Importance of surgical history in diagnosing mucopolysaccharidosis type II (Hunter syndrome): Data from the Hunter Outcome Survey

Nancy J. Mendelsohn, MD[1], Paul Harmatz, MD[2], Olaf Bodamer, MD[3], Barbara K. Burton, MD[4], Roberto Giugliani, MD, PhD[5], Simon A. Jones, MB, ChB[6], Christina Lampe, MD[7], Gunilla Malm, MD, PhD[8], Robert D. Steiner, MD[9,10], and Rossella Parini, MD[11], on behalf of the Hunter Outcome Survey Investigators

Purpose: To characterize surgical histories typical of patients with mucopolysaccharidosis type II, thereby broadening understanding of the natural history of these patients and helping physicians recognize the disease. **Methods:** Data on surgical interventions from the Hunter Outcome Survey—a multinational, observational database of patients with mucopolysaccharidosis type II—were analyzed. The study population comprised 527 patients for whom surgical data were reported on/before July 23, 2009. **Results:** Surgical interventions were performed in 83.7% of the study population. Patients underwent their first operation at a median age of 2.6 years. Tympanostomies, repairs of inguinal hernias, and operations for carpal tunnel syndrome were performed in a greater proportion of the study population than the general population. A median of 3.0 operations was performed per patient; repeat operations for hernia or carpal tunnel syndrome were common. The majority of patients (221/389) underwent at least one surgical intervention before diagnosis of mucopolysaccharidosis type II. **Conclusion:** Patients with mucopolysaccharidosis type II typically undergo surgical intervention at a young age, often before diagnosis. Repeated early surgical interventions, particularly for hernias or carpal tunnel syndrome, are characteristic of patients with mucopolysaccharidosis type II. We recommend that such patients are carefully examined for manifestations of mucopolysaccharidosis disorders and referred for diagnostic testing. ***Genet Med* 2010:12(12): 816–822.**

Key Words: *MPS II, Hunter syndrome, diagnosis, surgical intervention, lysosomal storage diseases*

From the [1]Department of Medical Genetics, Children's Hospitals and Clinics of Minnesota, Minneapolis, Minnesota; [2]Children's Hospital & Research Center Oakland, Oakland, California; [3]Institute for Inherited Metabolic Diseases, Paracelsus Medical University and University Children's Hospital, Salzburg, Austria; [4]Northwestern University Feinberg School of Medicine and Division of Genetics, Birth Defects and Metabolism, Children's Memorial Hospital, Chicago, Illinois; [5]Department of Genetics/UFRGS, Medical Genetics Service/HCPA and INAGEMP, Porto Alegre, RS, Brazil; [6]Genetic Medicine, Manchester Academic Health Science Centre, St Mary's Hospital, Manchester, United Kingdom; [7]Children's Hospital, University of Mainz, Mainz, Germany; [8]Division of Clinical Science, Intervention and Technique, Department of Paediatrics, Karolinska Institute, Karolinska University Hospital, Huddinge, Stockholm, Sweden; Departments of [9]Pediatrics and [10]Molecular & Medical Genetics, Oregon Health & Science University, Portland, Oregon; and [11]Pediatric Department, University Milano Bicocca, San Gerardo Hospital, Monza, Italy.

Dr. Nancy J. Mendelsohn, Department of Medical Genetics, Children's Hospitals and Clinics of Minnesota, 2525 Chicago Ave South, MS 32 T6 Minneapolis, MN 55404. E-mail: nancy.mendelsohn@childrensmn.org.

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Mucopolysaccharidosis (MPS) type II (MPS II; Hunter syndrome; OMIM #309900) is a rare, progressive, multisystemic disease, caused by deficiency of the lysosomal enzyme iduronate-2-sulfatase (I2S; EC 3.1.6.13). Causative mutations in the gene encoding I2S are X linked, and the disease occurs almost exclusively in males, with an incidence of 1.3 per 100,000 live male births.[1,2] I2S deficiency results in the accumulation of the glycosaminoglycans heparan and dermatan sulfate in lysosomes of cells throughout the body. The resulting phenotypes constitute a spectrum of disease severity but can be broadly categorized as either severe or attenuated.

