Hunter Syndrome: The Pediatric Surgeon's Point of View

Emmanuelle Seguier-Lipszyc MD[1,4], Keren Kremer MD[1,4], David Hoppenstein MD[2,4], and Yaniv Ebner MD[3,4]

[1]Department of Pediatric Surgery, Meir Medical Center, Kfar Saba, Israel
[2]Department of Anesthesiology, Meir Medical Center, Kfar Saba, Israel
[3]Department of Otolaryngology, Head & Neck Surgery, Meir Medical Center, Kfar Saba, Israel
[4]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Mucopolysaccharidosis type II (Hunter syndrome [MPS II]) is a rare, progressive, lysosomal storage disorder, often diagnosed late due to nonspecific early features and limited clinical awareness.

Objectives: To highlight the role of pediatric surgeons in early recognition based on clinical and surgical presentations.

Methods: We retrospectively reviewed patients diagnosed with MPS II at our institution focusing on presenting symptoms, timing of diagnosis, and factors leading to diagnostic suspicion and treatment.

Results: Four boys were diagnosed between 2012 and 2021. Three were diagnosed at 2.5–4 years of age following typical systemic manifestations. The fourth patient was suspected earlier by a pediatric surgeon, whose prior familiarity with similar reported cases enabled recognition of the clinical pattern and led to an earlier diagnosis.

Conclusions: Increased awareness and clinical familiarity among pediatric surgeons are essential for early recognition of MPS II. Recognition of early surgical patterns, such as hernias and recurrent procedures in early childhood, highlights the role of pediatric surgeons in raising diagnostic suspicion, facilitating earlier diagnosis, and enabling earlier initiation of enzyme replacement therapy before disease progression, ultimately improving clinical outcomes.

IMAJ 2026; 28: 285–288

KEY WORDS: diagnosis, Hunter syndrome (MPS II), glycosaminoglycans, mucopolysaccharidosis type II, surgical intervention

Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is a rare multisystemic X-linked recessive lysosomal storage disorder, almost exclusively affecting males, with a prevalence of approximately 1 in 100,000–170,000 male births [1-3]. This enzyme deficit causes the pathological accumulation of two glycosaminoglycans (GAGs) and dysfunction of many organ-systems in most patients. A great heterogeneity in disease presentation exists and the rate of symptom progression varies widely. Two of the most significant symptoms of variability concern the degree of mental impairment and the expected life span.

If a clinical suspicion of MPS exists, an assessment of increased urinary GAGs is made in case of MPS [4]. The diagnostic for Hunter syndrome is made by blood testing for absent or very low iduronate-2-sulfatase (I2S) activity and a second sulfatase testing is done to rule out multiple sulfatase deficiency [4,5].

Since 2006 an enzyme replacement therapy has existed for MPS II. It is not curative but early treatment before irreversible organ damage is clinically beneficial for these children [3,6,7]. The enzyme replacement does not cross the blood–brain barrier and thus does not prevent encephalopathy. Thus, recognition of Hunter syndrome in early childhood is important, but it requires special attention and experience. The pediatric surgeon is important in this process.

We reviewed cases of patients with Hunter syndrome, who were diagnosed during the past 12 years at our institution, and checked at the age they were diagnosed, why they were suspected of the syndrome, and which surgeries they underwent. These data enabled us to determine more awareness of the role of the pediatric surgeon in suspecting this diagnosis, thus enabling a diagnosis at an earlier age and an earlier enzyme replacement therapy before irreversible organ damage occurred [6,7].

PATIENTS AND METHODS

We retrospectively reviewed the patients who were diagnosed with Hunter syndrome at our institution between 2012 and 2021. We obtained ethics review board approval for the study (0270-25-MMC).

RESULTS

From 2012 to 2021, four boys were diagnosed and treated at our institution [Table 1]. Two brothers were diagnosed: the older at 4 years of age due to dysmorphic facial features and motor difficulties and the younger at 11 months following detection of a bicuspid aortic valve at 2 months old and a family history of Hunter syndrome. The eldest underwent a bilateral inguinal herniotomy at 19 months, a bilateral myringotomy with tube insertion because of chronic serous otitis media at 5 years 10 months, and a recurrent bilateral inguinal herniotomy associated with a recurrent tube insertion at 11 years 5 months. All the surgeries were conducted under general anesthesia without any complications. He has been treated with Elaprase® (Takeda Pharmaceutical Company, Japan) once a week since his diagnosis.

