Hearing Evaluation of Mucopolysaccharidosis patients and Effectiveness of Enzyme Replacement Therapy: A cross sectional study

Original Article

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ABSTRACT

Background: Mucopolysaccharidosis (MPS) are disorders which result from enzymes deficiencies which are responsible for breakdown of glycosaminoglycans (GAGs). The impact of MPS on various body systems is well-documented, including the skeletal, cardiovascular, and respiratory systems, while the effects on hearing function and the efficacy of enzyme replacement therapy (ERT) in preserving hearing remain less explored.

The rationale of our study is the need for a comprehensive understanding of hearing impairment in pediatric MPS patients, including its prevalence, characteristics, and response to ERT and this can contribute to early detection, appropriate intervention, and improved quality of life for these patients, ultimately enhancing their overall healthcare management and outcomes.

Patients and Methods: This study was carried out in the Audiology clinic to evaluate hearing profile in cases of MPS. Data were collected by reviewing past medical records. All cases had a confirmed diagnosis of MPS by using a dry peripheral blood spot on filter paper, to determine the activity of the deficient enzyme and confirmed by mutational molecular analysis. All cases had audiological evaluation including pure tone audiometry (PTA) and auditory bainstem responce (ABR).

Results: Our data demonstrates that among the 16 participants, about 75 % had hearing loss using PTA and ABR. About 25 % of those who received ERT had normal hearing.

Conclusion: We conclude that MPS can cause different types of hearing loss ranging from mixed (MHL), conductive (CHL) and sensorineural (SNHL) and that ERT can improve hearing status among these patients.

Key Words: Auditory brainstem responses, enzyme replacement therapy, Hearing loss, mucopolysaccharidosis.

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INTRODUCTION

Lysosomal storage diseases (LSDs) are rare disorders due to accumulation of macromolecules within the lysosomes. This accumulation is due to deficient activity of lysosomal enzymes which participates in the breakdown of proteins, carbohydrates, and lipids resulting in cellular dysfunction and clinical abnormalities. MPS is one of LSD which results from the excessive storage and GAGs[1].

Classification of Mucopolysaccharidosis depends on the differences between the cumulative GAGs and deficiency of the enzyme. All types are inherited in an autosomal recessive (AR) manner, but only MPS type II is inherited in an X-linked recessive manner[2]. The natural history of disease in MPS patients is progressive and multisystem. Most patients are asymptomatic at birth, symptoms usually appear in infancy or early childhood, but diagnosis is often delayed, and therapeutic intervention and treatment including Hematopoietic stem cell transplantation or enzyme replacement therapy (ERT), are also delayed in most types[3,4]. There are several different subtypes of MPS, each with its own unique clinical features.

MPS I (Hurler, Hurler-Scheie, and Scheie syndrome): Coarse facial features (thick lips, enlarged tongue, prominent forehead), Skeletal abnormalities (short stature, joint stiffness, kyphosis, scoliosis), Progressive organ involvement (hepatomegaly, cardiomyopathy, respiratory issues), Intellectual disability and developmental delay, Corneal clouding, Hearing loss, Enlarged spleen

MPS II (Hunter syndrome): Coarse facial features, Skeletal abnormalities (joint stiffness, dysostosis multiplex) Progressive organ involvement (hepatomegaly, cardiomyopathy, respiratory issues), Neurological

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symptoms (developmental delay, intellectual disability, behavioral problems), Hearing loss, Enlarged spleen and liver.

MPS III (Sanfilippo syndrome): Progressive neurodegeneration leading to severe cognitive decline Behavioral problems, hyperactivity, and sleep disturbances, Coarse facial features, Skeletal abnormalities (joint stiffness, scoliosis), Enlarged liver and spleen, Hearing loss, Seizures.

MPS IV (Morquio syndrome): Skeletal abnormalities (short stature, spinal deformities, joint laxity), Enlarged liver and spleen, Reduced mobility and joint pain, Respiratory problems, Corneal clouding, Hearing loss, Normal intelligence (usually not associated with intellectual disabilities).

MPS VI (Maroteaux-Lamy syndrome): Coarse facial features, Skeletal abnormalities (short stature, dysostosis multiplex, joint stiffness) Hepatomegaly, Respiratory problems, Corneal clouding, Hearing loss, Normal intelligence (usually not associated with intellectual disabilities).

Diagnosis is suspected clinically such as coarse facial features; skeletal deformities, corneal clouding, short stature; retinopathy, noisy breathing; chronic nasal congestion, glaucoma; hepatosplenomegaly; hearing deficits, spinal deformity (scoliosis, kyphosis, lordosis); and brain involvement with progressive cognitive delay[5].

