

Metachromatic Leukodystrophy: A Case Report

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Abstract:

Metachromatic leukodystrophy (MLD) is a rare neurometabolic disease caused by the deficiency of the enzyme arylsulfatase A. Deficiency of this enzyme results in intralysosomal storage of sphingolipid, cerebroside 3-sulfates (sulfatides), which are abundant in myelin of neurons. A pathological hallmark of MLD is demyelination and neurodegeneration,

A case of the juvenile form of MLD diagnosed by typical history, brain imaging and enzyme assay, is being reported here.

Key words : Metachromatic leukodystrophy, Arylsulfatase A, MRI

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Introduction:

Metachromatic leukodystrophy is an autosomal recessive disorder caused by deficiency of the lysosomal enzyme arylsulfatase A¹. Mutation in gene is the main reason for the development of Leukodystrophy.² The enzyme arylsulfatase A is necessary for the normal metabolism of sulfatides, which are important constituents of the myelin sheath. The accumulation of sulfatides occur not only in the central nervous system, but also in various other tissues, including the peripheral nervous system². The excessive cerebroside sulfate is thought to cause myelin breakdown and destruction of oligodendroglia. The most common symptom of a leukodystrophy disease is a gradual declination of development of infant or child who previously appeared well. The clinical features consist of progressive intellectual deterioration with varying degrees of pyramidal and cerebellar dysfunction. The course of the disease is usually progressive.¹ Seizures, though infrequent, may occur. Enlargement of the head is a feature in some varieties.

Clinically, MLD shows a wide range of spectrum with respect to the age of onset, the rate of progression and the initial symptoms. The suggested classification is as

following: (i) the late infantile form of disease that starts before the age of 2 or 3 years, (ii) the juvenile form that starts between 2 or 3 and 16 years, and (iii) the adult form that presents its first symptoms after the age of 16 years³. The incidence of MLD is reported as about 1 per 100,000 live births in the European population, and is found at even lower rate in Asia⁴⁻⁶. There rarely have been confirmed cases of MLD in Bangladesh. So we report a case of juvenile form of MLD that was confirmed by enzyme assay

Case Report :

A 5 years old male child of consanguineous parents admitted in Paediatric Neurology unit of BSMMU with the complaints of progressive impairment of walking for one and half month. Initially he walked with unsteady gait with frequent fall, but for the last few days he was unable to walk even with support. In addition, he also had progressive deterioration of speech. speech was slurred and dysarthric and he could speak only a few words with difficulty. However, hearing and vision seemed to be normal. He had 1 episode of GTCS one month back which persist for 4-5 minutes. There was no history of unconsciousness, bowel and bladder incontinence or head injury. His perinatal period was uneventful. His developmental milestones were age appropriate prior to this illness. There was no history of such illness among his

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family members. On examination the boy looks apathetic with unusual smile face, vital signs were within normal limit, no abnormal skin pigmentation was noted. His speech was disarthric. His all extremities were hypotonic with power 3/5, deep jerks were absent & planter response was bilaterally flexor. There was no sensory involvement. Cranial nerves were intact. The brain MRI revealed increased white matter signal in both hemisphere on T2 weighted image and tigroid stripes appearance which is a typical finding of metachromatic leukodystrophy (Fig. 1). Findings of NCS was reduced and EMG shows sensory motor polyradiculoneuropathy and mild feature of chronic re-innervation. EEG shows asymmetric sharp and slow wave with predominance over posterior temporal-parietal region from the beginning of recording. Laboratory tests, including those for muscle enzymes, ammonia, lactate, CBC and urinalysis showed no specific findings. Enzymatic assay for leukocyte Aryl Sulfatase A is in deficient range, 11 nmol/hr/mg. (Range in normal subject: 58-190 nmol .hr.mg). This patient was treated symptomatically by antiepileptic & antioxidant drug and discharged by counseling