The youngest brother underwent a right inguinal herniotomy at 5 months, a bilateral myringotomy with tube insertion because of chronic serous otitis media at 2 years, a bilateral orchiopexy for small retractile testes, a tonsillectomy and adenoidectomy, recurrent tube insertion at 3 years 6 months, and a left inguinal herniotomy at 3 years 9 months. All the surgeries were conducted under general anesthesia without any complications. He also has been treated with Elaprase® once a week since his diagnosis.

The third boy was diagnosed at 2 years 5 months. He underwent a tonsillectomy with adenoidectomy and a myringotomy with insertion of a tube at 3 years 3 months, an umbilical hernia repair with a recurrent tube insertion at 4 years 4 months, a recurrent tonsillectomy and tube insertion at 5 years 5 months, and a bilateral release of the carpal tunnel at 6 years 9 months. All the surgeries were conducted under general anesthesia without any complications. He has been treated by Elaprase® once a week since his diagnosis but required a desensitivity protocol at 3 years 9 months because of allergic reactions.

A pediatric surgeon suspected Hunter syndrome in the fourth boy after he presented with an umbilical hernia, an incarcerated right inguinal hernia, and otorhinolaryngology problems. Due to an incarcerated right inguinal hernia, the patient underwent surgery at 6 months of age. At 23 months he underwent a tonsillectomy with adenoidectomy, a myringotomy with tube insertion, and an umbilical hernia repair. All the surgeries were conducted under general anesthesia without any complications. He has been treated by Elaprase® once a week since his diagnosis.

DISCUSSION

MPS II, also known as Hunter syndrome, is an X-linked lysosomal storage disorder with a variable clinical presentation and progressive course. Early diagnosis remains challenging due to nonspecific initial features. However, patterns of surgical presentations in early childhood may provide important diagnostic clues [8-10].

Physical manifestations for some people with Hunter syndrome include distinct facial coarse features, a large head, and an enlarged abdomen due to enlarged liver and spleen [11]. Patients with Hunter syndrome may also experience hearing loss, thickening of the heart valves leading to a decline in cardiac function, obstructive airway disease, and sleep apnea. Range of motion and mobility may also be affected. In some cases of Hunter syndrome, central nervous system involvement leads to developmental delays and nervous system problems. Clinical presentation and disease progression in Hunter syndrome vary widely. However, Hunter syndrome is progressive and life-limiting. Approximately two-thirds of patients have the neurological form of the disease with central nervous system involvement and cognitive disorders [2]. Patients with the non-neurological form may survive into the fifth or sixth decade [12].

Table 1. Demographic information of the four patients

Patient	Age at diagnosis	Key pre-diagnostic surgeries	Trigger for suspicion	Diagnosed by
1	4 years	Bilateral inguinal hernia, ENT procedures	Dysmorphic features	Pediatrician
2	11 months	Inguinal hernias, ENT procedures	Family history	Cardiology/Pediatrician
3	2.5 years	ENT procedures + umbilical hernia + CTS release	Clinical progression	Multidisciplinary
4	< 2 years	Umbilical and inguinal hernias + ENT procedures	Surgical pattern recognition	Pediatric surgeon

CTS = carpal tunnel syndrome, ENT = ear, nose, and throat

The symptoms of MPS II are generally not apparent at birth but usually start to become noticeable between 2 and 4 years of age [11]. Because many early signs are common in infancy, they may not initially prompt suspicion or diagnosis of Hunter syndrome by a pediatrician. Coexistence of these symptoms with a high birth weight and recurrent infections of the respiratory tract may suggest MPS II [10].

Umbilical and inguinal hernias are a common reason for Hunter syndrome patients requiring surgery, with a prevalence of approximately 50%, which is much higher than the general population [13]. Hernias are among the first signs and symptoms of Hunter syndrome to manifest [13].

The pediatric surgeon may be one of the first physicians to suspect Hunter syndrome. In the Hunter Outcomes Survey (HOS), most patients (56.8%) underwent at least one surgical intervention before diagnosis of MPS II [13]. HOS data also showed that the median age of the first surgery was 2 years 6 months. In young patients under 3 years, the most repeated surgical procedures were tympanostomy (due to recurrent otitis media), tonsillectomy, adenoidectomy (due to enlarged tongue, tonsils, and adenoids), and hernia repair (umbilical and inguinal). The most common cause of carpal tunnel syndrome in children is an underlying MPS disorder [13]. Because surgery sometimes precedes the diagnosis, it is important for pediatric surgeons and otorhinolaryngology specialists to be familiar with this disease.

