Case Report

Audiological Profiling and Rehabilitation Outcomes in a Child with Mucopolysaccharidosis Type II

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Highlights

- Mucopolysaccharidosis type II (Hunter syndrome) and hearing loss
- Audiologist awareness for timely evaluation, monitoring and early intervention
- Follow up and reporting behavioural changes vital for rehabilitation

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ABSTRACT

Background and Aim: Mucopolysaccharidosis (MPS II) is a group of rare lysosomal storage disorders, with seven sub-types. MPS II also known as Hunter's syndrome is the only subtype that is affected by X-linked inheritance, while the others are of autosomal inheritance.

The Case: The study aimed to discuss the impact of Hunter syndrome, its pathophysiology, assessment diagnosis, audiological profiling, rehabilitation, and prognostic factors in a child diagnosed with MPS II at the age of 4 years. The auditory symptoms begin around at the age of 2–4 years, as the harmful molecule builds up in the middle ear bone sizes resulting in joint stiffness, and conductive hearing loss gradually progressing into mixed hearing loss with varying degree. Each audiological test finding was linked to the pathophysiology of MPS II, with the discussion emphasising suitable rehabilitative options and importance of multidisciplinary management of hunter syndrome.

Conclusion: The atypical manifestations of MPS II with fluctuating hearing loss is suggestive of the need for early identification, adequate profiling, appropriate rehabilitative measures and role of allied professionals in management of the disorder.

Keywords: Mucopolysaccharidosis II; auditory tests; Hunters; hearing loss; conductive; prognosis

Introduction

Mucopolysaccharidosis (MPS) type II commonly known as Hunter syndrome was first described in 1917 by Major Charles Hunter [1]. It is an X-linked recessive disease caused by a deficiency of the lysosomal enzyme iduronate-2-sulphatase [2]. This genetic condition has a global incidence of 0.27 to 1.3 out of every 100,000 live male births [3] and a low prevalence of 1 in 170,000 male live births [2, 4]

Patients with MPS exhibit a wide range of symptoms and phenotype severity. Hearing Loss (HL) is one of the most common clinical otolaryngologic signs of MPS, occurring in more than 80% of cases [5] with the most frequent types being sensorineural hearing loss (SNHL) and mixed HL. Hearing loss has been progressive in patients with MPS II, with a loss rate of 1-dB HL per year estimated. It varies in degree and can range from mild to profound degree [6]. Causes of HL are attributed to deposits of Glycosaminoglycans in the Eustachian tube and middle ear, frequent otitis media is typical for individuals with MPS II. Accumulation of Glycosaminoglycans also leads to dysostosis of the ossicular chain and tympanic membrane scarring [6]. Symptoms of HL aren't present at birth, but often begin around the age of 2–4 years, as the harmful molecules buildup [7].

MPS II exhibits considerable phenotypic heterogeneity, making it challenging to generalize findings from a few cases to the entire affected population. MPS II diagnosis can be complex and delayed due to its varied clinical manifestations, which often overlap with other disorders. Hence profiling the audiological characteristics and reporting them as case reports offer valuable insights into the diagnostic journey, aiding healthcare professionals in early and accurate detection. With limited patient data available in MPS II, particularly in an audiological domain, presenting audiological case reports can play a crucial role in enhancing the overall understanding of the disease, its varied presentations, and potential treatment approaches. The uniqueness of each case contributes to the comprehensive view of the clinical range of the condition.

Case presentation

Patient information

Four years, a five-month-old male child diagnosed with MPS syndrome reported to the clinical services department of the Institute (All India Institute of Speech and Hearing, Mysore) for the first time on Oct 23, 2019, when the child was one year six months. Complaints were of reduced hearing sensitivity in both ears since childhood. itching in both ears and limited speech output. Behavioral problems like poor sitting tolerance and hyperactivity were also reported.

Case history

Detailed case history was taken which included prenatal, perinatal, and postnatal history through a structured interview with the child's parent. Prenatal history revealed that the mother had a Dengue fever for one week during the 3rd month of pregnancy. Mother was under medication for thyroid problems since 9 years. According to family history, the child is the only issue of his parents (non-consanguineous marriage). The paternal uncle of the child has hearing loss by birth. Perinatal history reported full-term caesarean delivery at the hospital with the birth weight of 3 kgs. The birth cry was reported to be normal. The child was kept in the neonatal intensive care unit for three days due to fever after birth. Post-natal history revealed delayed developmental milestones. Head control and turning were developed at 7 months of age, sitting was achieved at the age of 10 months, and walking at the age of 1.5 years. Control of bowel and urine function, self-dressing, and self-feeding were achieved in 3.5 years. Fine motor skills such as grasping, holding objects in an effective and useful manner, tracing, and copying were achieved at the time of testing. His dominant hand is right.