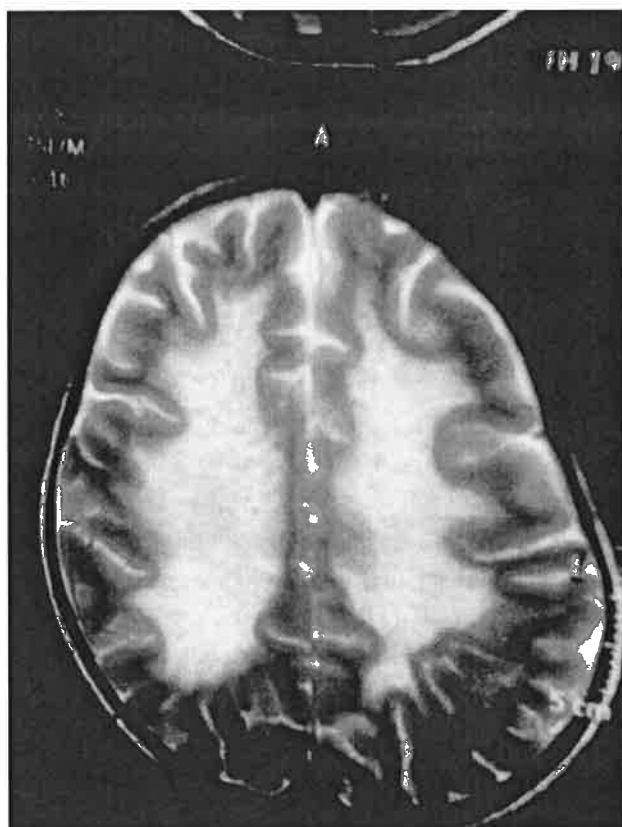


Fig-1: T2-weighted MR image demonstrates high signal intensity in the centrum semiovale white matter with

sparing of the sub-cortical U fibers (arrow shadow)

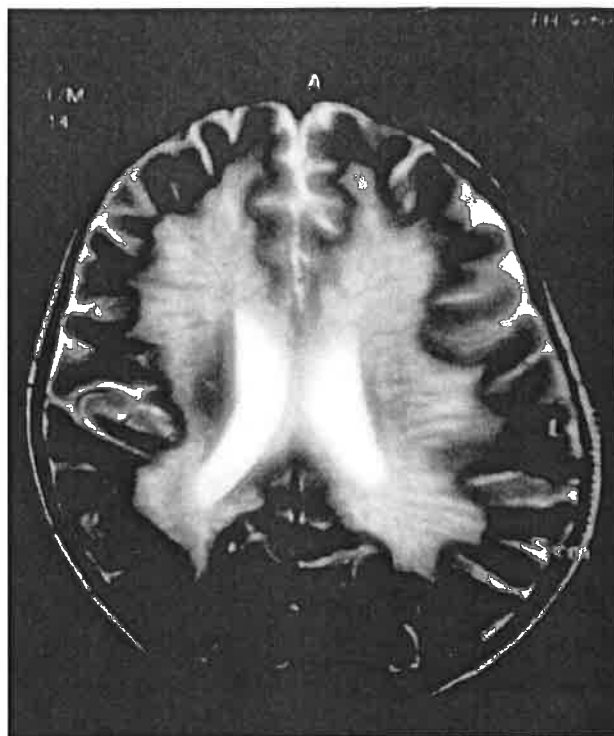


Fig-2: T2 image shows hyperintensity in the periventricular white matter with tigroid stripes appearance (arrow shadow)

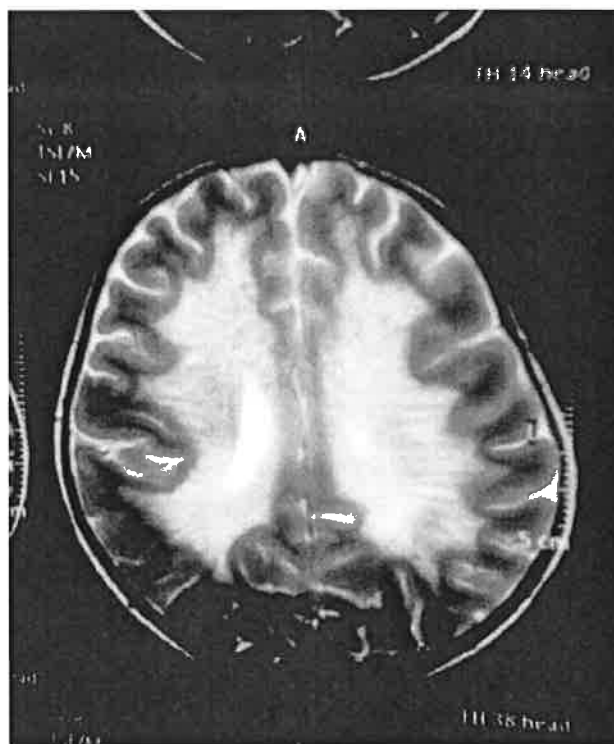


Fig-3 : T2 image shows hyperintensity in the periventricular region with tigroid stripes appearance (arrow shadow)

