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Case Report

An audiological profiling in metachromatic leukodystrophy: a case study

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ABSTRACT

Metachromatic leukodystrophy (MLD) is a lysosomal storage disease, which is characterized by damage of the myelin sheath that covers most of nerve fibers of the central and peripheral nervous systems. The disease occurs due to a deficiency of the lysosomal enzyme arylsulfatase A (ARSA) or its sphingolipid activator protein saposin B (SapB). Audiological test batteries were carried out, i.e.; behavioural observation audiometry (BOA), impedance audiometry, otoacoustic emission (OAE) and brainstem evoked response audiometry (BERA). Result showed there was no changes in behaviour towards the stimulus, has been noticed in BOA, bilateral A type tympanogram with absence of acoustic reflexes in all frequencies on Ipsi and contra-lateral stimulations and no wave Vth was found at 90 dBnHL in both ears even at repeated trials in BERA. Early identification of hearing loss offers children the opportunity to develop significantly improved language skills. Otologist and audiologist need to be taken care and to provide medical treatment as well as amplification device to the patients.

Keywords: Metachromatic leukodystrophy, Otoacoustic emission, Brainstem evoked response audiometry, Impedance audiometry

INTRODUCTION

Metachromatic leukodystrophy (MLD) is one of the rare neurometabolic disease.[1] This disease is characterized by the damage of the myelin sheath that covers most of the nerve fibres of the central (CNS) and peripheral nervous systems (PNS), resulting in progressive motor and cognitive impairment as clinical manifestations.[2]

MLD is a lysosomal storage disorder with an autosomal recessive pattern of inheritance.[3,4] Hence, carriers of one copy of the abnormal gene are not affected by the disease. The parents of an individual with an autosomal recessive condition each of them carries one copy of affected gene but they do not show sign and symptoms of the condition.[3,5] MLD is one of the most common leukodystrophies, and has a prevalence of 1 in 40,000-160,000 worldwide. In some isolated populations, the incidence of MLD is much higher. For example, in the group of Habbanite (Jews) it is estimated at 1 in 75, among the Navajo Indian people at 1 in 2,500, and among the Arab groups of Israel it is estimated 1 in 8,000.[2]

Causes and pathophysiology

MLD is a neurodegenerative disorder caused by deficiency of arysulfatase A (ARSA) and sphingolipid activator protein B (sap B, saposin B) enzyme, that leads to accumulation of sulfatide within the cells.[1,4,6] Arysulfatase A enzyme breakdown the sulfatide, due to improper function of ARSA and sap B enzyme sulfatide accumulate in the neurons and myelinating cells that causes severe demyelination.[3,6]

Accumulation of undegraded sulfatide in particularly relevant in myelin forming cells, both oligodendrocytes and schwann cells, leading to progressive demylination and dysfunction of CNS and PNS, respectively.[4]

A few individual with MLD have mutation in prosaposin (PSAP) gene.[5] This gene assists an enzyme for breaking down various fats one of these smaller proteins is called saposin B this protein works with arysulfatase A to break down sulfatide.[2] Mutation in the ARSA and PSAP gene result in an impaired ability to break down sulfatides, which causes accumulation of sulfatide in the nervous system excess sulfatides are toxic for the nervous system and gradually it destroy the myelin sheath.[5]

Classification of MLD

MLD is usually classified into three main clinical forms according to age at symptoms onset.[2,4]

Late infantile MLD

This is the most common form of MLD, affecting about 50% to 60% of all individual and incidence is estimated to range from 1 in 40,000 to 1 in 170,000 new-borns.[3] This form of disorder usually occurs before 30 months of age and typically characterized with gait disturbance, weakness, hypotonia, clumsiness, frequent falls, difficulty walking, and dysarthria. As the disease progresses, motor, cognitive, and language skills deteriorate, impaired vision, and hearing. Individual with late infantile MLD do not survive past childhood.[3,7]

Juvenile MLD

The clinical signs of this pathology appear between 30 months and 16 years of age. This clinical form of the disease represents 20 to 30% of MLD cases.[7] The incidence is estimated 1 in 150,000.[8] and typically characterized with behavioural problems, followed by gait disturbances, delay in fine motor skills and impaired attention concentration. Progression is similar but slower than in late infant form.[2,7]

Adult MLD

Adult MLD is the rarest form of MLD. This form of disorder occurs after 16 years sometimes up to the fourth or fifth decade and affect about 10% to 20% of the MLD cases.[7] Adult MLD is the less severe form of the disease. In this form behavioural, cognitive impairments and personality changes are found, patient experience sudden mood swings, depressive disorder, another typical feature is psychotic symptoms, such as illusions and hallucinations The final stage of the disease is similar to the late infantile and juvenile forms. Individual with adult form of MLD may survive 20 to 30 years after the diagnosis.[2,7]