Earlier medical Investigations

Other earlier investigations were done on 27 June 2020 using an MRI of brain-enlarged Virchow Robin (perivascular) spaces in the corpus callosum and periventricular region. Cardiac assessment on 20 December 2022 revealed redundant mitral valve, trivial mitral regurgitation, and normal biventricular function. Also, echocardiogram was normal. The ophthalmologic

evaluation (November 2022) revealed slight disc pallor with clear cornea, and blood culture revealed the low value of enzyme iduronate-2-sulfatase (<0.06 nmol/hr/mg). The diagnosis of MPS was confirmed by the centre of human genetics wherein an enzyme assay laboratory test (urine sample) was carried out with positive results.

Investigations and clinical findings at the institute

The general features noticed in the child were a large head, broad nose, large round cheeks, thick lips, and short hands with stiff curled fingers as shown in Figure 1.

Multi-disciplinary evaluations

The child was evaluated by a multi-disciplinary team of professionals which include an Audiologist, Pediatrician, Speech language pathologist, Psychologist, and Occupational Therapist.

Otorhinolaryngological evaluation

On October 23, 2019, the child underwent Otorhinolaryngology assessment. Impacted wax in both ears led to medication (waxonil ear drop). On December 12, 2020, and January 2, 2021, medication (wax rim ear drops) was given for right ear wax. After wax removal, on January 4, 2021, audiological evaluation was referred.

Speech and language evaluation

The child was evaluated on August 8, 2022, at 4 years of age with the complaint of limited speech output. Oro peripheral mechanism examination revealed no structural or functional abnormality. Vegetative skills such as blowing, sucking, swallowing, chewing, and biting were present, while the child's language development indicated timely milestones like babbling at 8 months and the first word at 1 year.

Parents reported that the child can recognize family members and shades of emotions. He comprehends lexicon, follows 2–3 step commands, expresses his needs verbally, and speaks 4–5 words with reduced clarity. Scales of early communication skills for hearing impaired children [8] showed that both combined receptive language age and expressive language age was 3.0–3.11 years. Assessment checklist for speech and language skills [9] showed receptive language age: 3.0–

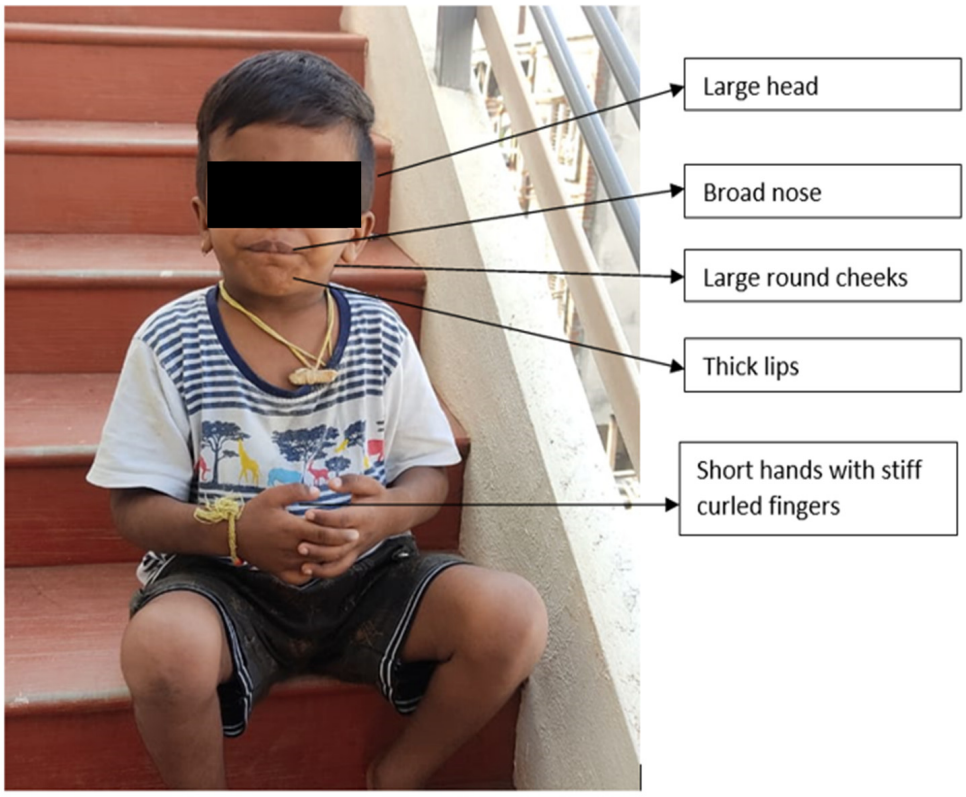

Figure 1. Illustration of the distinctive physical traits noticed in the child with Mucopolysaccharidosis type II

