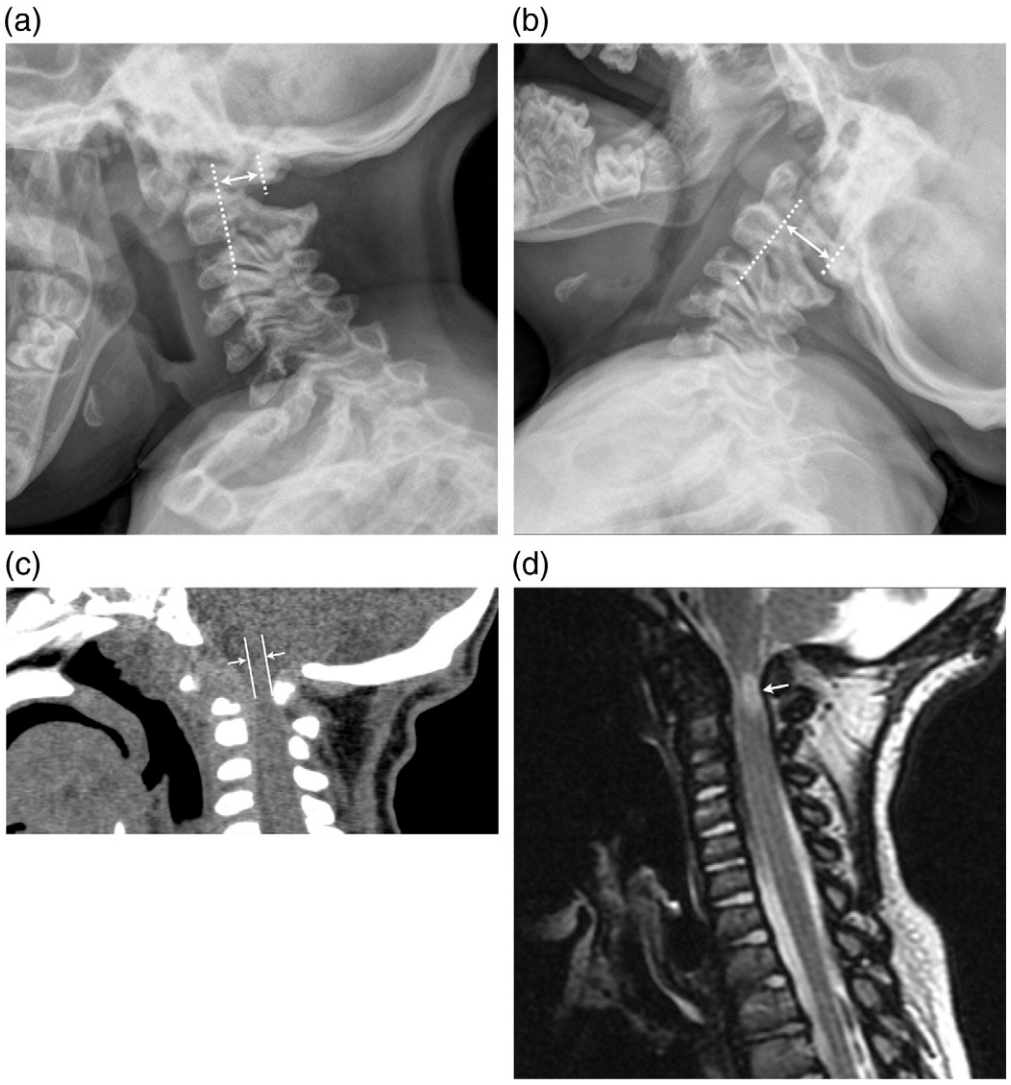

Fig. 5. A 3-year-old MPS VI subject presented with clinical myelopathy and pre-surgical imaging findings of cervical instability, stenosis, and myelomalacia. Surgical decompression and stabilization was performed without complications. *(a)* and *(b) Lateral flexion-extension radiographs.* During flexion and extension, there is atlanto-axial instability with narrowing of the bony spinal canal from 17 mm during extension to 10 mm during flexion. Measurements are made at the spinal canal as shown rather than at the pre-dental space. *(c) Cervical spine CT, soft tissue filter and window.* There is dysplasia and delayed ossification of the cartilaginous odontoid process of C2, thickening of the cruciate ligament, and hypoplasia of the posterior arch of C1. All contribute to severe spinal stenosis with space available to the cord measured at 5 mm in the antero-posterior plane (double arrow). Radiographs have underestimated the severity of stenosis. *(d) Cervical spine MRI.* T2 TSE sagittal shows stenosis at C1, cervical cord compression, and a 4x10 mm focus of high cord signal indicating myelomalacia (arrow).

