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Juvenile Metachromatic Leucodystrophy: A Rare Case Report

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Abstract:- Metachromatic leukodystrophy (MLD), also called arylsulfatase A deficiency (ARS-A) which is a rare demyelinating disease (prevalence 1:40,000, presents with neurological and psychiatric symptoms. Clinical assessment is difficult, due to nonspecific signs and symptoms. We report a case of a 7-year-old male child who is born of 3-rd degree consanguineous marriage with normal developmental milestones up to 3.5 years of age presenting with complaints of progressive impairment of walking over 3.5 years. Juvenile form of MLD was diagnosed by typical history, neuroimaging and confirmed by Clinical Exome Sequencing.

I. INTRODUCTION

Metachromatic leukodystrophy (MLD) is a rare demyelinating disease with a prevalence of 1:40,000 , the gene is located on chromosome 22q13.33, and the patient presents with neurological and psychiatric symptoms. Arylsulfatase A is essential for the normal metabolism of sulfatides. These are important constituents of the myelin sheath. Sulfatides accumulates in the central nervous system and in various other tissues, like the peripheral nervous system[1]. Increased in the amounts of cerebroside sulfate is thought to cause breakdown of myelin and oligodendroglia destruction. The most frequent symptom of leukodystrophy disease is a gradual decline of the development of an infant or child who has previously developed as per age. The clinical features includes progressive intellectual deterioration with varying degrees of pyramidal and cerebellar dysfunction. The course of the disease is usually progressive and Seizures thought infrequent may also occur. Enlargement of head is a feature in certain variants. It includes three types - (i) late infantile form of the disease starting before the age of 3 years, (ii) juvenile form that starts between 3 to 16 years, and (iii) adult form presenting its first symptoms after the age of 16 years[2]. The incidence of MLD is reported as to be 1 per 100,000 live births in the European population and at an even lower rate in Asia. [3].

II. CASE

A 7-year-old male born of third-degree consanguineous marriage through normal vaginal delivery had normal developmental milestones up to 3 years of age. He was admitted with us for complaints of progressive impairment in walking over the past 3.5 years. Initially, he had an unsteady gait with frequent falls which progressed to the inability to walk even with support. He also developed progressive deterioration of speech. The speech was dysarthric and slurred, with an inability to speak at the time of the presentation. Comprehension was intact. The child also had difficulty swallowing solid food with continuous drooling of saliva. There was a loss of bowel and bladder control. He had one episode of Generalised tonic-clonic seizure at 2 and a half years of age. The younger sibling has complaints with similar semiology. The younger sister is currently 5 years old. She presented to us with similar complaints of gradually progressive impairment in walking since she was 4 years old, speech difficulty, difficulty in swallowing food and continuous drooling of saliva.

On examination, the child had an apathetic look with normal vital signs, no abnormal skin pigmentation was seen. Only cooing was present in speech. Spasticity was present in all 4 limbs, power was 3/5, deep tendon reflexes were exaggerated, and the plantar response was bilateral extensor. Signs of meningeal irritation were absent. Cranial nerves examination was normal. No significant abnormalities were found in other systems.

III. DIAGNOSIS

Complete blood count, liver and renal function tests were normal. On Fundoscopy there was no evidence of optic atrophy. MRI Brain with Spectroscopy was suggestive of confluent hyperintensities in the periventricular and deep white matter of bilateral frontal, parietal, occipital lobes, and posterior limb of bilateral internal capsules. There was a reversal of choline and creatinine peaks at white matter abnormality which favors demyelinating pathology, suggestive of metachromatic leukodystrophy. Electroencephalography was suggestive of normal interictal sleep patterns. There was no epileptogenic focus seen on Electroencephalography.

Clinical Exome Sequencing was suggestive of heterozygous missense variation in exon 3 of TMEM106B gene hence a diagnosis of juvenile-onset metachromatic leukodystrophy was made.

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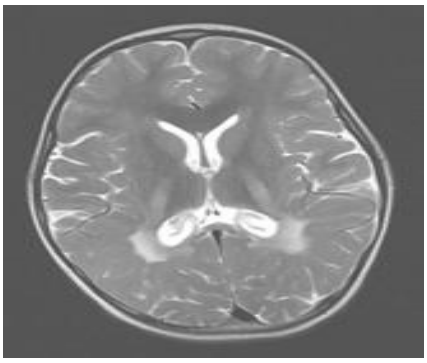

Fig 1:-T2 weighted MRI shows confluent hyperintensities in the periventricular and deep white matter of bilateral frontal, parietal, occipital lobes, and posterior limb of bilateral internal capsules.

IV. TREATMENT

The child was given supportive and symptomatic treatment. Physiotherapy was started to prevent contractures and maintain a normal tone. A diet chart was made and supplemented with calcium ,vitamin D, iron and folic acids to improve nutrition. The child was started on nasogastric tube feeding. Baclofen added to relieve spasticity. Child was discharged and parents were counselled regarding the prognosis of the child.

V. DISCUSSION

Metachromatic leukodystrophy which is an autosomal recessive disorder caused because of deficiency of the lysosomal hydrolase, Aryl sulfatase A (ARSA). It is defined by the lysosomal accumulation of sulfated glycolipids specifically 3-O-sulfagalactosyl-containing glycolipids. It mainly accumulates in the myelin sheaths of the central and peripheral nervous system. These glycolipids accumulate in the lysosomes. This results in the characteristic metachromatic staining of the tissues, hence the name of this disease.

Three different types of metachromatic leukodystrophy have been recognized according to patient's age at onset: late infantile, juvenile, and adult 2. The juvenile type presents between 3-16 years. Most are affected before 10 years. The Clinical features of MLD include mental deterioration, hypotonia, developmental delay, speech abnormalities, loss of mental abilities, blindness, rigidity, convulsions, paralysis, impaired swallowing , dementia, poor school performance, tremors, ataxia, seizures, and dementia.

A similar case was reported by Mohammad Ala Uddin et al of a 7-year-old female child presenting with a history of progressive weakness of all 4 limbs and loss of bowel bladder control. Mri was done with features suggestive of MLD. The diagnosis was confirmed after performing an enzyme assay which was markedly reduced. The patient was treated with supportive care and physiotherapy [4].

Another case was reported by Vaibhav S. Lokhande of a 2 year 6 month old male child presenting with complaints of inability to sit and stand with normal pattern development previously. Mri brain was done which was Suggestive of demyelination consistent with MLD. Arly sulfatase enzyme activity was tested which was decreased thus confirming the diagnosis.[5]

The indexed case presented the Juvenile form of MLD with symptom onset and progressive deterioration occurring over the last 4 years. Symptoms of the patient include the gradual deterioration in scholastic performance, progressive difficulty in walking, slurring of speech, and emotional and behavioral disturbances that relate to that of Juvenile MLD.

Metachromatic leukodystrophy manifests as symmetric confluent areas of high signal intensity in the periventricular white matter with sparing of the subcortical U fibers as seen in T2 weighted MR imaging. [6]

Clinical exome sequencing confirms the diagnosis of metachromatic leucodystrophy.

In the case of asymptomatic late infantile and early juvenile forms, , bone marrow or cord blood transplantation is the solution available primarily to improve neurocognitive functions. Here, in this case, drugs were introduced to improve the spasticity. Physiotherapy was initiated as a part of rehabilitation. Future treatment options including gene therapy, and potentially enzyme enhancement therapy are currently being explored [7.]

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