Signs and symptoms of MPS II classically appear in early childhood,[3] although diagnosis may be several years later.[4] Cardiopulmonary, musculoskeletal, peripheral nervous system, gastrointestinal, dermatological, and/or ear–nose–throat manifestations can be experienced by all patients, but those with the severe form of MPS II are distinguished by having neurocognitive decline.[3,5] A reduced lifespan is associated with both forms of the disease. Patients with the severe form of MPS II are expected to live for less than 2 decades; in contrast, those with the attenuated form may survive into their 50s or 60s.[3,5,6]

Historically, the treatments available for patients with MPS II were palliative but that is no longer the case. Today, enzyme replacement therapy (ERT) is available to treat the underlying lysosomal enzyme deficiency in patients with MPS II. ERT is not without limitations, but clinical trials in patients with the attenuated form of MPS II support its use to address certain aspects of the disease.[7] Hematopoietic stem-cell transplantation has also been used to provide the missing enzyme in some patients with MPS II, but its effectiveness remains controversial.[7,8] Supportive therapy continues to play an important part in management of the disease.[5] In particular, surgical intervention is often required at a young age to address specific pathologic features of MPS II, such as hernias and compression of the spinal cord, and is frequently needed to improve airway obstruction and orthopedic complications.[9] Important considerations for anesthesiologists managing patients with MPS II include upper-airway obstruction and cervical involvement that poses a risk of spinal cord injury.[10] Despite these concerns, and providing that suitable precautions are taken during anesthesia, many patients with MPS II will benefit from appropriate surgical intervention complementing other therapies, including ERT.

To monitor the natural history of MPS II and the long-term safety and effectiveness of ERT with idursulfase, the multinational observational database Hunter Outcome Survey (HOS) was established in 2005. This study explored the information available to date in HOS on surgical interventions in patients with MPS II. The aim was to provide a description of the types, timings, and frequencies of surgical procedures that were per-

formed. The typical surgical history of patients with MPS II was then compared with that of the general population to determine which operations—particularly those performed at a young age—were more prevalent in patients with MPS II.

MATERIALS AND METHODS

The Hunter Outcome Survey

HOS is a physician-led, multicenter observational database. It is the only global outcome survey of the natural history of MPS II and the long-term safety and effectiveness of idursulfase. Patient, physician, and medical center eligibility, and data entry and analysis have been described in previous publications.[4,6] Participating clinics enter the medical history of a patient at enrollment by an electronic data-submission application, and follow-up information is added thereafter.[4] Data-entry screens for medical history and follow-up information ask whether any of 20 types of surgical procedures were performed. The year in which a patient had their first and last surgical procedures can be entered as part of the medical history, and the dates of surgical interventions occurring after enrollment can be input as follow-up information. Details of any other surgical procedures are collected as free text under "other surgeries." HOS data are anonymized and confidential. Each participating medical center received approval to enroll patients in HOS according to local regulations, which are typically those of the Institutional Review Board or Ethics Committee. The processing of data in the HOS database has been adapted to comply with the Swedish Personal Data Act (1998: 204) and the EU Directive 2002/58/EC (July 12, 2002) on the processing of personal data and the protection of privacy in the electronic communication sector. All US-based centers and laboratories or entities providing support for this survey, must, where applicable, comply with the Health Insurance Portability and Accountability Act of 1996.

HOS data for this analysis were collected on or before July 23, 2009. At this time, 579 patients (alive at HOS entry) from 102 centers, distributed among 24 countries were enrolled in HOS. The population analyzed in this article consisted of 527 patients who were alive at HOS entry (four females, all of whom have been confirmed as having a karyotype of 46, XX) for whom data about surgical interventions were available. Of these 527 patients, the majority (385 patients) was reported to have received ERT at some time.

Parameters

Baseline demographics were assessed, and the following parameters were analyzed: medical history data recorded at HOS entry on the number of previous surgical procedures and the year in which the first of these was performed; and information entered subsequently on the number of operations performed between follow-up visits and the date on which they were performed. These demographics and parameters were used to determine the number of patients reported to have undergone at least one surgical procedure between birth and the last recorded clinic visit before July 23, 2009, the number of times operations were performed in individuals, the median age at first surgical intervention, the interval between diagnosis and first operation, and the number of patients whose first operation occurred before diagnosis. These parameters could be calculated with respect to each type of surgical procedure or for all surgical procedures. It was not possible to tell from the information reported in HOS whether repeat operations in an individual were duplications of a type of operation (e.g., for carpal tunnel syndrome [CTS]) or of the same operation (e.g., for CTS on one particular hand). If an operation relating to a paired body part such as a hand was reported more than twice, it could be inferred that it had been repeated on one body part of the pair. Data on the number of hernia repair operations performed per individual were stratified by gestational age ($n = 333$). The frequency of complications during surgical intervention was also assessed. Information in the comments section that accompanied each report of "other surgeries" was reviewed, and data on the implantation of venous access systems were extracted from this section manually.