cord compression, cervical decompression surgery, and surgical complications could be inaccurate. The true incidence of cervical cord compression in subjects without MRI data is not known. Much of the submitted information was in the form of free text; more extensive use of predefined variables may have yielded higher quality, more consistent, more quantitative and more comprehensive data. No pre-defined outcome measures were included, and only physician-reported data were collected. Although global in scope, the CSP does not currently include any sites from Latin America or the Middle East, where a significant number of MPS VI patients reside (particularly in Brazil and Turkey), or many sites from Asia Pacific. The strengths of this study lie in the large, multicenter, multinational cohort and the retrospective and prospective design of the CSP, enabling insight into the prevalence and onset of cervical cord compression in the MPS VI population and management practices in real-life clinical settings. Future studies to further elucidate the natural history of cervical cord compression in MPS VI and the impact of surgery and ERT would benefit from the development and inclusion of disease-specific MRI morphometric determinants of canal stenosis and cord compression, a spinal cord compression severity scoring system [9], and patient-reported outcome measures.

In conclusion, cervical cord compression is a common manifestation of MPS VI and can affect all patients at an early age, irrespective of phenotype. Routine MRI assessments from the time of MPS VI diagnosis are critical for prevention of irreversible spinal cord damage. Individuals with MPS VI are at high risk of perioperative complications. This study adds to our current knowledge of the natural history of MPS VI.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ymgme.2016.06.001.

Conflicts of interest

G. A. Solanki and K. W. Martin have received speaker honoraria and travel support from BioMarin Pharmaceutical Inc. (BioMarin). C. J. Hendriksz has received consulting fees, symposium support for himself and team personnel, and research grants from BioMarin. C. Lampe has received speaker's fees, consulting fees, travel support and research

