Taiwan's experience of otorhinolaryngological management in patients with mucopolysaccharidoses

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Abstract

Background: Mucopolysaccharidoses (MPSs) are lysosomal storage disorders in which glycosaminoglycans accumulate due to insufficiency of the enzymes to degrade them. Patients have organomegaly, short stature, and/or intellectual disability. The earliest symptoms are otologic and upper respiratory obstruction and are the main reasons for doctor consultation. Methods: We reviewed 42 patients (30 male and 12 female), with a median age of 20.5 years, who had MPS (16.7% type I, 35.7% type II, 19.0% type IIIB, 21.4% type IVA, and 7.2% type VI). Otorhinolaryngologic manifestations were collected, and quality of life after surgery was documented. Results: Ear, nose, and throat (ENT) symptoms occurred in patients with all MPS types. We found recurrent otitis media in 42.9% of cases. We noted hearing loss in 81.0% (mixed in 45.2%, conductive in 19.0%, sensorineural in 16.7%), adenotonsillar hypertrophy in 76.2%, frequent infections of the upper airway in 47.6%, and obstructive sleep apnea syndrome in 26.2%. Seventy-six percent of patients underwent ENT surgery, including adenoidectomy, tonsillectomy, tympanostomy with ventilation tube insertion, tracheotomy, and supraglottoplasty. Conclusions: ENT surgery reduced the severity of hearing loss, and decreased the degree of symptoms related to upper airway obstruction which improved patients' quality of life.

Keywords

Adenotonsillectomy; tympanostomy; mucopolysaccharidoses; obstructive sleep apnea syndrome; otorhinolaryngological; Taiwan.

What's already known about this topic?

- Ear, nose, and throat (ENT) problems frequently occur in MPS I, II, and VI and are often the earliest clinical manifestations of these diseases;
- Upper airway complications and obstructive sleep apnea (OSA) can be caused by macroglossia, tonsil-loadenoid of hypertrophy stiffness in the upper airway, temporomandibular joints, nasal dysmorphism, flaccid redundant supraglottic soft tissue, and tracheomalacia.
- Infiltration of the cochlear nerve afferents, cochlear nerves and stria vascularis with GAGs causes sensorineural hearing loss;
- Other ENT disorders like persistent copious nasal discharge, chronic recurrent rhinosinusitis, and adenotonsillar hypertrophy often occur in MPS patients.

What does this article add?

- Otorhinolaryngological management is very important for patients with MPS as they have problems of language development and poor quality of life due to the high frequency of ear disorders;

- Although conductive hearing loss can be improved by adenoidectomy and insertion of middle ear ventilation tubes, sensorineural loss is still progression and a problem to be overcome;
- It is necessary to perform adenoidectomy in patients with purulent, recurrent, and chronic symptoms such as otitis media with effusion, snoring and sleep apnea;
- Though tonsillectomy and adenoidectomy can help those with OSA at first, they may need nocturnal oxygen treatment, and even tracheostomy in extreme cases.

Introduction

Mucopolysaccharidoses (MPSs) are one group of lysosomal storage disorders. Most of their inheritance patterns are autosomal recessive, except MPS type II that is X-linked recessive. These diseases are manifestations of a deficiency of the enzymes that break down glycosaminoglycans (GAGs). There are eleven kinds of enzymes deficiency in MPSs, and MPS is classified into seven types (I, II, III, IV, VI, VII and IX) [1,2]. Due to accumulation of GAGs in lysosomes, dysfunction of cells, tissues, and organs occurs. This results in coarse facial features, hepatosplenomegaly, bone deformities with limitation of joint movement, variable intellectual disability, cardiac anomalies, and corneal clouding [3,4].

Ear, nose, and throat (ENT) problems frequently occur in MPS I, II, and VI and are often the earliest clinical manifestations of these diseases [5,6]. As there are abnormal accumulations of GAGs in the middle ear mucosa, nasal mucosa, and eustachian tubes, potential of stiffness and obstruction in eustachian tube was predicted. MPS patients usually have otitis media with effusion (OME), which could cause conductive hearing loss [7,8]. It is also believed that infiltration of the cochlear nerve, afferent cochlear nerve and stria vascularis in cochlear with GAGs causes sensorineural hearing loss [5]. However, most hearing loss patterns of MPS VI patients are conductive [9]. It means that Eustachian tubes play the dominant mechanism with conductive hearing loss in MPS VI. Other ENT disorders such as persistent copious nasal discharge, chronic recurrent rhinitis [10], and adenotonsillar hypertrophy often occur in MPS patients [7].