Ear, nose and throat (ENT) disorders are extremely common in patients with MPS[6]. The affection on hearing can be classified into sensory neural hearing loss (SNHL), conductive hearing loss (CHL), or mixed (MHL). Each type of MPS has a specific type of hearing loss[3]. It was found that in most MPS I, III, IV and VI patients, deficits are conductive in nature which is usually due to persistent upper respiratory tract infection, deformity of the bony ossicles or otitis media[7]. An unresolved mesenchyme is consistently noticed in nearly all previous reports of MPS in the temporal bone culture. There is relationship between existence of unresolved mesenchyme at the neonatal period and acute and silent otitis media and with other anomalies of the ear[8].

The etiology of SNHL is mostly due to infiltration of the stria vascularis, cochlear duct and cochlear nerve afferents. Also, it may be due to pilling up of GAGs in the cochlea, nerve, aural and brainstem. This type of hearing loss is the most common type found in MPS type II[9].

Unlike other MPS types, patients with MPS IX do not exhibit hearing loss among the few known reported cases. Although it was reported that the first patient with MPS IX had frequent episodes of otitis media, the patient did not exhibit hearing loss or any speech and language issues. No hearing issues were found in the other three cases of MPS IX[10].

Before development of ERT, management was attributed just to control symptoms, but now ERT has a good effect on improvement of symptoms in patients with variable MPS types who have mild manifestations on central nervous system. Recently, research work on Hematopoietic stem cell transplantation (HSCT) is the only way that shows long-term neurocognitive and metabolic improvement[11].

Rationale

The rationale of this study was to:

* Reveal the impact of MPS deficits on the auditory system.

* Evaluate the response of ERT on the hearing profile in those patients.

PATIENTS AND METHODS:

This cross section study was carried out in the audiology clinic to evaluate hearing profile in cases of MPS diagnosed and treated in the period from January to November 2022. Our study participants were 16 patients who were referred from outpatient genetic clinic of Mansoura University Children Hospital. Data were collected by reviewing past medical records, the study was approved by the institutional Research Board of Medical Faculty of Mansoura University, Egypt (Code Number: R.21.09.1446.RI). A written informed consent was obtained from legal guardians of all study participants.

All cases had a confirmed diagnosis of MPS by using a dry peripheral blood spot on filter paper, to determine the activity of the deficient enzyme and confirmed by mutational molecular analysis. At fixed intervals, Clinical surveillance visits were contracted and evaluations were collected by a clinical geneticist. At each visit, the anthropometric measurements (weight, height, and body mass index) were taken. The change or improvement in the clinical features specific to MPS including coarse facial features, pulmonary, ophthalmology, cardiac, skeletal and nervous system involvement were documented. Determination of Cardiac status was performed by electrocardiograms and echocardiography.

The specific dose and mode of administration of enzyme replacement therapy (ERT) in mucopolysaccharidosis (MPS) can vary depending on the specific MPS subtype, the enzyme being replaced, and the individual patient's characteristic and ERT is typically administered intravenously through regular infusions at our metabolic unit weekly and this replacement therapy for life.

Audiometry and tympanometry were performed for hearing loss. Radiological examination was performed on skull, chest, pelvis, long bones, and spine. From our participants eight patients were on ERT.

Patients with different middle ear disease as perforated drums, otosclerosis, patients with earache, hereditary hearing loss, otorrhea, acoustic trauma, ear trauma, trauma in skull or neck or operation of the middle ear, head and neck anatomical abnormalities and diabetes mellitus were excluded from our study .

Determination of recruited subjects in this study was carried out as reported by Khan *et al*., 2017. Applying the following equation proposed by[12]:

$$\text{Sample size}=\frac{(Z_{1-\alpha/2})^2 p(1-p)}{d^2}$$

$Z_{1-\alpha/2}$=Standard normal variable=1.96

P=expected share =1%

d=Absolute error or precision=0.05

By applying the previous figures to the equation, the minimum sample size was 16.

Audiological Estimation

1. Pure tone audiometry (PTA): Conducted in an acoustically treated room such that the maximum background noise level under European Economic Community law is not exceeded. PTA testing was performed using a clinical audiometer Madsen Itera 2 (Natus, Denmark). The measurement was performed by the ascending order method (Hughson-Westlake, up 5, down 10 method). The air conduction threshold is estimated to be between 250 and 8000 hertz (Hz). Hearing threshold was calculated in dBHL from 0.5 to 4 kHz. The audiogram classification was based on WHO criteria. Normal hearing loss (≤25 dBHL), mild hearing loss (26-40 dBHL), moderate hearing loss (41-60 dBHL), moderately severe hearing loss (61-80 dBHL), and severe hearing loss (≥81 dBHL).