RESULTS

Surgical interventions reported in HOS

Baseline demographics for the study population and for patients who were reported to have undergone surgical intervention are presented in Table 1. Patients who underwent surgical intervention attended clinics participating in HOS in Western Europe ($n = 221$), North America ($n = 134$), Latin America ($n = 38$), Eastern Europe ($n = 29$), and Asia ($n = 19$). Surgical procedures were performed in 441 (83.7%) of the 527 patients for whom information about surgical intervention was available.

Prevalence and frequency of surgical interventions reported in HOS

The most commonly performed operations (Fig. 1) were tympanostomy (placement of ear-drum ventilating tubes; in 51.4% of 527 patients), hernia repair (50.1%: 10.4% umbilical; 21.8% inguinal; 15.2% umbilical and inguinal; and 2.7% type not indicated), adenoidectomy (49.5%), tonsillectomy (35.5%), and carpal tunnel release (18.2%). Pelvic osteotomy, knee arthroscopy, femoral osteotomy, and hip replacement were each performed in fewer than four patients and were, therefore, not included in tables/figures. "Other surgery" was reported for 154

Table 1 Baseline demographics of patients with mucopolysaccharidosis type II (MPS II) who are enrolled in the Hunter Outcome Survey (HOS)

	Patients for whom information about surgical intervention was available ($n = 527$)		Patients reported to have undergone surgical intervention ($n = 441$)	
Characteristics	Patients with data on characteristic (n)	Median, yr (10th–90th percentiles)	Patients with data on characteristic (n)	Median, yr (10th–90th percentiles)
Age at onset of signs and symptoms of MPS II	424	1.5 (0.3–4.0)	362	1.5 (0.3–4.0)
Age at diagnosis of MPS II	493	3.3 (1.2–7.0)	420	3.3 (1.2–6.8)
Age at last visit	527	10.9 (4.1–24.3)	441	11.2 (4.6–23.5)

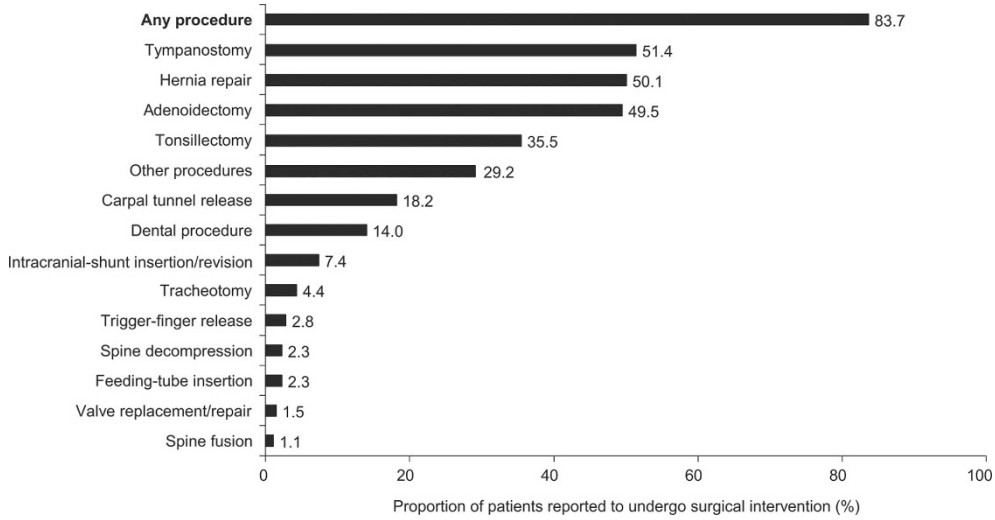

Fig. 1. Prevalence of undergoing surgical intervention in the Hunter Outcome Survey (HOS). Data are from patients for whom information about surgical intervention was recorded in HOS, as of July 23, 2009 ($n = 527$).

