

Role of the Otolaryngologist in Children with Mucopolysaccharidose; Review

Mukopolisakkaridozlu Çocuklarda KBB Uzmanının Rolü; Derleme

Mukopolisakkaridoz'da KBB'nin Rolü / Role of the Otolaryngologist in Mucopolysaccharidoses

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Özet

Mukopolisakkaridozlar (MPS) nadir bir hastalık grubu olmasına karşın otolaringolojik semptom ve bulgular oldukça yüksektir. Multidisipliner yaklaşımda kulak burun boğaz uzmanı MPS'li çocukların tanı ve tedavisinde tamamlayıcı bir rol oynar. MPS'li çocuklar tipik semptomlar olmadan doğar ve geçen zamanla belirtiler gelişir. Adenotonsiller hipertrofi, otolojik sorunlar ve hava yolu sorunları özellikle otolaryngolojik şikayetler olabilir. Bu makalede MPS hastalarında otolaringolojik sorunlar ve tedavileri değerlendirilmiştir.

Anahtar Kelimeler

Mukopolisakkaridoz; KBB; Adenotonsil Hipertrofisi; Otolojik Problemler; Havayolu Problemleri

Abstract

Mucopolysaccharidoses (MPSs) is a rare group of disorders with a very high percentage of otolaryngologic symptoms and signs. Otolaryngologists play an integral role in the multidisciplinary approach to the diagnosis and management of many children with MPSs disorders. Children with MPSs are born without typical symptoms and develop a variety of symptoms over time. Otolaryngological manifestations of MPSs disorders may be especially considered adenotonsillar hypertrophy, otological problems, and airways problems. Otolaryngologic problems and their treatments evaluated on MPSs patients in this article.

Keywords

Mucopolysaccharidoses; Otolaryngology; Adenotonsillar Hypertrophy; Otological Problems; Airways Problems

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Intraduction

Mucopolysaccharidoses (MPSs) represent a clinically diverse group of metabolic disorders within genetically inherited lysosomal storage diseases [1]. This disorders have an overall incidence reported as anywhere from 1 in 150,000 to as high as 1 in 10,000 live births with geographical differences in the frequencies of specific types [1,2]. Although MPSs are rare, the structures of the head and neck are nearly always involved. As a result, otolaryngologists are commonly the first clinicians to whom these individuals present. Otolaryngological manifestations certainly exert an effect on quality of life issues, perhaps more important is the recognition and management of upper airway obstruction, which may range from varying degrees of obstructive sleep apnea to life-threatening airway emergencies [3]. The aim of this article is to evaluate otolaryngologic problems (hearing, adenoid and tonsil hypertrophy, upper airway obstruction) and their treatments in MPSs patients.

Pathophysiology

MPSs are lysosomal storage disorders caused by deficiency of enzymes involved in the degradation of glycosaminoglycans (GAGs). The primary GAGs (dermatan sulfate, heparan sulfate, keratan sulfate, and hyaluronic acid) are an important constituent of the extracellular matrix, joint fluid, and connective tissue throughout the body [4,5]. This metabolic block leads to the accumulation of GAGs in lysosomes, resulting in cell, tissue and organ dysfunction. Musculoskeletal system, nervous system, heart, lung, eye and otolaryngologic involvement are common effected [3,6]. Hence clinical manifestations may be quite variable and are often multisystem.

MPSs are heterogeneous group of autosomal-recessive disorders (except for MPS II, which is X-linked-recessive) [3]. Seven types have been described to date (Table 1). Each disorder is caused by a deficiency of a specific enzyme required for GAG degradation [3]. It has a continuum of clinical manifestations from mild form to severe. The ubiquitous nature of GAGs in the body's connective tissues gives rise to a wide phenotypic spectrum usually characterized by coarse facial features, liver and spleen enlargement, bone deformities with subsequent reduction of joint mobility, variable mental retardation and cardiac and ophthalmologic involvement [3,7]. 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 [4].