A rule of twos was proposed whereby a child under age 2 years with two surgical problems including hernia and surgery for otitis media or sleep disordered breathing should be screened for MPS II [4]. Anesthesiologists will encounter these children before surgical procedures and may be aware of prior relevant surgeries. This screening is important as anesthesiologists may alert surgeons to the possibility of MPS II and initiate screening. In addition, a child with untreated MPS may present with increased risk for anesthesia. The main issues are related to potential difficult with mask ventilation and intubation as well as cardiac dysfunction [14,15].

Molecular genetic testing of the I2S gene is important, especially if there is no family history of MPS II. Once a disease-causing mutation has been identified, all family members should be tested to identify carriers, and counseling should be provided [4,5]. It is recommended that after diagnosis patients are monitored and evaluated every 6–12 months [5].

Treatment of MPS II should achieve improvement of symptoms or prevention of disease progression [16]. Initially, the treatment was only palliative multidisciplinary management of the signs and symptoms. Recombinant human I2S was approved for the treatment of Hunter syndrome in 2006 and is available in the United States, European Union, and other countries. The European guidelines for enzyme replacement therapy (ERT) propose a weekly infusion for a trial period of 6–12 months for all patients with a confirmed diagnosis, regardless of their phenotype [5,17,18]. ERT has been proven to reduce liver and spleen volumes, functional capacity (like walking and pulmonary function), and urinary GAGs levels [17]. The enzyme does not cross the blood–brain barrier and thus has no effect on cognitive and behavioral disorders [5,17]. More recently, because of improvements seen in patients treated at early stages and of reduced mortality, hematopoietic stem cell therapy is considered a therapeutic option for patients with CNS impairment [17,19].

CONCLUSIONS

Early recognition and diagnosis of Hunter syndrome are important to optimize management of the disease. In addition, a positive diagnosis of Hunter syndrome may allow for appropriate precautions to be taken during surgical procedures due to some of the clinical features of the disease, such as short neck, immobile jaw, and pathological changes in the upper airways. Pediatric surgeons and otorhinolaryngologists play an important role in suspecting this disease.

Correspondence

Dr E. Seguier-Lipszyc
Dept. of Pediatric Surgery, Meir Medical Center, Kfar Saba 4428164, Israel
Phone: (972-9) 747-2509
Fax: (972-9) 747-1306
Email: seguiere@clalit.org.il; seguiere@gmail.com

References

1. Bradley LA, Haddow HRM, Palomaki GE. Treatment of mucopolysaccharidosis type II (Hunter syndrome): results from a systemic evidence review. *Genetics in Medicine* 2017; 19: 1187-201.
2. Muenzer J, Beck M, Escolar ML, et al. Multidisciplinary management of Hunter syndrome. *Pediatrics* 2009; 124: e1228-39.
3. Whiteman DA, Kimura A. Development of idursulfase therapy for mucopolysaccharidosis type II (Hunter syndrome): the past, the present and the future. *Drug Des Devel Ther* 2017; 11: 2467-80.
4. Burton BK, Giugliani R. Diagnosing Hunter syndrome in pediatric practice: practical considerations and common pitfalls. *Eur J Pediatr* 2012; 171: 631-9.