Table 2 Repeat hernia repairs and operations for carpal tunnel syndrome (CTS) in patients enrolled in the Hunter Outcome Survey (HOS)

Surgical operation	No. times operation performed	No. patients, *n* (%[a])
Hernia repair	1	158 (59.8)
	2	78 (29.5)
	3	20 (7.6)
	4	2 (0.9)
	5	2 (0.9)
	6	2 (0.9)
	7	1 (0.4)
	8	1 (0.4)
Carpal tunnel release[b]	1	69 (71.8)
	2	24 (25.0)
	3	2 (2.1)
	4	1 (1.0)

[a]Calculated from the total number of patients in HOS who underwent hernia repair ($n = 264$) or carpal tunnel release ($n = 96$).
[b]Reports of operations for CTS did not specify whether the operation was performed on the left or right hand of a patient.

(29.2%) patients, including implantation of a venous access system in 87 patients. Data on the timing of implantation were available for 53 of the 87 patients with a venous access system; surgery was performed after diagnosis in 50 cases and before diagnosis in three cases. A median of 3.0 operations was performed per patient. Individuals often underwent repeated hernia repair and surgical procedures for CTS: more than one in four patients who underwent these operations had the procedure repeated, and eight patients had four or more hernia repairs (Table 2). The percentage of patients who had one or more hernia operations was 46.0% in full-term patients (born on or after 38–42 weeks of gestation; $n = 287$) and 41.3% in preterm patients (born before 38 weeks of gestation; $n = 46$; χ^2, $P = 0.55$).

Age distribution of surgical interventions reported in HOS

Patients experienced a surgical procedure for the first time at a median age of 2.6 years ($n = 405$; Fig. 2). First surgical procedures were reported to have been performed before the age of 3 years in 55.3% (224/405) of patients, and 46.0% (103/224) of these children underwent more than one type of surgical procedure before 3 years of age, most commonly tympanostomy, tonsillectomy, adenoidectomy, and hernia repair, in various combinations. Hernia repairs were among the earliest operations to be performed (at a median age of 3.0 years; 10th–90th percentiles, 0.3–12.0 years), whereas spine decompressions were among the latest, being carried out at a median age of 14.3 years (10th–90th percentiles, 5.8–36.1 year). Of note, carpal tunnel release was carried out at a median age of 8.7 years (10th–90th percentiles, 4.5–19.8 years). Surgical procedures were performed before diagnosis of MPS II in 221 (56.8%) patients (Fig. 3), who each underwent a median of 2.0 operations while undiagnosed. More than 40% of patients who underwent hernia repair, tympanostomy, or adenoidectomy had the operation before MPS II was diagnosed (Fig. 3; Table 3). Carpal tunnel release was performed before diagnosis in 3.6% of cases. Of the 221 patients who underwent procedures before diagnosis, 102 each underwent two or more different types of operation before being diagnosed.

For 428 of the 441 patients who were reported in HOS to have had surgical intervention, there were also details on whether problems with intubation and/or of being unable to extubate had been experienced. Difficulties with intubation were reported in 22.0% of the 428 patients (intubation dates were available for 74 patients; median age, 7.0 years; 10th–90th percentiles, 3.1–15.9 years), and investigators reported being unable to extubate in 3.7% (dates when unable to extubate were available for 14 patients; median age, 13.2 years; 10th–90th percentiles, 4.5–27.6 years). Problems with intubation were reported to occur before diagnosis in 18.6% of patients for whom dates of problems with intubation and of diagnosis of MPS II were known ($n = 70$). Problems with extubation were reported to occur before diagnosis in 7.7% of patients