Upper airway complications and obstructive sleep apnea (OSA) can be caused by macroglossia and stiffness of oropharynx, temporomandibular joint stiffness, nasal dysmorphism, flaccid and redundant supra-arytenoid soft tissue, and tracheomalacia [9-12]. Even though obstructed airways can be improved by conservative treatment, (such as positive airway pressure devices), early adenotonsillectomy, and even tracheostomy may be needed [7,13].

This retrospective study aimed to determine the occurrence of ENT manifestations in MPS patients in Taiwan, and to analyze the prognosis of surgical intervention, including the effect on symptoms and quality of life.

Materials and methods

Ethical compliance

This study was approved by Ethics Committee of the MacKay Memorial Hospital in Taipei, Taiwan.

Study population

Details of 42 MPS patients were reviewed at the Department of Pediatrics, MacKay Memorial Hospital, Taipei between January 2010 and June 2020. They were categorized as MPS I (7 patients, 16.7%), MPS II (15 patients, 35.7%), MPS IIIB (8 patients, 19.0%), MPS IVA (9 patients, 21.4%), and MPS VI (3 patients, 7.2%). There were 30 males and 12 females, with a median age of 20.5 years (range 5 to 40 years). Patients consulted an otorhinolaryngologist for an opinion on the need for surgery at a median age of 5.5 years. All patients were receiving ERT, except MPS III patients, and all were alive at the time of study.

Patient evaluations

Besides polysomnography, those patients who were able to cooperate had flexible laryngobronchoscopy, otoscopy, tympanograms, and audiometry. The following evaluations were carried out: the annual number of upper respiratory tract infections (URTIs) and OME episodes; the degree of adenoid hypertrophy (Grade

1: none of the adjacent structures such as vomer, soft palate and torus tubaris contact with the adenoid tissue; Grade 2: the adenoid tissue contacts with the torus tubaris; Grade 3: the adenoid tissue contacts with torus tubaris and vomer; Grade 4: the adenoid tissue contacts with torus tubaris, vomer and soft palate in resting position) [14]; the degree of tonsillar hypertrophy (Grade 0: absence of tonsillar tissue; Grade 1: within the pillars; Grade 2: extended to the pillars; Grade 3: extended past the pillars; Grade 4: extended to the midline) [15]; the apnea-hypopnea index (AHI, number of obstructive apnea and hypopnea events per hour of sleep), and oxygen saturation (Sat % O_2) to identify obstructive sleep apnea syndrome (OSAS).

We also used the infection score system [16] to evaluate the severity of respiratory tract and otological infections. This includes an evaluation of type of infection, systemic symptoms, daily activity, therapy, hospitalization, and resolution time (Table 1; Total score [?] 5: mild respiratory tract and/or otological infection; Total score 6-11: moderate respiratory tract and/or otological infection; Total score = 12: severe respiratory tract and/or otological infection).

Results

Of the 42 MPS patients, 32 (76.2%) underwent surgery (Table 2), including adenotonsillectomy (20 patients, 47.6%), adenoidectomy only (0 patients, 0.0%), tonsillectomy only (2 patient, 4.8%), insertion of middle ear ventilation tubes (24 patients, 57.1%), tracheotomy (3 patients, 7.1%), and CO2 laser supraglottoplasty (3 patients, total 9 times, 7.1%). All patients had at least one ENT symptom (Table 3). We also found that 15 patients (35.7%) had a history of chronic and recurrent OME ([?] 5 episodes) in a year.

Hearing loss (demonstrated by pure tone audiometry) was noted in 34 patients (81.0%, 5 in MPS I, 14 in MPS II, 4 in MPS IIIB, 8 in MPS IVA and 3 in MPS VI). Nineteen patients (42.5%) presented with mixed type hearing loss, 8 patients (19.0%) had conductive hearing loss, and 7 patients (16.7%) had sensorineural hearing loss. There were 34 cases (81.0%) with adenoid hypertrophy (degree [?] 2), and 34 cases (81.0%) with tonsillar hypertrophy (degree [?] 1). Twenty patients had been underwent polysomnography and eleven of them (55.0%) were diagnosed of OSA. The AHI ranged from 17.6 to 83.1.

Thirty-two patients (76.2%) underwent surgical treatment. Figure 1 showed the comparison between ENT manifestations before and after surgery. According to the infection score system, improvements in the severity of respiratory symptoms and ENT infections were seen after surgery (mean infection score before surgery 5.8 ± 1.6 *vs* . 3.8 ± 0.9 after surgery, $p < 0.05$). Nine patient (60.0%) still showed evidence of OSA after adenotonsillectomy due to macroglossia and dysmorphism. No patients had died at the time of writing.

