

Audiological Profile of a patient with MPS type IVA

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ABSTRACT

Mucopolysaccharidosis IVA is a rare metabolic disorder caused by the deficiency of N-acetylgalactosamine-6-sulfate-sulfatase, which is helpful in the degradation of keratan sulfate. Hearing loss is common in these individuals, which may be conductive, mixed or sensorineural. The disorder has a manifestation mainly in the skeletal and visceral organs; however, the presence of subtle neurological abnormalities has also been reported. Thus, a detailed audiological evaluation for differentiating sensory pathology with the neural pathology is warranted. The present case highlights the audiological characteristics of a 14 year old male child diagnosed with MPS IVA. Immitance audiometry, Pure tone audiometry, Speech audiometry, Oto-acoustic emission and Auditory brainstem responses (ABR) (for threshold estimation) indicated mild sensorineural hearing loss in right ear and moderate mixed hearing loss in the left ear. However, lack of replicability in the ABR waveforms and difference in the absolute latency for ABR peaks with different rate of stimulus presentation (11.1/sec and 90.1/sec) signifies the presence of retrocochlear pathology. The findings were further strengthened by the absence of speech ABR and the presence of late latency responses. The findings have a direct implication on the audiological rehabilitation of such individuals and the prescription of hearing aid should be made with caution.

KEYWORDS

mucopolysaccharidosis, mucopolysaccharidosis type IVA, Morquio's disease, keratan sulfate, glycosaminoglycans, retrocochlear pathology

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INTRODUCTION

Mucopolysaccharidosis IV (MPS IV), also known as Morquio-Brailsford Syndrome, is a rare, autosomal recessive disorder caused by the accumulation of mucopolysaccharides in various body tissues. It is caused by the deficiency of the lysosomal enzyme N-acetylgalactosamine-6-sulfate-sulfatase in MPS IVA and β -galactosidase in MPS IVB, which is helpful in the degradation of one major type of mucopolysaccharides (glycosaminoglycans; GAG), known as keratan sulfate. MPS IV can be distinguished from other forms of MPS in the sense that their intelligence is unimpaired [1]. Although intelligence is also unimpaired in MPS type VI, there is a marked difference in the skeletal characteristics between the two types of MPS. The differentiation between MPS IVA and MPS IVB is fuzzy and MPS IVB is generally considered to be a milder form of MPS IV [2]. The incidence rate of MPS IVA is reported to be 1 in 76,000 live births in Northern Ireland [3], 1 in 200,000 live births in British Columbia and 1 in 640,000 live births in Western Australia [4]. In India, no such statistics are available; however, research reported an overall incidence of MPS to be 13.8% of all the cases with inborn errors of metabolism [5].

Keratan sulfate is primarily found in cornea, bones and cartilages. In the cornea, keratan sulfate is assumed to be responsible for the tissue hydration [6] and regulation of collagen fiber spacing and diameter [7]. In bones and cartilages, keratan sulfate is veiled into serum and synovial fluid for the purpose of tissue repair in the conditions of joint and inflammatory diseases [8]. The highest-flying corneal symptom associated with MPS Type IVA is corneal clouding and corneal opacities [9]. The classical skeletal symptoms associated with MPS IVA involve spondyloepiphyseal dysplasia, genu valgum, growth retardation with short trunk and neck, and a wobbling gait [10]. Bone deformities entails platyspody, dens hypoplasia, chest deformities involving kyphoscoliosis, progeria, with overall size does not exceeding one meter [11].

Apart from the other symptoms, the literature wires the occurrence of hearing loss almost universally in such cases [12]. However, limited research on the type of hearing loss and site of lesion is available; most of the case studies indicated the presence of conductive hearing loss in early years, turning to mixed or sensorineural hearing loss in the later stages. Riedner and Levin (1977) [13] had verified hearing loss pattern in 18 children with Morquio's Syndrome. They indicated conductive hearing loss in all children below 8 years of age and mixed to sensorineural hearing loss in all children above 8 years of age. In another such study Schlieier and Steubel (1976) [14] specified serous otitis media secondary to upper respiratory tract infection. Conductive hearing loss in such cases may also be caused due to the deformity of middle ear ossicles [15].

