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Role of the pediatric otolaryngologist in diagnosis and management of children with mucopolysaccharidoses

Stephen M. Wold [a,*], Craig S. Derkay [a,b], David H. Darrow [a,b], Virginia Proud [c]

[a] Department of Otolaryngology-Head and Neck Surgery, Eastern Virginia Medical School, Norfolk, VA 23507, United States
[b] Department of Pediatrics, Eastern Virginia Medical School, Norfolk, VA 23507, United States
[c] Department of Pediatrics, Division of Medical Genetics, Eastern Virginia Medical School, Norfolk, VA 23507, United States

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ABSTRACT

Objective: Mucopolysaacharidoses (MPS) represent a spectrum of disorders characterized by the genetic deficiency of specific lysosomal enzymes occurring in as many as 1 in 10,000 live births and resulting in the accumulation of glycosaminoglycans within cells throughout the body. Children have highly variable, multi-systemic involvement that nearly always involves manifestations of the head and neck including recurrent otitis, hearing loss, upper airway obstruction, and characteristic coarse facial features. This places the otolaryngologist in a prime position for early recognition and initiation of treatment. We sought to examine our own experience in dealing with this diverse and often quite devastating clinical entity.

Methods: Retrospective chart review of children with mucopolysaccharidoses seen in our tertiary care pediatric otolaryngology clinic accompanied by review of the literature.

Results: Nine children were identified – five with Hurler syndrome, three with Hunter syndrome, and one with Maroteaux-Lamy syndrome. The median age of diagnosis/genetics referral was 15 months, while median age of presentation to an otolaryngologist was 12 months. Three patients were referred for genetics evaluation based upon initial evaluation/suspicion by an otolaryngologist. Two were diagnosed early because of an affected older sibling. All patients in the series had varying degrees of hearing loss, recurrent otitis, chronic effusions or abnormal facial features, and all patients required placement of at least one set of ventilation tubes.

Conclusions: Otolaryngologists have an opportunity to play an increasingly integral role in the multidisciplinary approach to the diagnosis and management of many children with mucopolysaccharidoses. Clinical suspicion, early recognition, and prompt diagnosis of these challenging disorders is crucial, as outcomes of treatment in many cases appear time-sensitive, with better results being achieved when intervention is initiated at a younger age or prior to progression of the disease.

1. Introduction

The mucopolysaccharidoses (MPS) represent a clinically diverse group of metabolic disorders within a larger family of genetically inherited lysosomal storage diseases [1]. MPS disorders have an overall incidence reported as anywhere from 1 in 150,000 to as high as 1 in 10,000 live births and are inherited primarily in an autosomal recessive pattern (except for MPS II, which is X-linked) [1–3]. In each of the seven recognized types of MPS (Table 1) there is a specific congenital deficiency of different lysosomal enzymes, though all forms ultimately result in cellular dysfunction from the progressive accumulation of partially degraded glycosaminoglycans (GAGs) within the cells of various body tissues. The primary GAGs (dermatan sulfate, heparan sulfate, keratan sulfate, and hyaluronic acid) are nearly ubiquitous throughout the body; hence clinical manifestations may be quite variable and are often multisystemic. Predominantly a disease of childhood, clinical features are frequently absent at birth, appearing gradually as the disease progresses along an unrelenting course that commonly ends with death before adulthood. A comprehensive description of all these features for each of the MPS disorders is beyond the scope of this paper, as they are well documented elsewhere throughout the literature, though some of the more unifying findings include facial dysmorphism, developmental delay, mental retardation, and skeletal or joint dysplasia, including contractures and characteristic broad hands. Recurrent respiratory and cardiovascular

* Corresponding author at: Eastern Virginia Medical School, 600 Gresham Drive, Suite 1100, Norfolk, VA 23507, United States. Tel.: +1 757 388 6200; fax: +1 757 388 6241.
E-mail address: woldsm@evms.edu (S.M. Wold).

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Table 1
Mucopolysaccharidoses (MPS).

MPS subtype	Enzyme deficiency	Glycosaminoglycan (GAG)
MPS I (Hurler, Hurler–Scheie, Scheie)	Iduronidase	Dermatan sulfate
MPS II (Hunter)	Iduronate-2-sulfatase	Dermatan sulfate
MPS IIIa–d (Sanfilippo)	Sulfamidase, N-acetyl-glucosaminidase, acetylCoA-glucosaminidase acetyltransferase, N-acetylglucosamine-6-sulfatase	Heparan sulfate
MPS IVa, b (Morquio A, Morquio B)	Galactosamine-6-sulfatase, B-galactosidase	Keratan sulfate
MPS VI (Maroteaux-Lamy)	N-acetylgalactosamine-4-sulfatase	Dermatan sulfate
MPS VII (Sly)	B-glucuronidase	Dermatan sulfate
MPS IX (Natowicz)	Hyaluronidase	Hyaluronic acid

complications are also prevalent and likely account for a significant portion of the severe morbidity and mortality associated with these conditions [4,5].

