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Metachromatic Leukodystrophy with PSAP Gene Mutation

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Abstract: ***Metachromatic leukodystrophy is a rare neurodegenerative lysosomal disease caused by deficiency of enzymes arylsulfatase A results in accumulation of cerebrosidesulfatide in white matter of central and peripheral nervous system. Mutation in gene ARSA and, in rare cases, due tovariations in the PSAP gene causes sapos in-B deficiency and is inherited in an autosomal recessive pattern. There are three types of MLD based on the age symptoms appear: late-infantile MLD, juvenile MLD, and adult MLD, they affect both intellectual and motor function. Symptoms vary by type but can include difficulty talking and walking, seizures, personality changes, and behaviour and personality changes. Here we report a case of late infantile onset metachromatic leukodystrophy with normal arylsulfatase A activity, mutations in the PSAP gene,presented with regression of milestone and myoclonic seizures and diagnosis of MLD suspected on the basis of peculiar clinical history and confirmed on the basis of MRI and clinical exome studies.***

Keywords: Metachromatic leukodystrophy; PSAP gene; Arylsulfatase A; saposin-B, MRI; restricted diffusion

1. Introduction

Metachromatic leukodystrophy (MLD) is an autosomal recessive neurodegenerative lysosomal disease characterized by accumulation of sulfatides, within the myelin sheath of the central and peripheral nervous system, leading to progressive focal or generalized white matter degeneration [1] [2] and loss of both cognitive and motor functions. It is one of the most prevalent inherited white matter disorders [3]. In vivo, the catabolism of sulfatide requires both the enzyme arylsulfatase A and a specific sphingolipid activator protein, saposin-B, encoded by the PSAP gene. Arylsulfatase A activity is deficient in the classical forms of MLD, but exceedingly rare cases of MLD are due to saposin-B deficiency. Its incidence of 1 in 40, 000 to 1,60 000 individuals, worldwide [4]

2. Case Report

We report a case of a 3 year old boy born of non-consanguineous marriage with normal birth history, presented with regression milestones at 18 months of age. The development milestones were normal till 15 month of age. The child attained neck holding at third month and was able to sit with support by sixth month, sitting without support by eighth month and was walking with support by ninth months. At the age of one year, the infant was able to walk without support and was speaking mono-syllables by sixth month and bi-syllables by nine months. He showed stranger anxiety by 10th month of age.

He had gradually progressive regression of milestonehad progressive inability to walk, sit and speak with in a time span of one to two months followed by dystonia, muscle weakness, delayed motor development, hypotonia, development of spascity followed by hearing and vision losswithin 6 month of onset of regression of milestones and later developed decebrate posture along with myoclonic seizures. The child required frequent hospitalization for recurrent seizures requiringmultiple anti-epileptic agents.

The antenatal period was uneventful and the infant was delivered by spontaneous vaginal delivery with birth weight of 3 kg. No history of perinatal asphyxia, neonatal seizures and neonatal jaundice. No significant maternal history and no family history of similar complaints. On examination, there were no neurocutaneous markers and no facial dysmorphism. Central nervous system revealed generalized spasticity, exaggerated deep tendon reflexes and extensor plantar response. Cardiovascular system and respiratory system were unremarkable.

Neuroimaging was done –MRI BRAIN showed a postero-anterior gradient predominantly affecting parieto occipital periventricular and deep white matter,splenium of corpus callosum with anterior progression and caudal extension along cortico spinal tracts without obvious enhancement and showing restricted diffusion in certain areas suggestive of metachromatic leukodystrophy.