A feasible rationale of sensorineural hearing loss in such cases may be accredited to the persistent chronic otitis media [16]. However, in the study by Reidner and Levin (1977) [13], it was found that sensorineural hearing loss occurred in one ear without any history of otitis media. The finding pointed towards some another mechanism responsible for sensorineural hearing loss. Sensorineural hearing loss in such cases may be due to the accumulation of GAGs in the inner ear [17]. Since GAGs are found in various parts of the inner ear viz., tectorial membrane, spiral ligament, basilar membrane, spiral limbus, spiral lamina, and bony labyrinth in various species [18], it is likely that in condition of MPS IV, the accumulation of GAGs increases in the inner ear.

However, a distinction between sensory and neural hearing loss in such patients has not been carried out. The plausible reason behind the lack of literature may be due to the fact that MPS IV does not affect the central and peripheral nervous system, as the disorder associated with keratan sulfate is purely visceral and skeletal in nature. The view was defied recently by Davison *et al.* (2013) [19] where reviewing of the existing MRI and MR spectroscopy reports for 8 such children, subtle neuroimaging abnormalities were demonstrated in more than half of the children. Moreover, in spite of the literature opinionated normal intelligence in such children, the researchers found intelligent quotient (IQ) to be below the normal range in 3/8 such children. The findings indicated strong presence of neurological abnormalities in these individuals. This increases a need of differentiating sensory and neural hearing loss in such cases.

CASE REPORT

A 14 year old male child was referred to the department of audiology at JSS Hospital, Mysore, for audiological evaluation. The case was diagnosed as MPS type IVA from the department of pediatrics at the age of 8 years. The diagnosis was made on the basis of increased keratan sulfate excretion in the urinary sample and the presence of other correlating skeletal and nervous system involvement. The urine sample was examined using ELISA (enzyme linked immunosorbent assay) test and the results indicated increased keratan sulfate in the urine in comparison to normal. Meticulous exploration of the available reports from the different departments revealed diffused cornea and corneal clouding in the eyes, short stature, spondyloepiphyseal dysplasia with very short trunk and neck with shortened limbs, genu valgum, kyphoscoliosis, pectus excavatum, cubitus valgus, hyperextension of waist, drooping of right shoulder, prominence of the lower costal margins, over-riding of ribs and coxa vara. Hyper-reflexia in upper limb and lower limb with wasting of the muscles was also reported by the neurologist indicative of central nervous system involvement.

Anthropometric measures of the child revealed the gross body weight of 14 Kg, height of 97 cm, head circumference of 55 cm and chest circumference of 60 cm. Upper segment-lower segment ratio was found to be 0.9 and arm span was 101 cm. The child was chronic malnourished and the general physical hygiene was poor. The child was not able to walk or

stand. On the contrary, the speech skills of the child were comparatively fair and the child was speaking in sentence level. The articulation, fluency and voice characteristics were appeared to be normal during conversation. The child was attending regular school in 4th standard and the academic skills were comparable, however, the child repeated 3rd and 4th standard twice. The child was having average intellectual functioning with the IQ of 90.

AUDIOLOGICAL EVALUATION

The audiological case history information revealed that the child had delayed motor and speech milestones. Birth history was normal with birth weight of 3.25 kg. There was no family history of any other congenital disease. Post natal history revealed recurrent fever and cough since 2 years of age with rate of recurrence of once in 5-6 months. The parents reported no significant history of ear infections, ear pain or any other ear related pathology.

The detailed audiological evaluation was carried out. Immittance measures revealed normal tympanogram in the right ear with ipsilateral reflexes present at 500 Hz, 1 KHz and 2 KHz at 85dBHL. The reflexes were absent at 4 KHz. Immittance measures for the left ear showed Ad type of tympanogram with increased static compliance and absent ipsilateral reflexes. Increased static compliance in the left ear may be due to the ossicular chain dysfunction, which is commonly seen in such individuals [15]. The normal tympanogram in the right ear indicates no middle ear pathology. Outer hair cell function was screened using distortion product otoacoustic emission and fair DP amplitude was found within the frequency region of 2-5 KHz with SNR more than 6 in each frequency, in right ear. However, reduced DP amplitude and SNR<3 was observed in the left ear. These results indicate normal cochlear outer hair cell functioning in the right ear. The reduced DP amplitude may be probably due to the presence of conductive pathology in the left ear. Pure tone thresholds were estimated and pure tone average (PTA) was calculated to be 33.3 dB in the right ear and 41.6 dB in the left ear. Speech audiometry revealed SDT scores to be within ± 6 dB of the PTA, and SRT was within ± 10 dB of PTA in both the ears. SIS could not be obtained as the task was difficult for the child. The audiological findings pointed out the presence of mild sensorineural hearing loss in the right ear and moderate mixed hearing loss in the left ear. The results were consistent with the literature [13] where it was found that mixed and sensorineural hearing loss was common in these individuals.