Importance of the otolaryngology

MPS is a rare group of disorders with a very high percentage of otolaryngologic symptoms and signs [6]. Otolaryngologists play an integral role in the multidisciplinary approach to the diagnosis and management of many children with MPS disorders. The most common otolaryngologic complaints of MPS patients are airway problems include obstructive sleep apnea (OSA), otitis media with effusion, sinusitis, frequent respiratory infections, adenotonsillar hypertrophy, irregular nasal septum, turbinate hypertrophy, speech disorders, dyspnea, restricted temporomandibular joint motion, thickened pharyngeal wall, laryngeal abnormalities, tracheomalacia, tracheal stenosis and short neck [3,5,8,9]. Otolaryngological disorders are extremely frequent, mostly in MPS I, II and VI, and are often the earliest clinical manifestations of these diseases [3]. Mesolella et al. [10] concluded that ear, nose and throat manifestations in all types of MPS; in particular, recurrent otitis media was present in 30% of cases, hearing loss in 75% (mixed in 43.33%, conductive in 43.33%, sensorineural in 13.33%), adenotonsillar hypertrophy in 75%, frequent infections of the upper airway in 75% and obstructive sleep apnea syndrome in 45% of cases.

Otolaryngologists are commonly the first clinicians to whom these individuals present [11-13]. Increased awareness of the features of MPS by otolaryngologists will lead to earlier diagnosis. Early diagnosis, as well as having important implications for the affected individual and surgical treatment of processes often significantly enhances the quality of life of these children. They often have a number of the patients undergo adenoidectomy, tonsillectomy or ventilation tube insertion prior to diagnosis the histological examination of the tissue could lead to an earlier diagnosis [12,14]. Children with MPSs are born without typical symptoms and develop a variety of symptoms over time. Otolaryngological manifestations of MPSs disorders may be especially considered adenotonsillar hypertrophy, otological problems, and airways problems.

Otological problems

Hearing loss is often present at the time of diagnosis in nearly all patients with MPS which is characterized by both conductive and sensorineural involvement. Otitis media with effusion (OME) is a recurrent problem in a great majority of patients with MPS [10,13]. It is particularly important to identify and treat hearing loss in MPS, as it has been demonstrated that children with hearing loss in the context of multiple disabilities experience improvements in communication ability, language development, social and emotional development, and behavioral regulation when a hearing loss is actively managed.

Hearing loss was present in literature data, in which the percentage varies from 59.7% to 89%, especially those with MPS I and II [6,15,16]. In this international cohort of patients with MPS II (HOS) over two thirds were identified to have a degree of hearing loss by the age of 5 years, of which 22% had severe hearing loss [11]. Conductive hearing loss (CHL) is usually secondary to recurrent upper respiratory tract infection and serous otitis media, or a deformity of the bony ossicles. MPS patients display an increased risk of otitis media with effusion (OME) due to the pathologic deposition of GAGs in the post-nasal space, eustachian tubes and middle ear [5]. There is some evidence to suggest that tympanomastoid abnormalities may contribute to conductive hearing loss as well. Temporal bone examination in a patient with MPS II and found that there was a marked absence of mastoid pneumatisation, the middle ear cleft was filled with fibrous tissue, and the tympanic membrane was of three to four times normal thickness as the disease progresses, patients with CHL may develop SNHL, resulting in a mixed hearing loss [11]. Motamed et al. [13] reported that young patients often undergo repeated insertions of short-term ventilation tubes before MPS is diagnosed.

Nearly three-quarters of the patients with otolaryngological data in HOS had a positive history of at least one episode of otitis (either acute otitis media or chronic otitis media), and about half had undergone adenoidectomy and/or insertion of ventilation tubes. About 60% of cases experienced improvement in hearing after surgical treatment [11]. Some practitioners may choose to use long-term ventilation tubes when CHL is seen because these patients will likely not outgrow their need for ventilation tubes and because patients with MPS have a substantially increased risk of adverse events when anaesthesia is attempted [17]. Whereas long-term ventilation tubes do