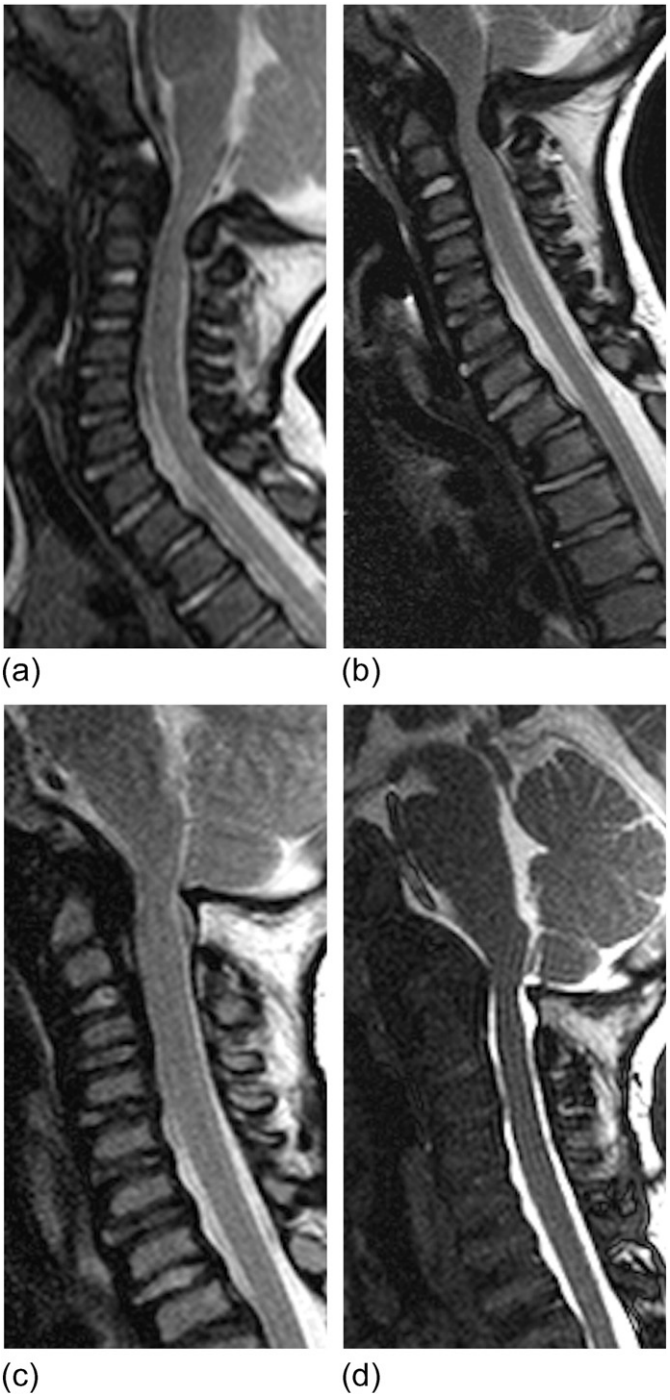

Fig. 6. An MPS VI subject with spinal cord compression at 1 year 7 months develops progressive stenosis and undergoes cervical decompression without fusion with excellent outcome. *(a)* and *(b) Cervical spine MRI.* T2 TSE sagittal at 1 year 7 months of age shows odontoid dysplasia, thickening of the cruciate ligaments, and hypoplasia of C1, all resulting in focal spinal stenosis measuring 5 mm and cervical cord compression. A follow-up study at 3 years 9 months of age shows progressive stenosis at C1 which now measures 4 mm with cord compression and complete effacement of CSF. Surgical decompression was performed. (*c*) *Cervical spine MRI.* Post-surgical T2 TSE performed 6 years later at 10 years of age shows adequate decompression with preservation of normal T2 signal within the cord. Note the pointed dural fold at the posterior margin of the foramen magnum, a post-surgical finding which can be monitored for progression. (*d*) *Cervical spine MRI.* This bTFE sagittal cine sequence offers superior depiction of flowing CSF at the foramen magnum.

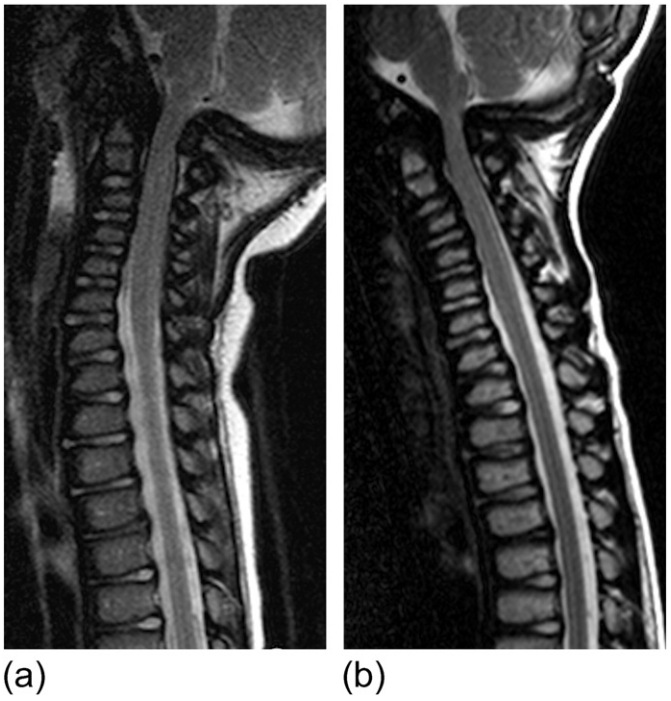

Fig. 7. This 4 year old MPS VI subject with asymptomatic cervical cord compression at C1 has been followed for 4 years without progression. There are regular neurological assessments and imaging studies to monitor for myelopathic symptoms, cord compression, and development of instability. (*a*) *Cervical spine MRI.* At 4 years of age, this T2 TSE sagittal shows odontoid dysplasia, thickening of the cruciate ligaments, and hypoplasia of C1. There is effacement of CSF and mild cord compression. (*b*) *Cervical spine MRI.* At 8 years of age, this follow-up T2 TSE shows a decrease in space available to the cord from 7 mm to 6 mm without change in normal T2 cord signal. The slight decrease was attributed to differences in flexion and extension during the studies. No surgical intervention was planned and the subject continued with monitoring.

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Disclosures

C. Lampe collected data for this publication while employed at Villa Metabolica, Mainz, Germany, where she was the CSP principal investigator.

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