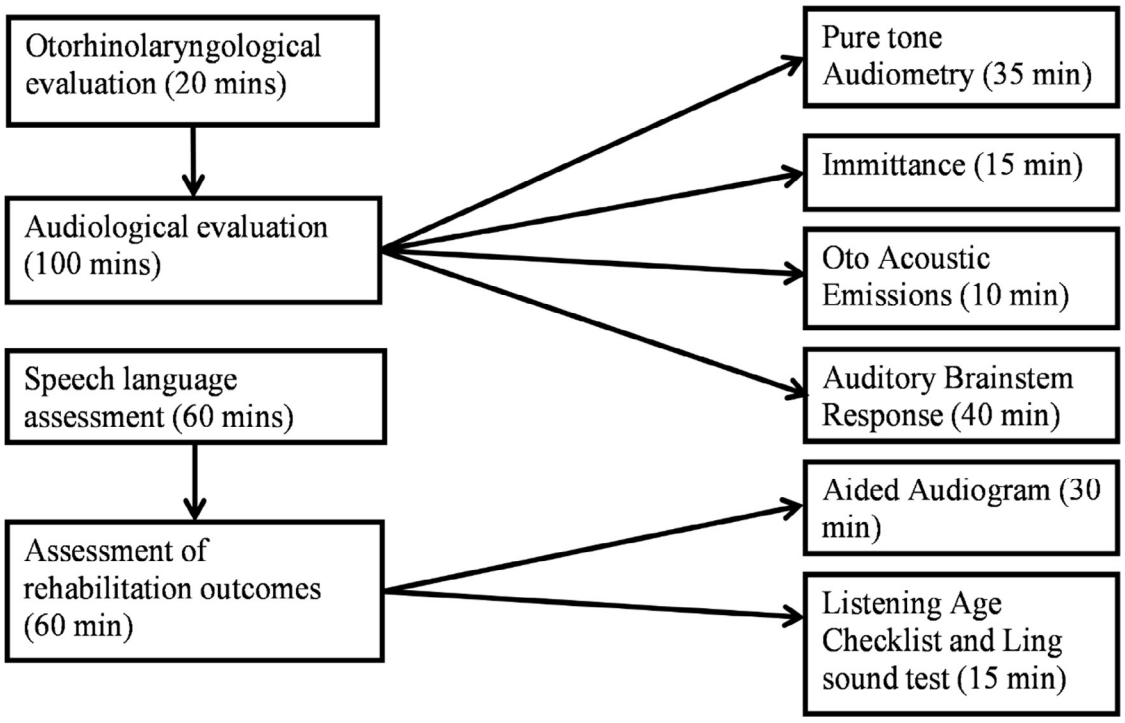

Figure 2. Procedural flowchart of auditory test battery administered on the child with Mucopolysaccharidosis type II

3.6 years and expressive language age: 2.7–2.9 years.

As the child exhibited symptoms of Attention Deficit Hyperactive Disorder (ADHD), the diagnostic and statistical manual of mental disorder, 5th edition were administered – ADHD symptom checklist was administered which confirmed the presence of ADHD. The questions used in the checklist and the child's responses on these items are shown in Appendix A.

Psychological evaluation

On March 7, 2022, psychological evaluation revealed a mental age of three years four months and an IQ of 85 using developmental screening test [10] and Wechsler intelligence scale for children [11], respectively. The child's history showed social and emotional concerns, with behaviours like distractiveness, aggressiveness, impulsivity, hyperactivity and restlessness. The child had self-injurious tendencies, recognized parents, showed social interactions but preferred solitary play. He refuses to go to strangers, makes eye contact, prefers to play himself, socializes easily with peers and elders, looks after himself, prefers to play with pets, quarrelsome for petty matters, exhibits temper tantrums and shifts frequently from one activity to another but does not get engrossed in one activity. Based on International classification of diseases [12], child was diagnosed to have borderline intellectual functioning.

Occupational therapy evaluation

Occupational therapy examination on March 8, 2022 found that child had age-appropriate gross motor skills. Fine motor abilities like reach, grasp, release of objects using tripod grip, handwriting, scissor use, and bilateral hand use skills were adequate. On questioning about activities of daily living, parents reported that the child managed self-feeding and dressing, needed moderate aid for toileting, and bathing. Due to the ADHD symptoms, such as poor sitting tolerance, reduced attention, hyperactivity and restlessness, sensory integration therapy was recommended.

Audiological profiling

To evaluate the status of outer middle, middle ear and inner ear detailed audiological profiling was carried out. It included otoscopic examination, pure tone audiometry, immittance audiometry, otoacoustic emissions, Auditory Brainstem Responses (ABR).