5. Scarpa M, Almassy Z, Beck M, et al. Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. *Orphanet J Rare Dis* 2011; 6: 72.
6. D'Avanzo F, Rigon L, Zanetti A, Tomanin R. Mucopolysaccharidosis Type II: one hundred years of research, diagnosis and treatment. *Int J Mol Sci* 2020; 21: 1258.
7. Muenzer J. Early initiation of enzyme replacement therapy for the mucopolysaccharidoses. *Mol Genet Metab* 2014; 111: 63-72.
8. Jezela-Stanek A, Pokora P, Młynek M, et al. Diverse clinical outcome of Hunter syndrome in patients with chromosomal aberration encompassing entire and partial IDS deletions: what is important for early diagnosis and counseling? *Clin Dysmorphol* 2021; 30 (2): 76-82.
9. Ben-Simon-Schiff E, Zlotogora J, Abeliovich D, et al. Hunter syndrome among Jews in Israel. *Biomed Pharmacother* 1994; 48: 381-4.
10. Żuber Z, Kieć-Wilk B, Kałużny Ł, et al. Diagnosis and management of mucopolysaccharidosis type II (Hunter syndrome) in Poland. *Biomedicines* 2023; 11: 1668.
11. Martin R, Beck M, Eng C, et al. Recognition and diagnosis of mucopolysaccharidosis II (Hunter Syndrome). *Pediatrics* 2008; 121 (2): e377–386.
12. Wraith JE, Beck M, Giugliani R, et al. Initial report from the Hunter Outcome Survey. *Genet Med* 2008; 10: 508-16.
13. Mendelsohn NJ, Harmatz P, Bodamer O, et al; Hunter Outcome Survey Investigators. Importance of surgical history in diagnosing mucopolysaccharidosis type II (Hunter syndrome): data from the Hunter Outcome Survey. *Genet Med* 2010; 12 (12): 816-22.
14. Zahra R, Hanindito E, Ramlan AAW, et al. Airway management of Hunter syndrome: a case series. *Bali J Anesthesiol* 2023; 7(4): 251-5.
15. Moretto A, Bosatra MG, Marchesini L, et al. Anesthesiological risks in mucopolysaccharidoses. *Ital J Pediatr* 2018; 44 (suppl2): 116.
16. ZStapleton M, Hoshina H, Sawamoto K, et al. Critical review of current MPS guidelines and management. *Mol Genet Metab* 2019; 126: 238-45.
17. Muenzer J, Botha J, Harmatz P, et al. Evaluation of the long-term treatment effects of intravenous idursulfate in patients with mucopolysaccharidosis II using statistical modeling: data from the Hunter Outcome Survey. *Orphanet J Rare Dis* 2021; 16: 456.
18. Hashmi MS, Gupta V. Mucopolysaccharidosis Type II. 2023 Jul 25. In: Stat Pearls [Internet]. Treasure Island (FL). Stat Pearls Publishing; 2025 Jan.

Capsule

A culprit for chronic kidney disease

Chronic kidney disease is very common all over the world, and its progression is usually irreversible past a certain threshold of renal impairment regardless of the underlying cause. Most cases of chronic renal disease are multifactorial, but there are some proteins involved in monogenic kidney disease that may provide insight into the mechanisms of normal kidney function and kidney disorders. **Isnard** and colleagues focused on one such protein, hepatocyte nuclear factor 1 beta (HNF1B), one of the most common monogenic causes of disordered kidney development. The authors found alterations in HNF1B function in more common types of kidney disease as well and showed that mice with a deficiency of this protein develop kidney disease characterized by aberrant cell cycle reentry and progressive abnormalities similar to those seen in human patients.

Science 2026;392: 269
Eitan Israeli

Capsule

Multicenter gene therapy for OTOF-related deafness followed up to 2.5 years

In this single-arm, multicenter trial conducted at eight centers, by **Jiang** et al. 42 participants (aged 0.8–32.3 years) received adeno-associated virus (AAV) serotype 1 carrying a human *OTOF* coding transgene (AAV1-hOTOF) at three vector dose groups, with up to 2.5 years of follow-up. The primary endpoint was dose-limiting toxicity within 6 weeks. The secondary endpoint assessed efficacy and adverse events. No dose-limiting toxicities were observed. Grade 3 adverse events included decreased neutrophil count. Hearing was recovered in 90% of participants treated with AAV1-hOTOF, with gradual and stable improvement in auditory brainstem response threshold from greater than 97 ± 1 dB normalized hearing level at baseline to 54 ± 3, 51 ± 3, 50 ± 3, and 42 ± 5 dB normalized hearing level at 1, 1.5, 2, and 2.5 years, respectively, and behavioral audiometry improving from greater than 96 ± 3 dB hearing level at baseline to 37 ± 5 dB hearing level at 2.5 years. Participants aged 0.5–18 years showed greater hearing improvement than adults. A higher number of present distortion product otoacoustic emissions at baseline or biallelic non-truncated *OTOF* variants was associated with better hearing recovery. Participants with hearing recovery demonstrated gradual improvement in speech perception. AAV1-hOTOF is well-tolerated and efficacious across a broader patient population, with sustained therapeutic benefits for up to 2.5 years.

Nature 2026 10.1038/s41586-026-10393-y
Eitan Israeli