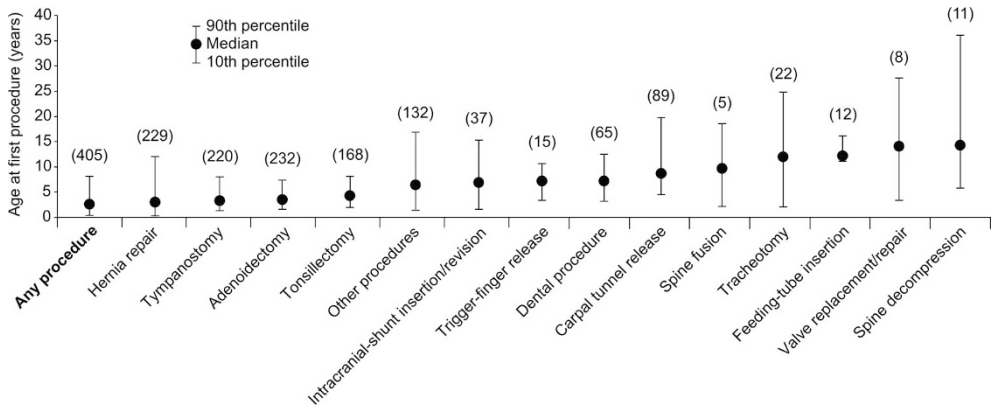

Fig. 2. Age at first surgical procedure of patients in the Hunter Outcome Survey (HOS). Data are from patients in HOS for whom the date of the first of the specified type of operation was known (numbers of patients shown in parentheses).

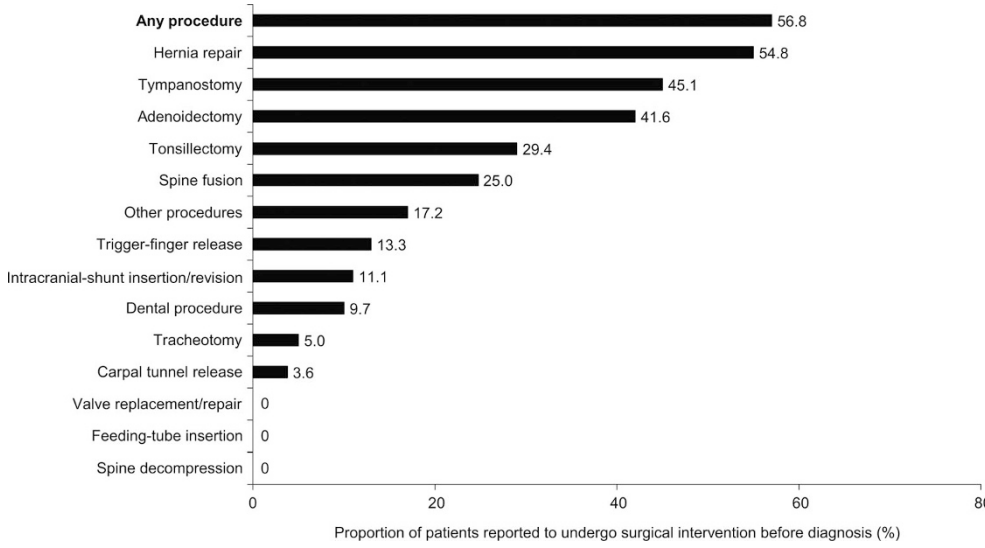

Fig. 3. Proportion of patients in the Hunter Outcome Survey (HOS) in whom the first specified surgical intervention preceded diagnosis. Data are from patients for whom the date of diagnosis of MPS II and the date of the first of the specified type of operation were known (Table 3).

for whom dates of problems with extubation and of diagnosis were available ($n = 13$).

DISCUSSION

Observational studies of patients with mucopolysaccharidoses and several case reports have suggested that patients with MPS II are likely to undergo particular types of surgical intervention.[9,11–14] This is the first study to document surgical histories comprehensively in a large population of patients with MPS II. It shows that more than 80% of the study population from HOS required surgical intervention and that operations were performed commonly before the age of 10 years and often before MPS II was diagnosed.

Surgical intervention is required to address various manifestations of MPS II, including hernias, enlarged tonsils/adenoids, chronic recurrent otitis media, and CTS. There is evidence that some of these manifestations, such as CTS and hernias, are more prevalent in patients with MPS II than in the general population.[4,15–24] In children, the most common cause of CTS is an underlying MPS disorder.[13,25–28] Operable manifestations such as hernias and otitis media are among the first signs and symptoms to occur in patients with MPS II.[4] This raises the possibility that particular surgical histories that differ substantively from those seen in the general population might be used to indicate patients who should be suspected of having MPS II.