These audiological tests were administered by a Rehabilitation Council of India certified Audiologists, who were not aware of the objectives of the study. A total of 3 evaluations (23 October 2019, 04 January 2021, 08 January 2022) were conducted on three visits based on the fluctuating complaints and behavioral responses to sound as reported by parents. All tests were performed on successive days, and were completed in a week. The authors only profiled the test results obtained from the audiological test battery. The procedure flowchart of all evaluations including audiology is presented in Figure 2.

Immittance

GSI Tympstar (GrasonStadler, Eden Prairie, MN, USA) was used to check the status of middle ear. Bilateral tympanometry at 226 Hz was conducted. Reflex thresholds were derived at octave frequencies (500, 1000, 2000, 4000 Hz) in both ipsilateral and contralateral mode for both ears. Initial evaluation showed bilateral B-type tympanogram with absent reflexes, indicating middle ear pathology. Subsequent evaluations (2nd and 3rd) had As-type and Cs-type tympanograms, with absent reflexes in the right and left ear respectively, confirming persistent bilateral middle ear issues.

Pure tone audiometry and speech audiometry

These tests were done in an acoustically treated room, with strict adherence to ambient noise condition standard prescribed by ANSI S3.1-1999. A calibrated dual-channel clinical audiometer, Inventis Piano (Inventis Inc, Padova, Italy) was used to measure the pure tone threshold and speech detection threshold. The thresholds were tracked in free field, as the child was not co-operative to wear headphones. The thresholds were tracked at octave frequencies from 250 Hz to 4000 Hz for air conduction using free field. A provisional diagnosis of bilateral moderately severe HL (first evaluation), bilateral mild HL (second evaluation based on ABR), bilateral moderate HL (third evaluation) was established in pure tone audiometry, showing the fluctuations in the degree of HL. Pure tome audiometry was done only during the first and the third evaluations. As the child responses in audiometry were inconsistent, the interpretations of all three evaluations were based on ABR.

Distortion product otoacoustic emissions

Distortion product otoacoustic emissions were absent bilaterally across all the frequencies indicative of outer hair cell dysfunction in both the ears. The frequency band tested was from 1000 Hz to 6000 Hz, with the ratio of F2: F1=1.2:1. The stimulus intensity was maintained constant with level of stimulus 1 (L1)=65 dB SPL and level of stimulus 2 (L2)=55 dB SPL. A signal-to-noise ratio of at least 6 dB with a reproducibility score of at least 70% for at least 3 out of 6 frequencies tested is considered for the presence of Distortion product otoacoustic emissions.

Auditory brainstem reponses

ABR was carried out to check the integrity of the auditory nervous system with Natus Biologic Navigator pro (Natus Medical Incorporated, San Carlos, CA, USA) system using Eartone 3A insert phones (Etymotic Research, Elk Grove Village, IL, USA; electrode impedance <5 kOhms). ABR was obtained in two paradigms: click and tone burst (500 Hz) evoked ABRs. The thresholds were tracked using click stimuli with rarefaction polarity presented at 30.1/sec. The threshold search started at an intensity at 90 dB nHL. The acquisition modalities had a high pass filter setting of 30 Hz and a low pass filter setting of 1500 Hz. A notch filter at 60 Hz was kept on to prevent contamination from electrical artifacts and a time window of 12 ms was used. A minimum of two traces was recorded for each paradigm to account for the replicability. Wave I, III, and V were tracked, and their absolute latencies were determined.

In the first evaluation, wave V could be traced in click ABR at 80 dB nHL, indicating moderately severe hearing loss in both ears. Subsequent evaluations revealed mild (60 dB nHL) and moderate (70 dB nHL) HL. The ABR waveforms corresponding to the second evaluation is shown in Figure 3. Although bone conduction testing would give an idea about the conductive pathology and the air bone gap, it could not be done as the child was not cooperative for bone conduction ABR testing owing to headband pressure of the bone vibrator. However, the child was recommended for bone conduction ABR evaluation in the future follow ups.