In order to confirm the audiometric findings objectively, auditory brainstem responses (ABR) were administered to the child using IHS-Smart EP for threshold estimation. The thresholds were estimated at the rate of 27.1/sec by the presence of 5th peak at the minimum intensity level using click stimulus. Only those waveforms with the residual noise (RN) level of less than 0.08 μ V, and signal to noise ratio (SNR) of ≥ 1.0 were considered for the analysis. The presence of the peak was considered where the peak amplitude was at least 4-5 times greater to the RN. The results revealed the presence of 5th peak within the latency of 6.13 ms at 50 dBnHL in right ear portentous of mild hearing loss. In the left ear the 5th peak was visible at 60 dBnHL at the latency of 7.22 ms. The peak was slightly prolonged, probably because of the presence of middle ear pathology (refer Table 1) suggesting mild to moderate hearing loss. These findings were in accordance with other audiological findings, and the diagnosis of mild sensorineural hearing loss in the right ear and moderate mixed hearing loss in the left ear was confirmed.

Table 1: Absolute latencies of ABR peaks at various intensity levels. Cross correlation coefficient of the waveforms at same intensity to measure the degree of replicability was also shown.

RIGHT EAR					LEFT EAR			
PEAK 1 (MS)	PEAK 3 (MS)	PEAK 5 (MS)	CORRELATION COEFFICIENT	INTENSITY	PEAK 1 (MS)	PEAK 3 (MS)	PEAK 5 (MS)	CORRELATION COEFFICIENT
1.13	3.75	5.62	0.190	90 dB	1.48	3.83	6.48	0.319
1.53	3.47	5.40		90 dB	1.67	3.98	6.31	
1.45	3.96	6.12	0.254	70 dB	1.70	3.99	6.65	-0.527
1.67	4.12	6.01		70 dB	1.92	4.21	7.47	
-	-	-	-	60 dB	NP	NP	7.22	-0.346
-	-	-	-	60 dB	NP	NP	7.60	
NP	NP	6.13	0.265	50 dB	NP	NP	NP	-
NP	NP	6.39		50 dB	NP	NP	NP	-

*NP: No Peak Observed

However, when the waveforms were analyzed for replicability, a significant disparity was observed in the absolute latencies at all the intensity levels in both the ears. The waveforms were cross correlated in order to estimate the correlation between

the waveforms while keeping the intensity and polarity as constant, and it was found that the correlation coefficient was less than 0.4, indicating a poor correlation between the waveforms. The findings increased the suspicion of the presence of retrocochlear pathology. Thus, an in depth investigation was carried out by following the neurodiagnostic protocol of ABR at 80 dBnHL in right ear and 90 dBnHL in left ear. The waveforms were measured for the stimulus rate of 11.1/sec and 90.1/sec and the absolute latencies of various peaks were compared. The results indicated the presence of all five peaks in both ears within the normal latency region at slower rate (11.1/sec), whereas, all the five peaks were delayed at higher rate (90.1/sec) of the stimulus presentation. The difference in the absolute latencies was beyond the normal limits (≤ 0.8 ms). The 5th peak was delayed by 1.2 ms in the right ear and 1.37 ms in the left ear (see Figure 1). These results were indicative of the presence of retrocochlear pathology in both the ears.