2. Tympanometry: It was performed using an Interacoustics AT 235 impedance audiometer (Interacoustic, Assens, Denmark). Patients were instructed to swallow 8-10 times to compensate for the overpressure or underpressure caused by the tympanic membrane of the middle ear. Type A tympanograms were found in all cases.

3. Acoustic reflex (AR): Ipsilateral AR was measured at 500, 1000, 2000, and 4000 Hz using an Interacoustics AT 235 impedance audiometer (Interacoustic, Asens, Denmark). The intensity started from 70–80 dB HL to 105 dB HL in 5 dB steps until the acoustic reflection threshold was reached.

4. Auditory brainstem responses (ABR): Responses are evoked by 0.1 ms clicks that alternate polarity with decreasing intensity in 10 dB steps from 90 dB nHL across the onset of ER3A. The electrode structure was A1/A2-Cz-Fpz. electrode impedance <5 kOhm; thresholds were obtained by visually inspecting wave V starting from 90dBnHL down to the minimum detectable amplitude. For younger children, this procedure was performed during spontaneous sleep. In some cases, they were acquired during the sedation required for MRI imaging. The criteria for marking a reaction as "abnormal" are:

O Main III wave peaks were absent.

O Increased peak latencies compared to normative data for corresponding age groups in hearing services.

O Increased interpeak delay (IPI) compared to standard data.

O Interaural delay difference > 0.20 ms.

Statistical analysis

Data were analyzed using the statistical package for the social sciences (IBM Corp. Published 2017. IBM SPSS Statistics for Windows version 25.0. Armonk, NY: IBM Corp.). Chi-Square examined the relationship between 2 qualitative variables. Pearson and spearman correlations were done for parametric and non-parametric correlations respectively. It would be significant if *P value* less than 0.05.

RESULTS:

Our study registered 16 MPS patients with age about 9 y (1.5-17y), In (Table 1 and Figure 1) all demographics are demonstrated.

Among our participants, four patients (25%) had normal hearing and 12 of them (75%) had hearing loss regardless type. This means a significant correlation between MPS and hearing loss (*P* value= 0.077).

Regarding otoscopy, tympanometry and acoustic reflex, three cases (18.5%) of our patients had normal otoscopy, type A tympanogram and acoustic reflex, i.e., normal middle ear function, while 13 (81.5%) had retracted tympanic membrane, and type B tympanogram and absent reflexes which means affected middle ears. A significant *P* value (0.021) was found between MPS and middle ear affection (Table 2).

Regarding effect of ERT on hearing, we found six cases (75%) out of 8 who didn't receive ERT yet, having hearing loss regardless type. Also, six cases (75%) were found having hearing loss under different ERT durations. *P* value was 0.289

Regarding effect of ERT on otoscopy, tympanometry and tympanometry, we found all the eight cases (100%) who didn't receive ERT having retracted TM, type B tympanogram, absent AR. Also, six cases (75%) out of eight who were on ERT were found having retracted TM, type B tympanogram, absent AR under different ERT durations. *P value* was 0.131. (Table 3).

ERT: Enzyme replacement therapy; TM: tympanic membrane, AR: acoustic reflex.

Regarding effect of ERT on PTA cases, all cases not received ERT had hearing affection, while in those received ERT, four cases (57.1%) had normal hearing (*P value*= 0.031).

Effect of ERT on ABR cases showed that one case out of 3 cases (33.3%) showed hearing affection in those cases not received ERT, while the only case received ERT, (100%) had normal hearing (*P value*= 0.248). (Table 4).

Among six treated cases, there was no significant correlation between treatment durations and different PTA frequency thresholds. (Table 5).