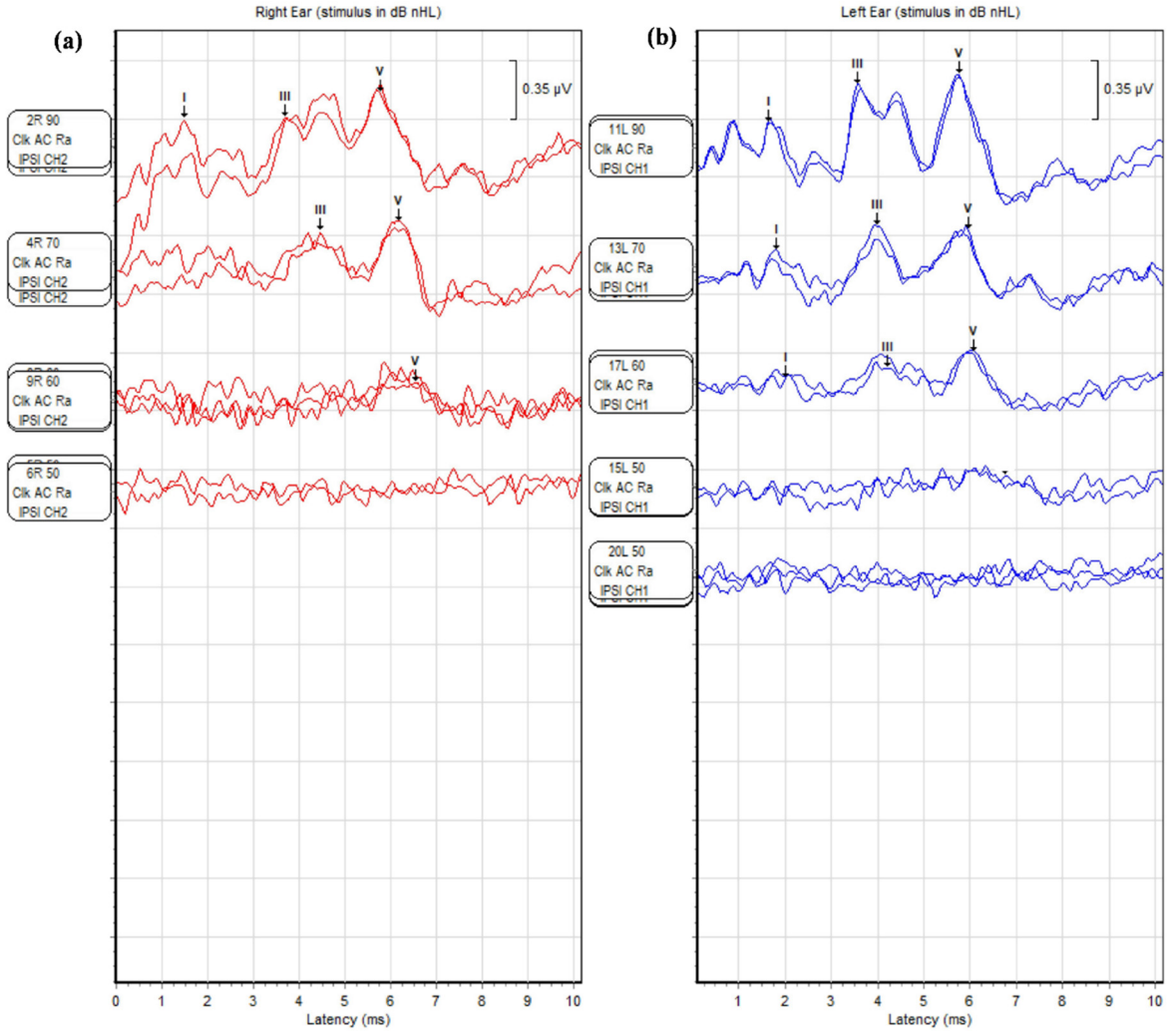

Figure 3. Auditory brainstem response waves of the child with Mucopolysaccharidosis type II for the (a) right and (b) left ears in the second evaluation

Counselling

Parents of the child were counselled regarding the nature, cause, severity, evaluation outcomes, types of rehabilitation services, importance of early intervention, and importance of home training. They were recommended to bring the child for speech therapy and follow up.

Management

The treatment of hunter syndrome depends on function effected. Rehabilitation is symptomatic treatment.

Hearing aids and listening therapy

Due to bilateral moderate HL with a conductive component, child was Alps Turbo CAR III, hearing aids bilaterally. The hearing aids prescribed had optimum gain (maximum 12 gain channels), maximum power output (40–85 dB range), frequency range of operation (100–4350 Hz) and a fitting range (50 and 120 dB) to suit the degree of HL. The aided audiogram was within speech spectrum range as shown in Figure 4.

In Listening therapy, listening age was measured using listening checklist developed by integrated scales of development (Cochlear ltd, Australia) and the pre-therapy listening age was 19–24 months (achieved till identification). The activities in listening therapy aimed at enhancing auditory expansion, categorization, and comprehension skills. For example, an activity of auditory comprehension included preparing fruit salad. Parents were counselled about activities for home