In children affected by MPS disorders, the structures of the head and neck are nearly always involved and often at an early age. As a result, the otolaryngologist is in a prime position to initiate diagnostic workup and referral for definitive testing [2]. In order to further characterize the role of the otolaryngologist, we present herein a series of nine children evaluated in our pediatric otolaryngology practice diagnosed with an MPS disorder (five MPS I – Hurler, three MPS II – Hunter, one MPS VI – Maroteaux-Lamy).

2. Methods

Approval was obtained through the institutional review board at Eastern Virginia Medical School and subsequent retrospective chart review was undertaken to document clinical features, morbidities, and therapeutic interventions including operative procedures, bone marrow transplant, and targeted enzyme replacement. Several representative case presentations are detailed as well to better illustrate these interactions. Where possible, special note was taken of the manifestations that prompted diagnostic workup, the age at diagnosis, the age at first otolaryngology referral, and the incidence of the initial referral for genetic testing being made by an otolaryngologist.

3. Results

The timeline and clinical course of all nine patients examined in the series is summarized in Table 2. The median age of diagnosis by genetic testing was 15 months of age, while the median age of presentation to an otolaryngologist for any reason was 12 months. Presentation to the otolaryngologist preceded diagnosis in at least five patients, and three of the nine (33%) were referred for genetics testing based upon clinical suspicion raised via this encounter. Two patients were ultimately diagnosed, one as early as 10 days of age, because of an affected sibling, and these pairs were the only subjects with positive family history. Otologic concerns including recurrent otitis media and hearing loss were the predominant chief complaints amongst all referrals. Every patient in the series underwent placement of at least one set of tympanostomy tubes for management of persistent/recurrent ear effusions or eustachian tube dysfunction, and in most cases multiple sets (>2) were required for long-term ventilation. Hearing loss was demonstrated on audiogram or ABR in seven patients (78%). Of these, five were mixed-type (71%), one was sensorineural alone (14%), and one was solely conductive (14%). Four patients (44%) exhibited clinically significant upper airway obstruction, though only two were diagnosed with obstructive sleep apnea (OSA) on sleep study. Fortunately, symptomatic improvement was observed in each of these patients following adenotonsillectomy. Two patients had a reported history of particularly difficult intubation, but none of the children in our series required tracheostomy or prolonged intubation at any point in their clinical course. At this point, five patients have successfully completed bone marrow transplantation, the mean age of which was 11.8 months, and there were no failures. One patient has been treated with galsulfase (Naglazyme, BioMarin Inc.) enzyme replacement therapy with overall good results thus far. All patients in the series are still living at the time of this publication.

3.1. Case 1

KD (Fig. 1) is a 7-year-old female initially referred to an outside otolaryngologist at 10 months of age for concern of snoring, witnessed apneas, and recurrent otitis. She was noted at that time to have several coarse facial features, a widened nasal bridge and glossoptosis that roused suspicion for the possibility of an MPS disorder. A referral was made for genetics evaluation and testing which confirmed the diagnosis of Hurler syndrome. Tympanostomy tube placement and adenoidectomy were performed uneventfully at that time. She presented to our office at the age of 4 for progressive hearing loss, ongoing bouts of otitis media, and

Table 2
Summary of Clinical Findings in Nine Children with MPS disorders.

	Diagnosis	Age of diagnosis	Age of ENT presentation	Genetics referral made by ENT	Hearing loss	Ear tubes (sets)	Upper airway obstruction	Age at bone marrow transplant (BMT)/enzyme replacement
K.D.	MPS I	19 months	10 months	Yes	SNHL	Multiple	Yes	None
T.B.	MPS I	13 months	12 months	No	Mixed	Multiple	No	BMT – 26 months
H.C.	MPS I	5 months	3 months	Yes	Mixed	Multiple	Yes	BMT – 8 months
C.G.[a]	MPS I	10 days	16 months	No	CHL	Single	No	BMT – 2 months
H.G.[a]	MPS I	3.5 months	20 months	No	None	Multiple	No	BMT – 6 months
M.S.	MPS II	2 years	<10 years[b]	No	Mixed	Multiple	No	None
A.J.[a]	MPS II	4 years	3 years	Yes	Mixed	Single	Yes	None
B.J.[a]	MPS II	15 months	12 months	No	Mixed	Multiple	No	BMT – 17 months
K.B.	MPS VI	13 years	16 years	No	None	Multiple	Yes	Enzyme – 18 years

[a] Indicates siblings.
[b] Incomplete records fail to identify exact age of first ENT contact.