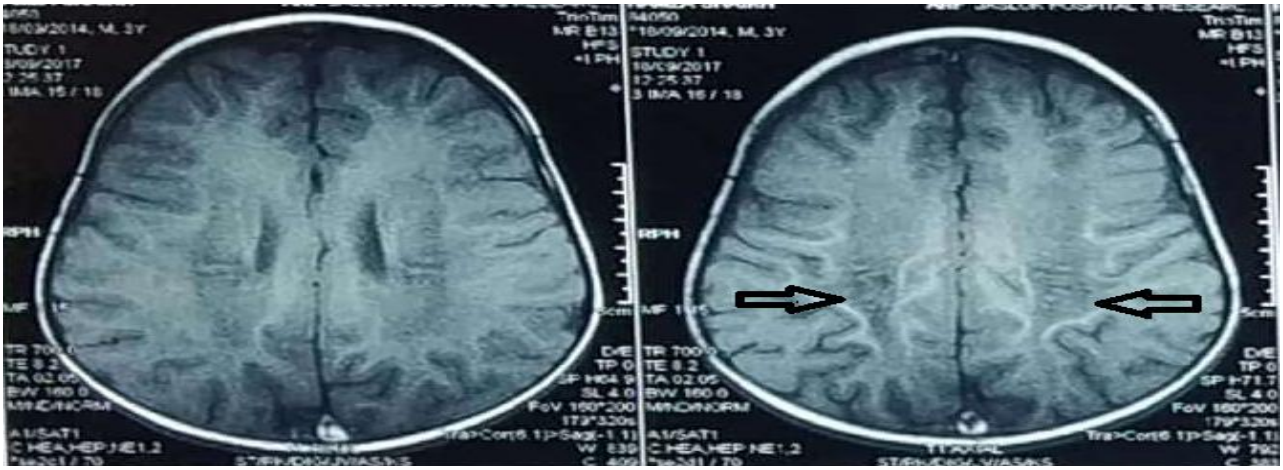

Figure 1: T1 weighted axial showing conspicuous tigroid and leopard skin pattern

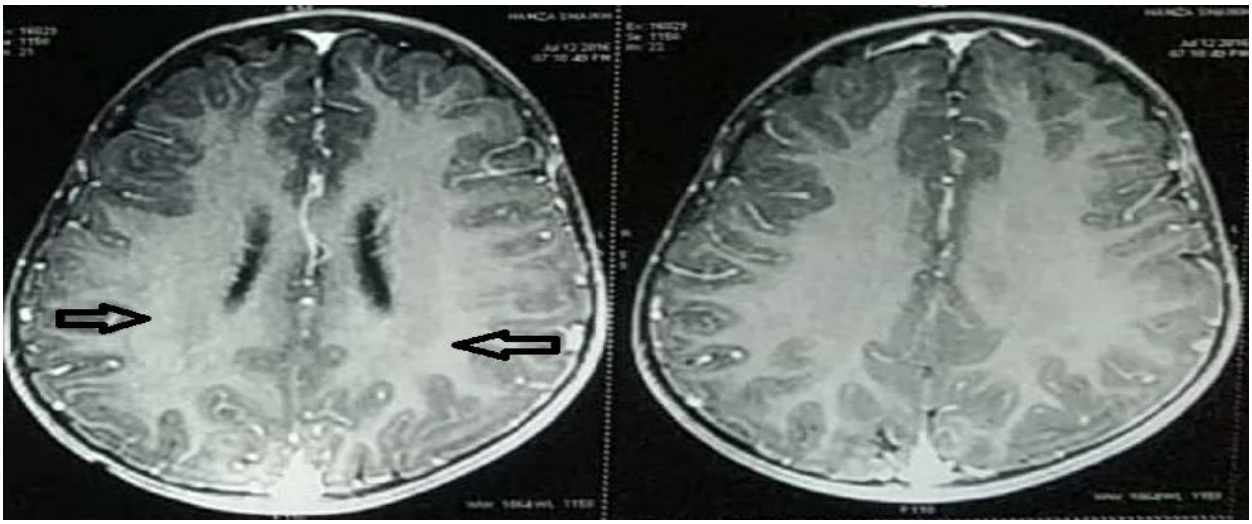

Figure 2: Inferior & superior centrum semiovale levels show tigroid and leopard skin pattern -less conspicuously