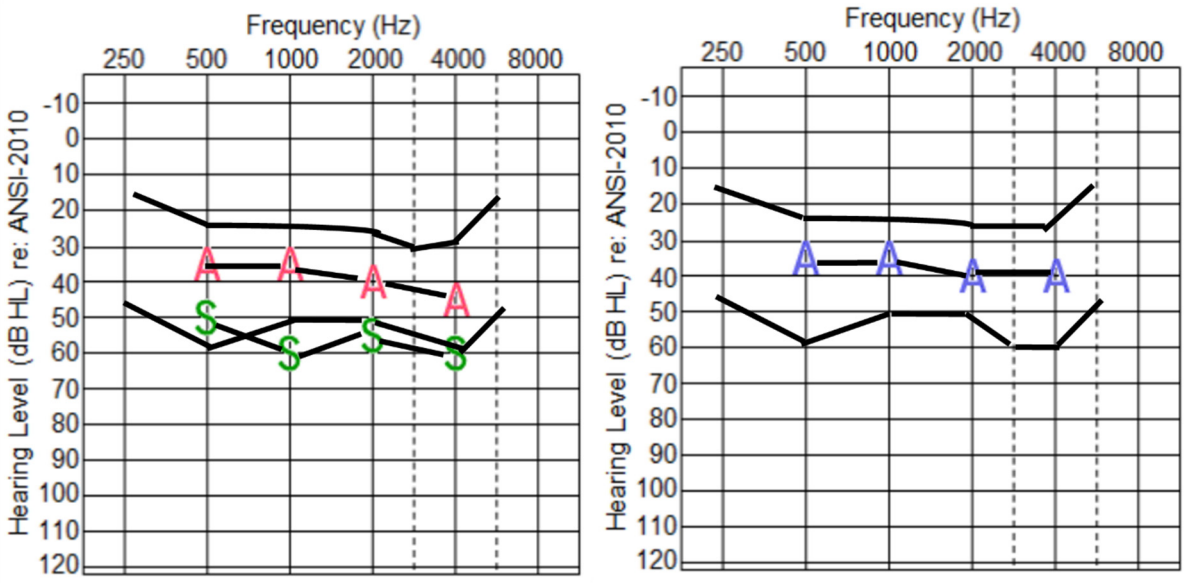

Figure 4. Aided audiogram of the child with Mucopolysaccharidosis type II for the (a) right and (b) left ears after III evaluation following an auditory training of 5 months

training. Therapy was given for 3 days a week for 5 months. Post-therapy, listening age improved to 31–36 months with achieved comprehension, memory and sequencing of 4–5 items, and emerging cognition skills.

Speech and language therapy

After speech and language assessment, recommendations for speech and language therapy included were to improve comprehension and expression of lexical categories (colours, common objects, verbs and step commands etc.), syntactic skills (preposition, opposites), mean length of utterance and child's memory. Child is yet report for speech therapy.

Other management procedures including hematopoietic stem cell transplantation

The child has not been given any other management with respect to cardiac, ophthalmology, etc. till date and is awaiting Hematopoietic Stem Cell Transplantation (HSCT). Hematopoietic stem cell transplantation is a technique along with other management options such as hearing aids, tympanostomy tube insertion and enzyme replacement therapy. HSCT is a superior therapy compared to enzyme replacement therapy where the stem cells cross the blood brain barrier, and is also cost effective as it is a one-time procedure. It is best done before the appearance of neurological symptoms [6].

The procedure of HSCT is as follows: the healthy donor stem cells (peripheral blood, bone marrow, umbilical cord blood) are transfused into the recipient where they enter into the bloodstream as monocytes and differentiate into macrophages. These macrophages secrete lysosomal enzymes into extra-cellular space where the cells take up the enzymes through cross correction. Age of the patient, severity of clinical phenotype, type of donor, and the course of preparative regimen are the major factors affecting the clinical consequences of HSCT. Hematopoietic stem cell transplantation is proved to be effective for patients with MPS II as it decreases Glycosaminoglycans levels in the blood and urine (the deposit of which is the primary cause), and it also normalizes or stabilizes Iduronate 2-sulfatase enzyme activity in leukocytes. In addition, genetic counselling is also an option to help parents who have a family history of the mucopolysaccharidoses to determine if they are carrying the mutated gene that causes the disorders [13].

Discussion

This study profiles audiological features in a 4-year-old male with MPS II. The age and gender of the patient is in consensus with literature reports that suggest MPS II predominantly affects males, and symptoms show up between 18 months to 4 years of age [14, 15]. The physical features reported in earlier studies like large