CASE REPORT

A non-consanguineous parents came with their 2-years-old male child having a complaint of reduced hearing sensitivity after the age of 1.5 years and the problem is progressive in nature. There were two miscarriages happens (2nd child during 3 months of pregnancy and 3rd child during 5 month of pregnancy). At the time of 4th child, mother was under routine medical evaluation, during 5th month of pregnancy she came to know that there is a swelling in the kidney of the child and mother was under the treatment by the doctor. And finally, the child born with full term normal delivery, birth cry was present, birth weight was 2.7 kg, after 9 days of birth, child was suffered from jaundice and there was no history of NICU admission.

From birth to till the age of 1.5 years of age there is a normal motor milestones development, at the age of 1.5 years the child got high fever after admitting him to a hospital the parents came to know that the child has a neurological disorder (MLD). After the onset of a disease child faced some balancing issues, not able to stand or walk properly (cerebellar ataxia), language skills are deteriorating, loss of speech what he has developed, loss of hearing ability, also shows some motor problem such as difficulty in standing, walking, frequent falls and some behavioural issues such as irritability, distractive. He was undergone for a neurological evaluation MRI for prognostic purpose and result showed subtle diffuse confluent T2/FLAIR hyperintensity seen along bilateral periventricular region and deep white matter sparing subcortical U-fibres. Inherited metabolic disorder/MLD.

Audiological assessment

In the present study, a complete case history focused on hearing problems was taken from the child and his parents. First of all, otoscopic examination was performed by otolaryngologist. And it was found that external auditory canal is free from any obstruction and intact tympanic membrane bilaterally. First test administered was behavioural observation audiometry. The stimuli used include the following: calibrated rattles, drum, bells and clacker, warble tones of 0.5, 1, 2, and 4 kHz narrow band noise and speech. Result showed there was no changes in behaviour towards the stimulus, has been noticed.

Immittance audiometry was performed by GSI Tympstar. This procedure was done for both the ears separately. Tympanometry was performed by presenting 226 Hz probe tone into the ear canal while air pressure changed from +200daPa to -400daPa.

Reflexometry was done by presenting 0.5, 1, 2, 4 kHz tone to the ear. Result showed, normal middle ear pressure with normal compliance, absence of acoustic reflexes in all frequencies on ipsi and contra lateral stimulations. Otoacoustic Emission test was done using GSI Audera. This procedure was done for both the ears separately. Click evoked distortion product OAEs were measured at 65 and 55-dB peak sound pressure level for the f1 and f2 components. Test result showed bilateral Refer that suggests bilateral abnormal functioning of outer hair cells (OHCs).

Brainstem evoked response audiometry (BERA) test was performed by using GSI Audera. BERA test was done by using click stimuli at a rate of 11.1 Hz with rarefaction polarity for threshold estimation and the finding was, no wave V was found at 90 dBnHL, suggests bilateral severe hearing loss.

Table 1: Details of test administered, instrumentation and their findings.

S. no.	Test administered	Instrument used	Right ear	Left ear	Impression
1.	Behavioural observation audiometry	Interacoustic AC-40	No response was obtained	No response was obtained	Bilateral hearing loss.
2.	Immittance audiometry	GSI tympstar	A type of tympanogram along with absence of acoustic reflexes	A type of tympanogram along with absence of acoustic reflexes	Bilateral normal middle ear functioning
3.	Otoacoustic emission	GSI Audera	Refer	Refer	Bilateral abnormal functioning of outer hair cells
4.	Brainstem Evoked Response Audiometry (BERA)	GSI Audera	No peaks was found at 90 dBnHL	No peaks was found at 90 dBnHL	Bilateral severe hearing loss.