Table 1. Mucopolysaccharidoses syndrome

MPS type	Subtypes	Eponym	Enzyme deficiency	Storage material
MPS I	MPS I H	Hurler	Iduronidase	Dermatan sulphate, Heparan sulphate
	MPS I S	Scheie	Iduronidase	Dermatan sulphate, Heparan sulphate
	MPS I H/S	Hurler—Scheie	Iduronidase	Dermatan sulphate, Heparan sulphate
MPS II		Hunter	Iuronidate sulphate sulphatase	Dermatan sulphate, Heparan sulphate
MPS III	MPS III A	Sanfilippo A	Heparan-N-sulphatase	Heparan sulphate
	MPS III B	Sanfilippo B	N-acetylglucosaminidase	Heparan sulphate
	MPS III C	Sanfilippo C	Acetyl-CoA-glucosaminidase acetyltransferase	Heparan sulphate
	MPS III D	Sanfilippo D	N-acetylglucosamins-6-sulphatase	Heparan sulphate
MPS IV	MPS IV A	Morquio A	Galactosamine-6-sulphatase	Keratan sulphate
	MPS IV B	Morquio B	B-galactosidase	Keratan sulphate
MPS VI		Maroteaux-Lamy	N-acetylgalactosamine-4-sulphatase	Dermatan sulphate
MPS VII		Sly	B-glucuronidase	Dermatan sulphate Heparan sulphate, Chondroitin sulphate
MPS IX		Natowicz	Hyaluronidase	Hyaluronic acid

confer a higher risk of persistent perforation and subsequent chronic otitis media [18].

Sensorineural hearing loss (SNHL) aetiology remains unclearin hovewer it may result from GAGs accumulation in the cochlea, auditory nerve, and brainstem MPS. Excessive GAGs deposition may occur within the cochlear duct, stria vascularis, and cochlear nerve sufficient to disrupt function and result in anywhere from a mild to profound loss bilaterally [19,20]. Although auditory brainstem response (ABR) is an objective test of hearing threshold that does not require the patient's cooperation, the risks of sedation for MPS patients make it difficult to use in routine clinical practice [11]. It is reasonable to conduct an ABR directly after the insertion of ventilation tubes while the patient is still under general anesthesia, but it is known that the results of the ABR in this situation are not as reliable.

Insertion of ventilation tubes can improve CHL resulting from chronic otitis media with effusion but ventilation tubes with or without adjuvant adenoidectomy will obviously not ameliorate SNHL, either alone or as a component of mixed hearing loss [21]. Rehabilitation of hearing loss in MPS disorders may be achieved by fitting conventional hearing aids for mild to moderate conductive, mixed or sensorineural hearing loss. Cochlear implant (CI) is an established method of rehabilitating profound hearing loss in children [22]. However, technique is being developed to facilitate MR imaging in the presence of a CI it is more likely that the risks of surgery and general anesthesia will be considered acceptable

Adenotonsillar hypertrophy

Adenotonsillar hypertrophy is almost universal in this group of patients due to the deposition of GAGs [6]. Therefore, adenoidectomy and tonsillectomy are among the most commonly performed operations in patients with MPS, often prior to diagnosis [12]. Patients with MPS had significantly smaller retropalatal and retroglossal spaces compared to healthy persons [9]. Radiological and endoscopic examination may play an important role by evaluating backward displacement of posterior tonsillar pillars toward the posterior oropharyngeal wall; thus, during endoscopy may determine the percentage of oropharynx tonsils are occupying in sagittal axis [12]. Gönüldaş et al. [6] discovered that most of the tonsillar enlargement was toward the tonsillar bed instead of the lumen in MPS patients; thus indicating that actual tonsil size might be larger than it appeared on oropharyngeal examination. Therefore more careful oropharyngeal examination on MPS patients whose tonsils appear to be grades 1 and 2, because tonsils contribute a lot to airway obstruction.

MPS patients also have odontoid hypoplasia which predisposes them to atlantoaxial dislocation. Therefore, the surgeon has to be careful while inserting mouth gag and extending head on neck during adenotonsillectomy [6]. Tonsillectomy should not be performed on MPS patients with severe mouth opening restriction. In case of possible postoperative hemorrhage intubation of the patient and control of bleeding may be very difficult or even impossible [6].