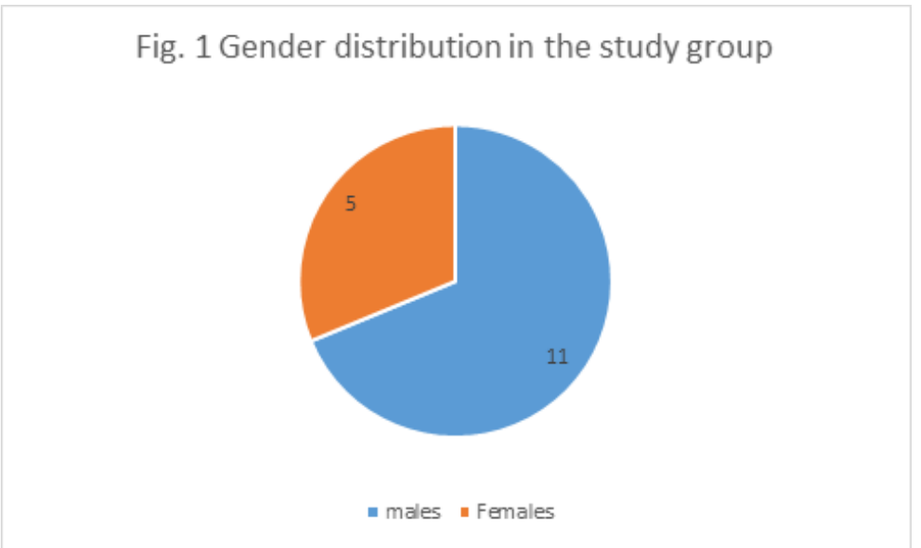

Table 1: Age and duration of patients who received ERT in the study group:

Age in years	Median (min-max)	9 y (1.5-17y)
Patients with MPs on ERT (No. & %)		8 (50%)
Duration of ERT in patients who received	Median (min-max)	5.5 months (2-48)

MPS: mucopolysaccharidosis, ERT: enzyme replacement therapy.

Table 2: Correlation between MPS and hearing loss.

		No.	Percent%	*P value*
MPS cases (n=16)	Patients with normal hearing	4	25.0	0.077
	Patients with hearing loss	12	75.0	
	Patients with normal TM, type A tympanogram and having AR	3	18.5	0.021
	Patients with retracted TM, type B tympanogram and absent AR	13	81.5	

MPS: mucopolysaccharidosis, TM: tympanic membrane, AR: acoustic reflex

Table 3: Correlation between ERT and hearing, otoscopy, tympanometry and acoustic reflex.

		No.	Percent %	*P value*
No ERT	Normal hearing	2	25.0	0.289
	Affected hearing	6	75.0	
On ERT	Normal hearing	2	25.0	
	Affected hearing	6	75.0	
	Retracted TM, type B tympanogram, absent AR	8	100	0.131
	Normal TM type A tympanogram, AR	2	25	
	Retracted TM, type B tympanogram, absent AR	6	75	

ERT: Enzyme replacement therapy; TM: tympanic membrane, AR: acoustic reflex.

Table 4: Effect of ERT on PTA and ABR.

		Frequency	Percent	*P value*
No ERT	Normal PTA	0	0	0.031
	Affected PTA	5	100%	
received ERT	Normal PTA	4	57.1	
	Affected PTA	3	42.9	
No ERT	Normal ABR	2	66.7	0.248
	Affected ABR	1	33.3	
received ERT	Normal ABR	0	0	
	Affected ABR	1	100	

ERT: Enzyme replacement therapy, PTA: pure tone audiometry, ABR: auditory brain stem response.

Table 5: Correlations between treatment duration and different frequencies of PTA.

	250.Hz	500.Hz	1000.Hz	2000.Hz	4000.Hz
Correlation Coefficient	.687	.258	.563	.687	.652
Sig. (2-tailed)	.132	.622	.245	.132	.161
N	6	6	6	6	6

**. Correlation.is.significant.at the 0.01 level (2-tailed). *. Correlation is significant at.the 0.05.level (2-tailed).

DISCUSSION

Mucopolysaccharidosis is a group of rare lysosomal storage defects. MPS were divided into seven subtypes due to deficiency of some enzyme that are involved in degradation of GAGs[13]. Hearing improvement can occur after Hematopoietic stem cell transplant (HSCT) [14]. Ossicular chain abnormalities and thickening of tympanic membrane are considered precipitating factors that causes CHL[15,16]. On the other hand, the pathogenesis of the sensorineural component in all recognized subtypes is thought to result from the loss of cochlear outer and inner hair cells[17]. Accumulation of GAGs can lead to damage to inner ear structures. Abnormalities of the organ of Corti, Reisner's membrane, stria vascularis, and vestibulocochlear nerve were also observed[18].