There are limited published data on how often surgical interventions typical of MPS II are performed in the general population. In the adult general population, the prevalence of surgical intervention for CTS can be approximated as 0.5%.[20] Prevalence data during childhood are lacking, although CTS is generally thought to be rare in children. This compares with a prevalence of 18.2% in the HOS study population. This is consistent with previous reports suggesting that, in the absence of trauma, MPS disorders are probably the most common cause of CTS during childhood.[28] In the United States and Canada, the prevalence of tympanostomies was <10% in cohorts of children/infants,[29,30] whereas in the HOS study population, it was 51.4%. Persistent umbilical hernias requir-

Table 3 The median length of time between diagnosis of mucopolysaccharidosis type II (MPS II) and the first operation of the type specified in patients in the Hunter Outcome Survey (HOS)

Surgical procedures	Median interval between diagnosis of MPS II and first operation, yr (10th—90th percentiles)	No. patients for whom dates of diagnosis of MPS II and first operation were known
Any procedure	**−0.4 (−4.6 to 4.0)**	**389**
Tympanostomy	0.3 (−2.8 to 3.5)	213
Hernia repair	−0.3 (−5.2 to 7.4)	221
Adenoidectomy	0.4 (−2.1 to 3.5)	226
Tonsillectomy	0.8 (−1.4 to 4.1)	163
Carpal tunnel release	4.4 (0.6 to 11.5)	83
Dental procedure	3.3 (0.1 to 8.5)	62
Intracranial-shunt insertion/revision	5.6 (−0.2 to 11.3)	36
Tracheotomy	6.1 (0.4 to 18.2)	20
Trigger-finger release	2.7 (−1.4 to 7.2)	15
Feeding-tube insertion	9.3 (6.2 to 13.1)	12
Spine decompression	10.3 (0.8 to 31.8)	9
Valve replacement/repair	6.3 (1.1 to 25.6)	8
Spine fusion	6.3 (−0.4 to 17.1)	4
Other procedures	2.9 (−1.3 to 12.5)	128

Negative numbers indicate surgical interventions that precede diagnosis.

ing surgical intervention are rare in the general population.[16,31,32] This is in contrast to the situation with the HOS study population, in which 25.6% of patients underwent repair of an umbilical hernia. The prevalence of inguinal hernia repairs in the general population was <2% in males aged 0–24 years,[33] but in the HOS study population, it was 37.0%. In the normal population, the risk of inguinal hernias was greater in babies born before 36 weeks of gestation than in full-term babies.[16,34] HOS data, in contrast, showed that the prevalence of hernia repair was not significantly different between preterm and full-term infants and, therefore, suggested that the risk of hernias in patients with MPS II was independent of gestational age.

In patients with MPS II, the time delay between the onset of symptoms and diagnosis of disease has implications for disease management.[35,36] One benefit of diagnosing MPS II at a young age is that ERT is likely to be most effective when started early.[5] Prompt diagnosis may also mean that complications during surgical intervention can be avoided.[12,14,37–39] Patients with MPS II who require general anesthesia may experience difficulty or complications with elective intubation/extubation, possibly leading to emergency tracheotomy or even death.[10–12,40] If a patient is recognized preoperatively to have MPS II, a well-prepared team of anesthesiologists and surgeons can be primed for any surgical intervention required and will know to use specific intubation/extubation techniques that are recommended for patients with MPS II. Of the approximately 100 patients in this analysis who experienced difficulties with intubation and/or extubation, a greater proportion had difficulties after diagnosis than before. However, it should be acknowledged that the difficulties reported did not necessarily arise during surgical intervention and that MPS II was probably more advanced in diagnosed patients than undiagnosed patients. Theoretically, earlier diagnosis of MPS II, increased awareness in the medical community of the anesthetic complications associated with the disease, and refined techniques for airway management should all reduce the risks of surgical intervention and anesthesia in patients with the disease.

This study indicates that the majority of children with MPS II undergoing operations will be undiagnosed at the time they are referred to a surgeon. Classically, physicians have been trained to recognize MPS II by the associated phenotype, in particular coarse facial features, joint stiffness, and hepatosplenomegaly. The knowledge gained from the HOS database broadens this list of indicators of MPS II to include early and repeated surgical intervention. HOS data show that a child with an unexplained need for multiple or repeat hernia repair or early adenoidectomy, tympanostomy, or tonsillectomy, particularly warrants investigation for MPS II. This is well illustrated by a case study of a patient enrolled in HOS whose experience of MPS II is typical. The patient had a surgical history of two adenoidectomies, two tympanostomies, and an inguinal hernia repair and a medical history of arthrogryposis and airway obstruction. At the age of 5.5 years, the patient was scheduled for a third tympanostomy, and at this point, an anesthesiologist suspected that the patient might have an MPS disorder. A diagnosis of MPS II was made on referral to a geneticist. Treatment was initiated as soon as possible after diagnosis, and the patient remains stable. Primary-care providers, general and pediatric surgeons, and anesthesiologists have an important part to play in promoting the early diagnosis of MPS II by being aware that patients scheduled for early, unusual, repeat, and/or multiple types of operations should undergo diagnostic testing for the disease. Importantly, it should not be assumed that the need for hernia repairs in preterm babies is necessarily associated only with premature gestational age. Hernia repairs and, in particular, recurrent hernia repairs, could also be related to underlying MPS II.