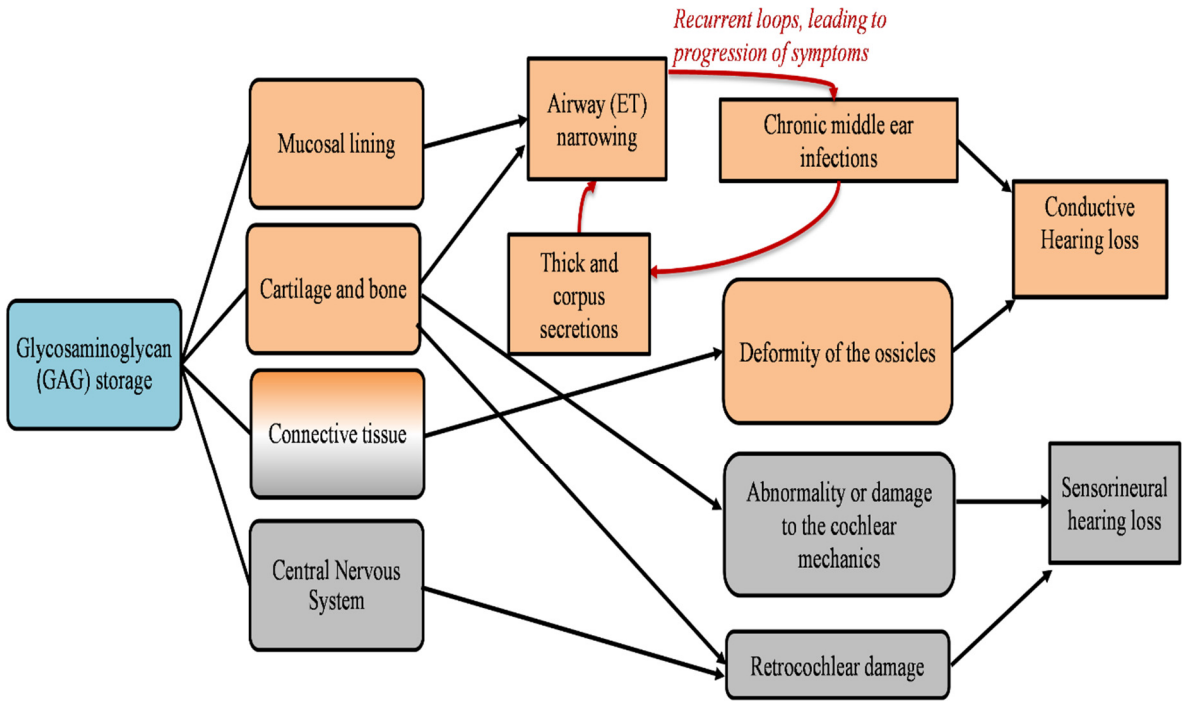

Figure 5. Postulated pathophysiology for the conductive and sensorineural hearing loss in Mucopolysaccharidosis type II

round cheeks, broad nose, thick lips, large tongue, bushy eyebrows, large head, slowed growth, thick and tough skin, short and broad hands with stiff curled fingers also correlated well with the child features (Figure 1). The cardiac deficits seen in the child also align with literature reports that reveal an overall decrease in cardiac efficiency [16] in MPS II children. Although visual defects are most common in MPS II, with ocular findings such as hypertelorism and bulged eyes, leading to other chronic conditions related to corneal overexposure, the present case had slight disc pallor. The presence of visual deficits although mild hint at the initial stages of the disease progression. As the disease progresses, Hunter patients have been reported to have a moderate incidence of optic nerve abnormalities and retinopathy [17].

Child was diagnosed to have bilateral moderate hearing loss with a conductive component. The conductive component present in the patient was reflected in the Tympanometry findings having B, As, Cs type pattern which can be attributed to chronic otitis media, Eustachian tube narrowing, deformity of the ossicles, thick secretions in the middle ear. Numerous factors are attributed to the hearing loss in MPS II resulting from Glycosaminoglycans depositions in mucosal linings, connective tissue, cartilages, bones, and the central nervous system [6]. Beyond early childhood, all forms of chronic otitis media or persistent middle ear effusion are common, leads to persistent conductive hearing loss. Frequent middle ear effusion in MPS patients is most likely brought on by their vulnerability to viral infections, which may also contribute to structural alterations in the tympanic membrane and ossicular abnormalities. It is thought that a vicious cycle between chronic otitis media, collections of viscous secretions, and airway narrowing accelerates the growth of the conductive component.

Given the patient's age, the emergence of a conductive component aligns with early disease progression. It's conceivable that as the condition advances, a SNHL component might emerge, possibly resulting in mixed hearing loss. Absence of distortion product otoacoustic emissions could be due to either conductive or cochlear issues. It could be postulated that the SNHL is mild to moderate, potentially exacerbated by varying degrees of conductive component, resulting in mixed hearing loss. The SNHL could stem from losses in outer and inner cochlear hair cells, observed in MPS I, MPS IV, and MPS IIIB murine models [6]. Glycosaminoglycans accumulation could damage inner ear structures like the organ of Corti, Reisner's membrane, stria vascularis, and vestibulocochlear nerve [6]. Additionally, collection

of Glycosaminoglycans has been demonstrated to extend beyond cochlea and may lead to retrocochlear damage. Figure 5 illustrates the pathophysiology behind sensorineural and conductive components of MPS II-related HL.