We have studied 16 cases diagnosed as MPS cases with enzyme essay and confirmed with molecular study, eight cases (50%) were diagnosed as MPS type I (4 of them were on ERT), 3 cases were MPS type II (18.75%), two brothers were MPS type IV (12.5 %), and two sisters were MPS VI (12.5%). Eight cases were on ERT while other eight cases haven't been started treatment yet. Two cases with MPS (type I) were on hearing aids one of them was SNHL and the other was chronic otitis media, they have been receiving ERT for 4 years and now they have only mild hearing affection. None of our patients had received ventilation tubes, they were all on otitis media medications and on ERT.

In our study, the relation between hearing alterations in MPS patients and effect of ERT on hearing were studied. About (75%) of patients had hearing loss that was mostly conductive in nature, and this meets with by Papsin *et al*, 1998[19] who reported that 63.6% of MPS patients had CHL and history of recurrent otitis media, supporting our data. Also, another study performed by Murgasova *et al*., on 61 MPS patients reported HL in 53% of patients and CHL was the most common type. Recurrent rhino sinusitis, and acute otitis media were recorded in 77%, 49% of patients respectively[20].

CHL was easily diagnosed in cases where PTA were used as both bone and air conduction thresholds were measured. Twelve cases underwent PTA, six of which had CHL and two had MHL. But concerning ABR cases which were four cases, two of which were affected, hearing loss was detected with latency shift of wave V, also these cases had type B tympanogram and retracted TM from which we anticipate the presence of air bone gap and this was found also in study of Kariya *et al*, 2012[18]. A high ratio (33%) of retraction in tympanic membrane was found. Unfortunately, we couldn't assure the exact hearing loss type either mixed or conductive as bone conduction ABR was not available.

Factors have been considered important in causing CHL were Eustachian tube dysfunction, middle ear effusion and thickening of the middle ear mucosa due to GAGs accumulation.

Other factors that cause CHL include hypertrophy of the middle ear and Eustachian tube mucosa, presence of middle ear effusion, inflammation/ infection, retention of mesenchymal tissue, mucosal epithelium and ciliary body disorders. This was the case in our patient, possibly including Eustachian tube lysis. Temporal and ossicular lesions, recognizable by large confluent lacunae[21]. The improvement of air conduction after ERT might be due to improvement of chronic otitis in young age children and due to the helpful impact of ERT specially on the mucosal tissue, that cause decreasing in number of otitis attacks.

Only one case had SNHL, but the definite mechanism of SNHL not exactly known, however Silveira *et al*., 2018[22] described inner ear affection in six postmortem MPS patients. The organ of Corti was affected in MPS patients in relation to norms, with a decreased number of hair cells. Histopathological animal studies on inner ear changes have shown similar results. It is unclear to what extent HCT alters these changes in the inner ear of patients. In a study by Bicalho *et al*., 2021[21], they stated that most of patients having MPS types, I, II, III, IV & VI had mixed and conductive hearing loss of mild to moderately severe degrees, type B tympanogram and absent reflexes. In contrast, Ahn *et al*., 2019 conducted a study on 124 MPS patients and reported that the most common type of hearing loss was SNHL. Also, they reported that the change in hearing level was not correlated with duration of ERT[23].

MPS are rare diseases, so there is small number of results in this study, which is considered a limitation. Furthermore, after ERT, hearing assessment is used to diagnose the degree of hearing loss early, start treatment for hearing loss, and ensure that these patients are likely to achieve adequate speech, language development, and academic performance. The results obtained in this study demonstrate the importance of hearing assessment in children diagnosed with MPS in the first few years of life to prevent communication difficulties and delayed language development. Multidisciplinary interventions improve the quality of life of affected people by allowing early diagnosis and early initiation of the most appropriate treatment.

RECOMMENDATIONS

In this study, we emphasize the importance of early diagnosis of hearing loss and frequent follow-up with hearing tests in patients with MPS. Due to the high prevalence and progressiveness of hearing loss in MPS, regular hearing assessments are necessary to determine the progression of hearing loss and to determine appropriate therapeutic procedures for rehabilitation with hearing aids or surgical intervention with placement of a T- tube. Early detection and intervention of the disease are necessary to improve the quality of life of people with MPS.

ABBREVIATIONS

MPS	Mucopolysaccharidosis
GAG	Glycosaminoglycan
PTA	Pure tone audiometry
ABR	Auditory brainstem response
CHL	Conductive hearing loss
SNHL	Sensorineural hearing loss
MHL	Mixed hearing loss
ERT	Enzyme replacement therapy
LSD	Lysosomal storage disease
AR	Acoustic reflex
ENT	Ear, nose, throat
HSCT	Haemopoietic stem cell transplantation

CONFLICT OF INTEREST

There are no conflicts of interest.

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