Discussion

To the best of our knowledge, this is the first report to describe the otorhinolaryngological management in Taiwanese patients with MPS. Our results emphasize that otorhinolaryngological management is important for patients with MPS as they have problems of language development and poor quality of life due to the high frequency of ear disorders [17]. For better prognosis of MPS, it is important to treat in early stage. The otorhinolaryngologist and audiologists play important roles in follow-up and treatment of MPS patients. Patients need better and long-term follow-ups due to high incidence of recurrent serous otitis media with conductive hearing loss and progress to sensorineural hearing loss.

In previous studies, an average of 75% of cases (range 59.7% to 89%) have hearing loss [18]. Various types and degrees of hearing loss can be seen in MPS patients [7-8, 19-21]. Conductive hearing losses are more common in MPS patients due to frequent chronic middle ear effusion and Eustachian tube dysfunction. The incidence and etiology of sensorineural hearing losses are unknown [7]. In our study, conductive hearing losses are more than sensorineural hearing losses (19.0% v.s. 16.7%). Although conductive hearing loss can be improved by adenoidectomy and tympanostomy with ventilation tube [21], sensorineural hearing loss is still a problem to be overcome. In our study, 34.3% of patients had improved hearing after surgery. Besides, according to the infection score system, we noticed that the severity of respiratory tract and otological infections improved after ENT surgery. It may cause by the improvement of adenoid hypertrophy, tonsillar hypertrophy and OME with decreased infection risk.

Ventilation tubes are advised to apply in MPS patients with recurrent OME and hearing loss. However, some families rejected to undergo ventilation tubes insertion because they were afraid of the risk of general anesthesia during operation. In some cases, the operation was very difficult or impossible because of the severe deformity of external ear canal that the ear drum was difficult to approach. And in some cases, we advised patients to apply hearing aids, but the socioeconomical inadequacy made them hard to come to follow-ups and obtain these aids. This is the reason that some patients still have conductive hearing loss after ERT. Besides, ERT could not improve sensorineural hearing loss [22].

Whereas otologic problems influence the quality of life, upper airway obstruction can cause serious morbidity and mortality. Most respiratory problems are caused by the changes of soft tissue of the tonsils, adenoids, tongue, lingual tonsils and the stiffness of oropharynx and temporomandibular joint. Oropharyngeal stiffness and collapse become severe when the disease deteriorates and can cause significant airway obstruction [23]. The degree of upper airway obstruction may range from OSA to life-threatening airway emergencies, and airway evaluation is necessary and challenging. The results of airway examinations vary in case-by-case patients [24]. In our study, the upper airway obstruction (patients who had stridor, suprasternal retractions, and change of voice) rate was 76.2%, compared with 38% [20], 48% [18], and 92% [25] in other studies. All types of MPS patients had similar symptoms. Consequently, it is necessary to perform adenoidectomy in patients with purulent, recurrent, and chronic symptoms such as OME, snoring and sleep apnea [14]. Though tonsillectomy and adenoidectomy can help those with OSA at first, they may need nocturnal oxygen treatment, and even tracheostomy in advanced cases [26]. Anesthetic risks increase in patients with MPS because they have macroglossia, temporomandibular joint stiffness, difficult or failed intubations, abnormal laryngeal anatomy, trachea deformity and subglottic narrowing [27, 28]. Before surgery, these patients need examination using a flexible bronchoscope to survey the exact extent and severity of airway obstruction [7, 9].

The patient history and physical examination are necessary for evaluation of OSA initially, but the degree of obstruction before and after surgery should be studied by polysomnography and laryngobronchoscopy [25,29]. In our study, 28.6% of our patients still had OSA after adenotonsillectomy due to macroglossia and oropharyngeal stiffness. This condition is also found in other OSA patients without MPS. The reason may be that even though the structure and the tension of upper airway improved after surgery, it could deteriorate after years. We should also pay attention to whether the dose of ERT is enough or not. ENT care and airway evaluations should be provided before we take these patients to the operation room and it could provide more safe intubation and extubation. Choosing the suitable size of endotracheal tube and the method of intubation potentially decrease the risk of complications related to intubation during general anesthesia and surgery [30].

This study has several limitations. We had only 42 patients in this study because they had complete medical histories of otorhinolaryngological treatments. Besides, we did not perform sleep studies in every patient because this study was designed for medical retrospect. It is necessary to complete their examinations in the future. It is also needed to evaluate the quality of life of patients formally by visual analogue scale (VAS) as previous study [16].