Knowledge of the pattern of surgical histories performed in patients with MPS II should facilitate improvements in diagnosis, disease management, and anticipatory guidance. This work illustrates that children with MPS II are likely to require tympanostomy, hernia repair, tonsillectomy, and/or adenoidectomy at approximately 3–4 years of age and/or surgical intervention for CTS approximately 4 years later. It was also noted that the interval between diagnosis of MPS II and first operation was relatively long for CTS. This is consistent with CTS being one of the later recognized manifestations of MPS II,[4] although it should be noted that carpal tunnel release was carried out before diagnosis in a small proportion of patients in this study. One reason for the late recognition of CTS may be that the condition is not easily clinically recognized in children,[25,27,41] and it is, therefore, important to assess median nerve conduction in patients diagnosed with MPS II. Furthermore, the risk of a patient having multiple CTS operations necessitates regular follow-up. Long-term monitoring for hernias is also recommended on the basis of the prevalence of repeat hernia operations in the HOS study population. As therapies for MPS II continue to improve, it might be expected that the need for operations addressing connective-tissue involvement will decrease in patients with the disease but that this will be balanced by a greater requirement for those surgical interventions that are indicated in patients with increased activity and lifespan.

Recently, data on surgical intervention in patients enrolled in the MPS I Registry were published.[42] Types of surgical procedure performed in patients with MPS I were similar to those

reported in this study for patients with MPS II. However, common procedures such as hernia repair and adenoidectomy/tonsillectomy were performed at slightly younger median ages in patients with MPS I (hernia repair, 2.5 years; and adenoidectomy/tonsillectomy, 2.8 years) than in patients with MPS II (hernia repair, 3.0 years; adenoidectomy, 3.5 years; and tonsillectomy, 4.3 years). This parallels other clinical data showing that the onset of signs and symptoms occurred earlier in patients with MPS I than in those with MPS II.[35]

To date, no clinical trials of patients with MPS II that include information on surgical intervention have been published. This analysis of longitudinal surgical data on large numbers of patients enrolled in HOS provides a unique insight into the history of surgical procedures that can be expected in patients with MPS II. The study is unavoidably subject to limitations associated with the use of registry data, such as reduced internal validity. There may also be a degree of systematic bias due to the optional nature of data submission to HOS and reliance on accurate reporting. This means that there may be minor errors in the estimates of the prevalence of some procedures. In particular, information entered as free text may be subject to underreporting. Another limitation is that detailed reports of operations were not available in HOS, and thus, it was not possible to tell whether repeat operations for CTS/hernias were performed on the same hand/hernia. Furthermore, it is not possible to rule out data duplication errors in all places, although apparent outlying repeated surgeries were verified with the relevant center. It should also be borne in mind that surgery to implant a venous access system had been carried out in some patients; however, this type of surgery is likely to have been conducted to facilitate treatment and is, therefore, not strictly related to the natural history of the condition. Despite these considerations, the HOS database includes multinational data from patients with a range of disease severities, unlike many retrospective studies on patients with MPS II, which tend to be based on small cohorts from a single country.

CONCLUSION

This analysis suggests that most patients with MPS II will experience at least one operation in their lifetime, often undergoing their first before diagnosis. Earlier diagnosis of this severe potentially life-limiting disease could be facilitated by early recognition of the pattern of surgical histories that are representative of patients with MPS II. Early recognition and diagnosis of MPS II are important to optimize management of the disease, allowing for timely implementation of therapy and for appropriate precautions to be taken before, during, and after any surgical interventions. In addition to increasing awareness of surgical histories that are typical of patients with MPS II, this analysis adds to the current understanding of the natural history of the disease.