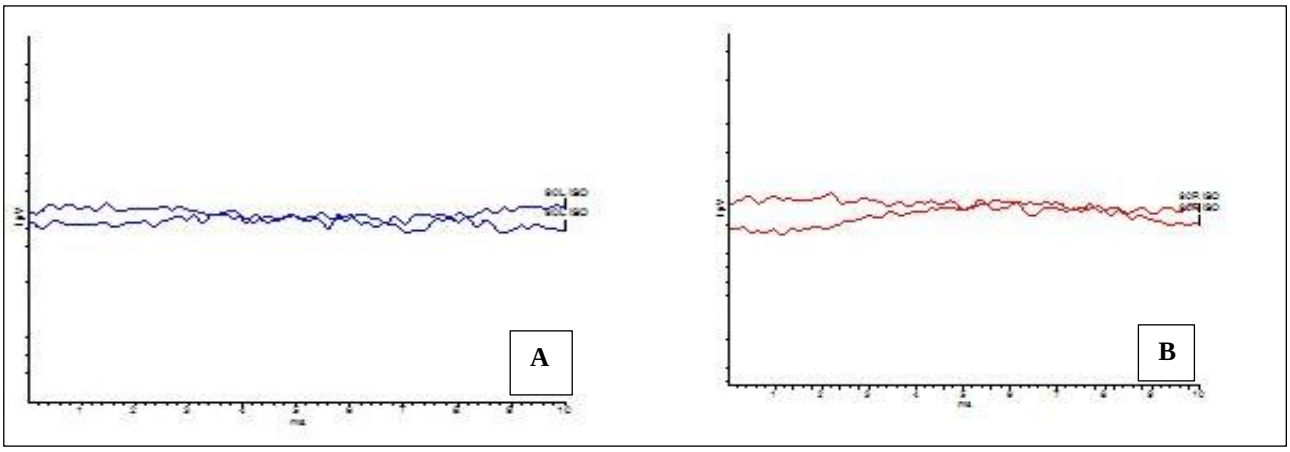

Figure 1: ABR wave form of both (a) left ear; and (b) right ear.

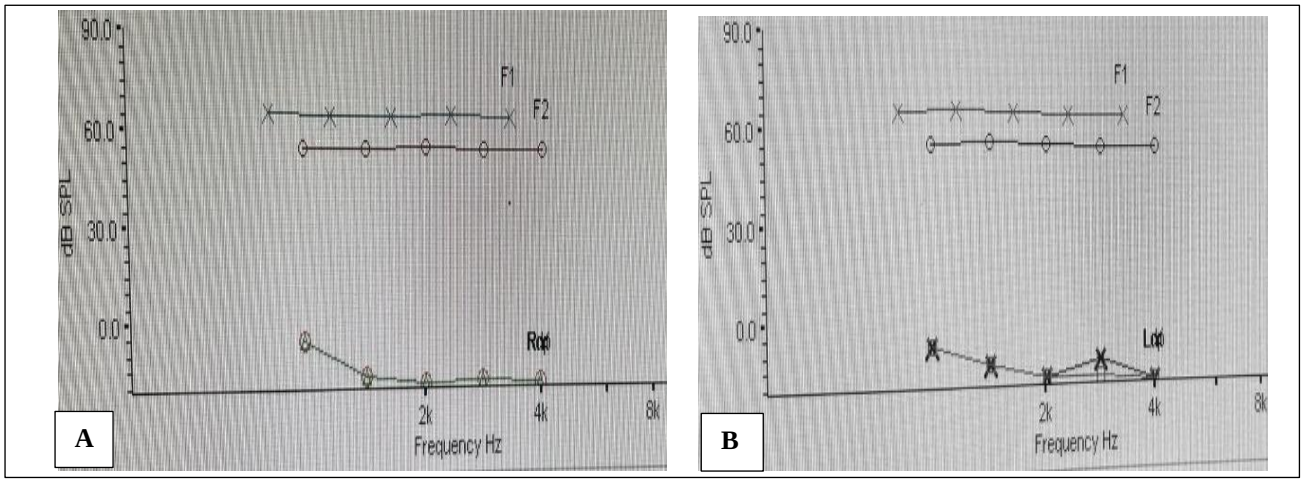

Figure 2: DP gram (a) right ear; and (b) left ear.

DISCUSSION

Metachromatic leukodystrophy is one of the rare lysosomal diseases. In the late infantile form and juvenile form of this disorder, the motor deterioration is a key feature. Lugowska et al. showed that in patients with neuro imaging findings and ataxia, metachromatic leukodystrophy should be considered as diagnosis. Their diagnosis was based on demyelination in brain MRI and detection of low activity of arylsulfatase A.[9] Our study showed the prevalence of gait impairment and ataxia in patients with metachromatic leukodystrophy. In our patient, MRI showed the leukodystrophic pattern as periventricular white matter involvement with U fiber and subcortical rim sparing in the patient.

Sevin et al. in their review article demonstrated the demyelination as a pathological hallmark in patients with MLD.[10] Yang et al showed that the rapid and progressive regression of motor skills in patients with late infantile MLD.[11] Kehrer et al done their study in 59 patients with MLD including 27 males and 32 females. 21 patients with late infantile MLD showed loss of the all gross motor function and 38 patients with juvenile MLD had a more variable motor decline.[12]

CONCLUSION

Early identification of hearing loss offers children the opportunity to develop significantly improved language skills. This report aimed to spread awareness about the audiological findings in late infantile metachromatic leukodystrophy among otologist, audiologist, and paediatrician and take further steps to provide service to the patient. Regular audiological evaluation and speech and language evaluation should be done using objective and subjective test is highly recommended.

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