The child also had delays in speech and language development reflected in assessment checklist for speech and language skills with receptive language age being 3.0 to 3.6 years and expressive language age being 2.7 to 2.9 years. Normal hearing is an essential component of speech and language development, especially in the first five years of life even mild SNHL may causes problem with normal speech and language development [18]. The present child had mild to moderate hearing loss with borderline intellectual functioning which could have attributed to speech and language delays as it has been pointed out in case studies by Rao et al. and Kiaer et al. [19, 20] a 7.6-year-old male with receptive and expressive language age to be around 9 to 10 months and 6 to 7 months respectively (receptive expressive emergent language scale and three dimensional language acquisition test), and a 30 months old boy with delayed language and motor functions with previous history of acute otitis media.

Prognosis

Prognosis depends on the phenotype of the disease in MPS II. Previous studies have shown that neurologic impact of hunter syndrome varies considerably with respect to phenotype (mild and severe) [21]. The child has mild phenotypic symptoms. In severe phenotype high mortality (death by second decade of life; pulmonary dysfunction, cardiac valvular issues or both) and in attenuated phenotype, better life expectancy (till fifth decade) has been reported [16].

The child is yet to undergo HSCT so the expected improvement in post HSCT have been reported in studies which showed higher activities of daily living scores in patients with MPS II undergoing HSCT before age five years compared with those undergoing HSCT after age 5 years. The present child is currently 4.10 years and we can expect a better improvement after the transplant, considering the age. HSCT has been shown to either stabilize or improve cardiac valve regurgitation contributing to heart failure, the most common cause of death in patients with MPS II. As the cardiac issues in present child were identified at an early stage, we expect an improved cardiac efficiency due to early treatment [13].

Taylor et al. [13] reported improvements in speech and neurologic symptoms in patients with the severe MPS II phenotype after HSCT. HSCT can improve hearing in patients with MPS II if the procedure is performed before age 25 months. Since the child is currently exhibits mild phenotypic symptoms, we expect his speech and neurologic symptoms to improve. However, since he has crossed the age of 25 months, an improved hearing sensitivity might not be experienced.

Conclusion

The occurrence of hearing loss linked with Hunter syndrome highlights the necessity for healthcare professionals to direct such cases to audiologists. Audiologists should possess an awareness of Hunter syndrome to facilitate timely and proper evaluation and management. Equally important is the education of parents and teachers about the disease and effective management strategies. This education is crucial for overcoming the challenges imposed by the syndrome and fostering enhanced inclusion of individuals with Mucopolysaccharidosis II within the society. Given the fluctuating nature of the disorder, audiologists need to monitor hearing deficits in the child periodically (for every three months) by carrying out hearing evaluations and reprogramming of the hearing aid. Teachers and parents need to be counselled to monitor the behavioural changes in the child secondary to treatment variables wherein they've to report to the physician or rehabilitation professionals within 1–2 days of the change in behaviour in order to help in early identification and rehabilitation.

Ethical Considerations

Compliance with ethical guidelines

The review board of the All-India Institute of Speech and Hearing (AIISH) granted ethical approval (SH/CC_07/2022-13). The study's objectives were described to the parent, and signed informed consent was obtained from the child's parent prior to the commencement of the study.

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Authors' contributions

KVN: Study design, supervision, interpretation of the results, and drafting the manuscript; GT, NMT, NT, PV, SPR: Data collection and drafting the manuscript; PP: Study design, supervision, and critical revision of the manuscript.

Conflict of interest

There is no conflict of interest to disclose. This is non-funded research.

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Appendix A. The profile of attention deficit hyperactive disorder symptoms reported in the child

	Inattention symptoms	Not at all	Just a little	Often	Very often
1	Fails to give attention to details or makes careless mistakes in school work or during other activities			✓	
2	Has difficulty sustaining attention to tasks or play activities			✓	
3	Does not seem to listen when spoken to directly		✓		
4	Does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace		✓		
5	Has difficulty organizing tasks and activities			✓	
6	Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort		✓		
7	Loses things necessary for tasks or activities	✓			
8	Is easily distracted by extraneous stimuli		✓		
9	Is forgetful in daily activities		✓		
	Hyperactivity symptoms				
10	Fidgets with or taps hands or feet or squirms in seat			✓	
11	Leaves seat in situations in which it is inappropriate			✓	
12	Unable to play or engage in leisure activities quietly				✓
13	Has difficulty playing or engaging in leisure activities quietly			✓	
14	Is “on the go” or acts as if “driven by a motor”		✓		
15	Talks excessively			✓	
	Impulsivity symptoms				
16	Blurts out an answer before question has been completed		✓		
17	Has difficulty waiting his or her turn			✓	
18	Interrupts or intrudes on others			✓	