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HOS Investigators: Cordoba, Argentina: N. Guelbert; Graz, Austria: B. Plecko; Salzburg, Austria: O. Bodamer; Brussels, Belgium: L. De Meirleir; Fortaleza, Brazil: E. Ribeiro; Porto Alegre, Brazil: R. Giugliani; Rio de Janeiro, Brazil: R. Tavares Boy da Silva; Salvador, Brazil: A. Acosta; São Paulo, Brazil: A. Martins; Sofia, Bulgaria: R. Tincheva; Calgary, Canada: R. Casey; Edmonton, Canada: A. Chan; Toronto, Canada: J. Clarke; Vancouver, Canada: L. Clarke; Zagreb, Croatia: I. Barišić and I. Barić; Prague, Czech Republic: J. Zeman; Copenhagen, Denmark: A. Meldgaard Lund; Lyon, France: N. Guffon; Paris, France: V. Valayannopoulos and B. Héron; Mainz, Germany: M. Beck, G. Schulze Frenking, and C. Lampe; Hamburg, Germany: N. Muschol; Magdeburg, Germany: S. Klose; Berlin, Germany: J. Hennermann; Thessaloniki, Greece: D. Zafeiriou; Budapest, Hungary: Z. Almássy; Dublin, Ireland: E. Treacy; Ancona, Italy: O. Gabrielli; Rome, Italy: C. Feliciani; Padua, Italy: M. Scarpa; Genoa, Italy: M. Di Rocco; Bologna, Italy: A. Cicognani; Monza, Italy: R. Parini; Bari, Italy: F. Papadia; Warsaw, Poland: A. Tylki-Szymanska; Porto, Portugal: E. Leão Teles and E. Martins; Lisbon, Portugal: A. Gaspar; Moscow, Russia: P. Novikov; Barcelona, Spain: M. del Toro and M. Pined; Badalona, Spain: G. Pintos; Badajoz, Spain: E. Galán; Bilbao, Spain: L. Aldámiz; Las Palmas, Spain: M. Marti; Linares, Spain: P. Munguira; Madrid, Spain: L. González; Murcia, Spain: R. Domingo; Palma de Mallorca, Spain: B. de Azua; Salamanca, Spain: A. Hernández; Seville, Spain: D. Lluch; Ourense, Spain: G. Novoa; Valencia, Spain: J. Dalmau; Valladolid, Spain: J. Manuel Muro; Zaragoza, Spain: J. Pérez, A. Baldellou, and C. Alcalde; Stockholm, Sweden: G. Malm and I. Dahlman; Lund, Sweden: D. Papadopoulou; Halmstad, Sweden: N. Nilsson; Gothenburg, Sweden: N. Darin; Taipei, Taiwan: S.-P. Lin; Rotterdam, The Netherlands: A. van der Ploeg; Manchester, UK: E. Wraith, S. Jones, and S. Waldek; Cambridge, UK: U. Ramaswami; Birmingham, UK: C. Hendriksz; London, UK: A. Vellodi; Amersham, UK: UK MPS Society; Houston, TX: C. Eng; Iowa City, IA: S. Copeland; Minneapolis, MN: N. Mendelsohn; Charlottesville, VA: W. Wilson; Norfolk, VA: V. Proud; Baltimore, MD: A. Hamosh; Kansas City, MO: L. Smith; Salt Lake City, UT: D. Viskochil; Omaha, NE: W. Rizzo; Lebanon, NH: J. Moeschler; New York City, NY: G. Pastores; Cincinnati, OH: N. Leslie; Columbus, OH: K. McBride; Seattle, WA: R. Scott; Chicago, IL: B. Burton; Chapel Hill, NC: J. Muenzer; Atlanta, GA: P. Fernhoff; Hartford, CT: R. Greenstein; Oakland, CA: P. Harmatz; Denver, CO: J. Thomas; Miami, FL: P. Jayakar; Phoenix, AZ: K. Aleck; Minneapolis, MN: C. Whitley; Portland, OR: R. Steiner; Sioux Falls, SD: L. Keppen; Washington, DC: C. Tifft; Jackson, MS: O. Abdul-Rahman; Boston, MA: K. Sims; St Louis, MO: D. Grange; Greenville, SC: C. Rogers; and Paterson, NJ: J. Ibrahim.

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