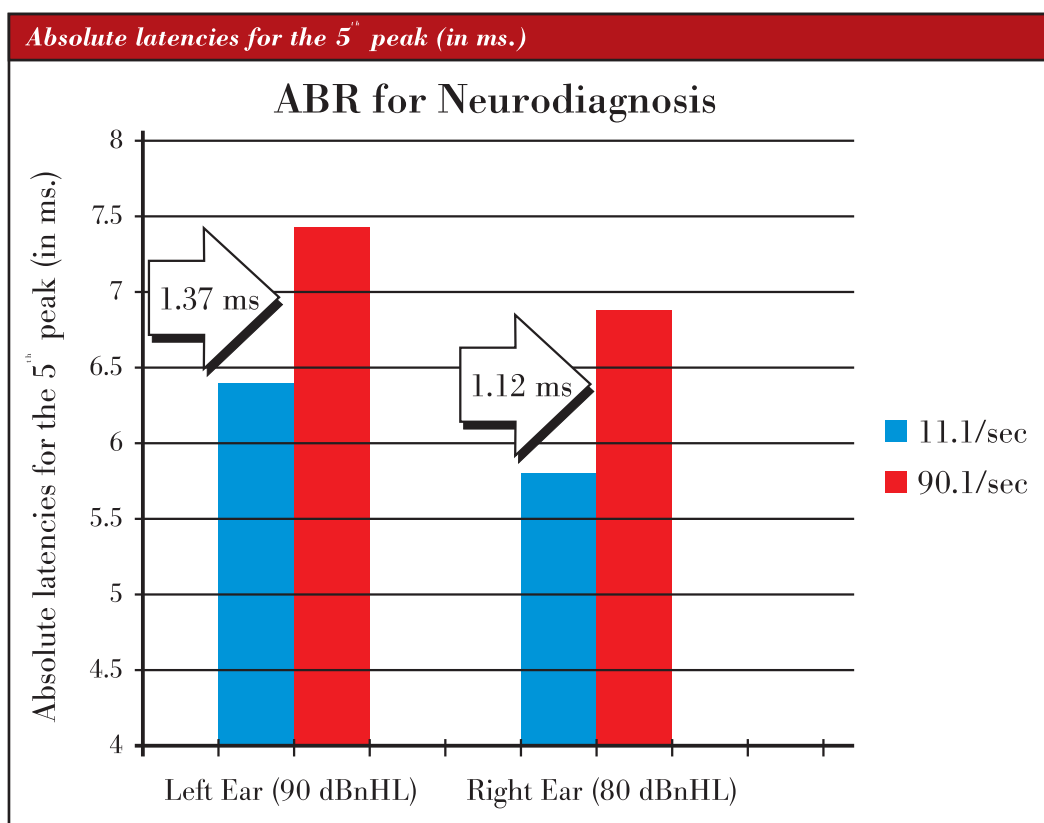
The presence of retrocochlear pathology was further explored by the speech evoked ABR using standardized “40 ms da” stimulus at the rate of 11.1/sec and the intensity of 80dBnHL. The results revealed the presence of only V-A complex, whereas the later peaks were absent in both the ears. These results significantly indicated the presence of retrocochlear pathology in both the ears, as the spectral features of speech was not processed adequately in the auditory system. The processing of the spectral features of the speech are characteristic trait of the retrocochlear system, and inability in such processing clearly shows the presence of retrocochlear pathology. These findings were further confirmed by the presence of late latency response (LLR) with click stimulus, where a clear N_1 - P_2 complex was observed at 80dBnHL in right ear and 90 dBnHL in left ear with the stimulus presentation rate of 1.1/sec, in both the ears. The presence of late potentials and the absence of early potential are commonly seen in retrocochlear pathologies. However, the absolute latencies of ABR for neurodiagnosis, speech ABR and LLR was slightly prolonged in left ear in comparison to the right ear, the latencies were within normal limits.

The findings of the present case have direct implications on the audiological rehabilitation in such cases. In the presence of neural causation, the benefit from the hearing aid is limited, and thus, the medley of the hearing aid should be trailed with prudence.

CONCLUSION

Mucopolysaccharidosis (MPS) is a type of metabolic disorders caused due to inability to break down GAGs. MPS is a heterogeneous set of disorders ranging in seven different types [20]. Among them, MPS type IVA is a rare congenital disorder caused due to the deficiency of N-acetylgalatosamine-6-sulfate-sulfatase (GALNS) which is helpful in the degradation of GAGs resulting in the increased secretion of keratan sulfate.

The case report illustrates a detailed audiological profile of a patient with MPS IVA and proves the presence of retrocochlear pathology in both the ears. The presence of retrocochlear pathology was confirmed with the absence of replicable waveforms, presence of the peaks at lower stimulus rate within normal latency limits but prolonged peaks at higher rate of stimulus presentation, absence of speech evoked ABR and the presence of LLR. The presence of retrocochlear pathology should be further investigated to generalize the findings, and the information may be considered while prescribing the hearing aids.



Consent: Informed consent form was dually signed by the parents regarding acceptance for investigation and publication.

Competing Interest: None

Authors Contribution: Saransh J.: Principal investigator.

Vikas M.D.: Co-Investigator, correspondence with various departments.

Suman S.: Preparation of test setting, make available the client for testing.

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