After adenoidectomy in normal population recurrence rate is between 0.55 and 1.5% [23]; however, the recurrence rate in our MPS population is 56% [6]. Despite recurrence the need for revision surgery is rather low in MPS patients. Althought this mechanism does not appear to explain Monroy at al claimed that recurrent adenoid did not as much obstruct choana as preop adenoid tissue [24].

Upper-airway obstruction

MPS patients have airway narrowing due to GAGs accumulation in airway walls [6,25]. Deposition of the GAGs in the walls of the pharynx and larynx can cause alterations of normal airway function [5]. This changes in soft tissues including tonsils, adenoids, tongue, lingual tonsils, larynx and trachea are responsible for most respiratory problems. As the disease progresses, pharyngomalacia and tracheomalacia may develop and become severe, leading to significant airway obstruction [26]. Additionaly, facial features, predominantly found in MPS I, II, VI and VII, include the macro- and retroglossia and the unfavourable ratio of tongue size to oral cavity predispose to pharyngeal collapse (pharyngomalacia) and obstructive sleep apnea [15].

Involvement of the larynx is almost universal in severe forms of MPS I and II, whereas it is less severe in other forms of MPS [15]. Laryngomalacia, typically caused by the GAGs deposits in epiglottis and arytenoid mucosa was expanded and flaccid, so that it prolapsed into the laryngeal inlet causing glottic stenosis seem to be related to respiratory problems in MPS patients [25]. Hypertrophy of the false vocal cords reduces the glottic space and was one of the reasons for obstructive sleep apnea in MPS patients, but was not related to dysphagia.

OSA evaluation should begin with history and physical examination. However, airway evaluation is very difficult, typically non-uniform among different providers and varies from case to case

the degree of ostruction should be studied with polysomnography and rhino-oro-laryngoscopy. Lin et al. [27] determined 88% moderate to severe OSA, while Yeung et al determined 55% moderate to severe OSA on MPS patients depending on polysomnographic data [28]. Addionaly, Mesolella et al. [10] determined upper airway obstruction in 75% of cases while literature data describes percentages varying from 38% to 48% to 92% [29]. Pelley et al. [30] concluded that symptoms during sleep were not associated with PSG findings, which suggested that this population should undergo routine PSG as early as possible. Adenotonsillectomy is the initial treatment of choice, although it does not always resolve the condition due to the multifactorial origin of the obstruction, with nocturnal noninvasive ventilation being recommended in such cases [5]. Despite adenotonsillectomy being a routine procedure in most children, the risks are usually higher in an MPS child including post-operative hemorrhage, airway edema, and failure to extubate [31]. The initial intervention is often adenotonsillectomy, which may provide temporary improvement. Subsequent steps in MPS patient may include continuous positive airway pressure or bi-level positive airway pressure. Ultimately tracheotomy may be required to relieve severe upper airway obstruction during wakefulness [15].

Tracheotomy

Tracheotomy, which is typically performed for severe upper airway obstruction, may alleviate tracheal narrowing by stenting the component caused by tracheal collapse. Tracheal stenos is also be narrowing of the tracheal lumen due to GAG deposition in the wall and may lead to tracheomalacia [8,32]. With progressive tracheomalacia a regular tracheostomy tube may be insufficient and attempts have been made to bypass the obstruction with longer and wider tracheostomy tubes [8]. These carry the risk of mucosal irritation and injury potentially resulting in granulation tissue and further accumulation of GAG deposits.

Tracheotomy is also a difficult operation in MPS patients; because the neck is short and with neck extension and lowest possible cervical incision the surgeon only reaches cricoid cartilage, thus high tracheotomy is almost unavoidable, carrying the risk of laryngotracheal stenosis [6]. Additionally, MPS patients also have odontoid hypoplasia which predisposes them to atlantoaxial dislocation. Therefore, the surgeon has to be careful while giving the position on head and neck during tracheotomy [6].

Finally, otolaryngologists must be familiar with the symptoms and signs related to MPS. They should have a basic knowledge of MPS in order to avoid the possible complications of otolaryngologic treatments.

Competing interests

The authors declare that they have no competing interests.

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