Conculsion

The high incidence of ENT problems in MPS patients means that ENT surgery is still a fundamental treatment to help resolve OME to improve hearing acuity, and to relieve upper airway obstruction. ENT surgery can improve the quality of life of patients with MPS.

Author Contributions

C.-L.L. performed data acquisition, statistical analyses, data interpretation, and drafted the manuscript. K.-S.L., S.-P.L. and H.-Y.L. participated in the study design and data interpretation and helped to draft the manuscript. C.-K.C. performed biochemical analyses and revised the manuscript. C.-H.S., H.-C.C. and R.-Y.T. were responsible for patient screening and revised the manuscript. All of the authors have read and have approved the final manuscript.

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Figure 1: Comparison between otorhinolaryngological manifestations before and after surgery (OSAS, obstructive sleep apnea syndrome; AHI, apnea-hypopnea index; URTI, upper respiratory tract infections).

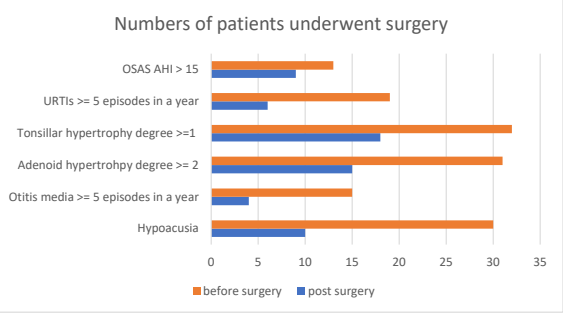

Table 1: Total score ≤ 5: mild respiratory tract and/or otological infection; Total score 6-11: moderate respiratory tract and/or otological infection; Total score = 12: severe respiratory tract and/or otological infection.

		Score
Type of infection	Rhinitis	0
	Rhinitis + otitis and/or tonsillitis	1
	Pneumonia	2
Systemic symptoms	Absent	0
	Slight fever and/or some aches	1
	Definite elevation of temperature	2
Daily activity	Not limited	0
	Some limitation	1
	Severely incapacitated	2
Therapy	Local	0
	Systemic (oral administration)	1
	Systemic (intravenous administration)	2
Hospitalization	No	0
	Single entry followed by home therapy	1
	Admission	2
Resolution	< 7 days	0
	7-10 days	1
	> 10 days	2

Table 2: Surgical procedures performed

Patients	Adenoidectomy	Tonsillectomy	Adenotonsillectomy	Insertion of middle ear ventilation tubes	Tracheotomy	Laser supraglottoplasty
2					x	x
4			x	x	x	x
5			x	x		
6			x			
7				x		
8		x		x		
9			x	x		
10				x		
12				x		
14			x	x		
15			x			
16			x	x		
17			x	x		
18			x	x		
19			x	x		
20				x		
21			x	x		
22			x	x		

Table 3: Otorhinolaryngological manifestations of 42 patients with mucopolysaccharidoses (MPSs) before and after receiving any ENT surgeries.

(URTI, upper respiratory tract infection; OSAS, obstructive sleep apnea syndrome; AHI, apnea-hypopnea index.)

Patient	MPS	Age	Gender	Numbers of otitis media episodes per year	Hypoacusia	Degree of adenoid hypertrophy before surgery	Degree of adenoid hypertrophy after surgery	Degree of tonsillar hypertrophy before surgery	Degree of tonsillar hypertrophy after surgery	Numbers of URTI episodes per year	OSAS AHI
1	I	39	male	3	sensorineural	1	No surgery	0	No surgery	2	29.1
2	I	28	female	5	normal	2	2	0	0	5	
3	I	40	male	2	sensorineural	1	No surgery	0	No surgery	4	
4	I	7	female	7	sensorineural	4	3	2	1	6	
5	I	7	female	6	mixed	4	3	2	0	5	
6	I	19	male	2	normal	2	1	2	1	1	49.8
7	I	21	male	3	conductive	4	3	3	2	3	
8	II	26	male	1	mixed	2	1	2	0	3	
9	II	23	male	5	mixed	3	1	2	0	7	
10	II	29	male	3	sensorineural	2	1	1	1	1	
11	II	27	male	1	mixed	1	No surgery	1	No surgery	2	
12	II	31	male	3	mixed	2	1	2	1	3	56.1
13	II	26	male	4	mixed	1	No surgery	1	No surgery	3	
14	II	16	male	6	mixed	3	2	3	2	6	
15	II	26	male	8	mixed	3	2	3	1	8	