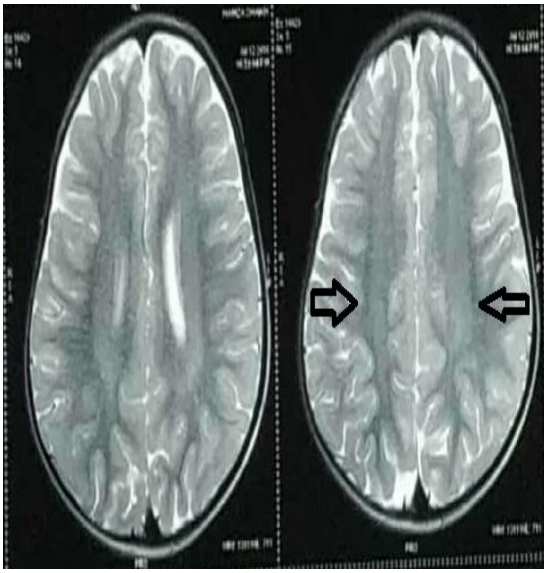

Figure 3: Show hypointensity with indistinct pattern

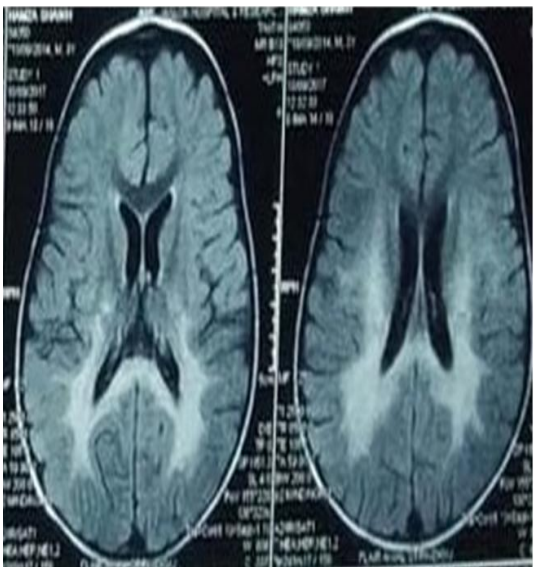

Figure 4

EEG was done suggestive of abnormal bilateral epileptiform abnormality.EMG/NCV test was suggestive of demyelinating sensory motor generalized neuropathy. Enzyme analysis of Arylsulfatase A was within normal limit. Clinical Exome test of PSAP (NM_002778) gene in exon 4 detected variant - chr10:73591001A>T c.257T>A p.lle86Asn with homozygosity in recessive inheritance pattern in child while the parents both had heterozygous variant of the same gene.

Thus clinching the diagnosis of infantile metachromatic leukodystrophy.The patient was treated with supportive care and physiotherapy was advised

3. Discussion

MLD is a lysosomal storage disease from the family of leukodystrophies and among the sphingolipidoses it affects the metabolism of sphingolipids. It has an autosomal recessive inheritance pattern. [5,6]A leukodystrophy is a genetic disorder that disrupts myelination in the brain. It affects the growth and/or development of myelin, the fatty covering which acts as an insulator around nerve fibre throughout the central and peripheral nervous systems.

Aryl sulfatase A, a lysosomal enzyme aids in degradation of sulfated glycolipids, especially galactosyl sulfatide. Classical type MLD results from this arylsulfataseA enzyme deficiency, which leads to accumulation of sulfatide in central and peripheral nervous system, progressive demyelination, motor and cognitive dysfunction. It is called metachromatic leukodystrophy because sulfatide accumulation in cells appears as granules that are coloured differently than other cellular material (metachromatic) when viewed under a microscope.

MLD has been categorized depending on the age of presentation as late-infantile type (onset before three years of age), juvenile type (onset before 16 years) and adult type [7]. Late infantile and the juvenile variants are characterized by rapid motor decline, while adult form presents with cognitive and behavioural problems. This case is considered as late infantile variant of MLD, based on the age of onset and clinical presentation. The child presented with typical regression of milestones followed by seizures. Another characteristic feature of MLD in this child is recurrent seizures and their increases inincidence with duration of illness.

Generalized seizures are common in infantile type as in this case, while partial seizures are more common in juvenile type. Older children present with gait abnormalities, seizures, behavioural changes and deterioration of scholastic performance. Along with regression of milestones, spasticity is a characteristic manifestation of MLD was also seen in the child [8] [9].

The important diagnostic modalities used to confirm this degenerative disorder are arylsulfataseA enzyme activity, molecular genetic testing of arylsulfatase A, estimation of urinary sulfatide and detecting metachromatic lipid deposits in the nervous tissue [10]. Gene sequence analysis of arylsulfatase A is an important tool for prenatal diagnosis.

Prosaposin (PSAP) gene mutations, affecting saposin B (Sap-B), cause a rare metachromatic leukodystrophy (MLD) variant in which arylsulfatase A (ARSA) activity is normal. To date, only 10 different PSAP mutations have been associated with a total of 18 unrelated MLD patients worldwide.

In this case MRI wassuggestive of leukodystrophy and on the basis of combined clinical and MRI finding further tests were performed to confirm the diagnosis. ArylsulfataseA enzyme activities were normal, so genetic test clinical exome studies were performed and a variant in PSAP gene with homozygosity was detected thus conforming the diagnosis of late infantile MLD with a PSAP gene mutation ; furthermore parents were also tested and were found to have the heterozygous variant of the same gene.

MLD is a progressive degenerative disease and does not have a definitive mode of treatment. Bone marrow transplantation, stem cell transplantation, and genetic engineering are possible options to halt the progression of neurologic dysfunction before the development of symptoms.[11,12] Bone Marrow Transplantation which is a new mode of treatment is not feasible for this patient as diagnosis was made at a progressed stage of disease. Administration of recombinant human aryl sulfatase A is an experimental tool but it lacks universal recommendation and adaptation [13].

In conclusion, patients with MLD show a rapid and devastating clinical course. Clinical history of neuro-regressive symptoms, demyelination pattern on MRI brain along with peripheral demyelinating polyneuropathy, metachromatic leukodystrophy should be strongly suspected.

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