Discussion :

Metachromatic leukodystrophy (MLD) belongs to a family of disorders identified as lysosomal storage diseases. This disorder is characterized by the lysosomal accumulation of sulfated glycolipids, specifically 3-O-sulfogalactosyl-containing glycolipids, as a consequence of defects in the lysosomal hydrolase, aryl sulfatase A (ARSA)^{5,6}. The major site of 3-O-sulfogalactosyl-containing glycolipids is the myelin sheaths of central and peripheral neurons. Because of this location the clinical manifestations of MLD are predominately neurological in nature. Histopathologically, MLD is characterized by demyelination of central and peripheral nerves. The accumulation of sulfated glycolipids in the lysosomes results in the characteristic metachromatic staining of the tissues, hence the derivation of the name of this disease⁵.

MLD classically presents in 3 forms⁶. They are the infantile, juvenile and the rarer adult forms of MLD. The infantile variety is the commonest phenotype (1 in 40,000) followed by the juvenile type (1 in 150,000)⁷. European surveys reveal 40-50 % of patients have a late infantile form, 30-40 % a juvenile form, and around 18-20% an adult form^{6,7}. The juvenile type presents between 3-21 years. Most are affected before 10 years and Clinical features of MLD include mental deterioration, hypotonia, developmental delay, speech abnormalities, loss of mental abilities, blindness, rigidity, convulsions, impaired swallowing, paralysis, dementia, impaired school performance, ataxia, tremors, seizures, dementia.

In brain MRI of our indexed case tigroid stripes was seen in the way of extending radially within the abnormal white matter frequently low density.

Though this is the typical finding of MLD, it is not very specific as it can also be observed in other leukodystrophies^{8,9}. The proton MR spectroscopy of our patient was consistent with reported findings of MLD patients. In MR spectroscopy, elevation of choline can be interpreted as a sign of enhanced membrane turnover associated with demyelination, and reduction of N-acetylaspartate in gray and white matter as the result of neuronal and axonal loss¹⁰. Since brain MRI and MR

pectroscopy of the patient made us suspicious of MLD, arylsulfatase A enzyme activity was carried out to confirm it. Indexed case presented the Juvenile form of MLD with symptom onset and progressive deterioration occur last 5 years. The symptoms of the patient like gradual deterioration in scholastic performance, difficulty in walking, slurring of speech, emotional and behavioral disturbances relate to that of Juvenile MLD. The MRI scan of the current patient suggested cerebral and cerebellar atrophic changes with bilateral periventricular symmetrical hypersensitivity.

At T2-weighted MR imaging, metachromatic leukodystrophy manifests as symmetric confluent areas of high signal intensity in the periventricular white matter with sparing of the subcortical U fibers⁸. The tigroid patterns are specific feature of MLD in MRI. The nerve conduction velocities (NCVs) of the peripheral nerves were significantly reduced⁹. The above laboratory findings were suggestive of metachromatic leukodystrophy. Enzymatic assay revealed decreased leukocyte arylsulfatase A activity which was definite for metachromatic Leukodystrophy¹⁰.

There has been no satisfactory treatment for Metachromatic Leukodystrophy to reverse the deterioration and loss of function. To reduce the subject's symptoms and relieve pain, a number of medicines can be prescribed such as: muscle relaxants, seizure medications, psychiatric medications and analgesics. In individuals with asymptomatic late infantile and early juvenile forms of the disease, bone marrow or cord blood transplantation may stabilize neurocognitive function^{11,12}. In addition to bone marrow transplantation, gene therapy is under experiment as a possible solution to correct the underlying genetic abnormality^{13,14}.

Metachromatic leukodystrophy is to be strongly suspected in infancy and childhood when they present with features of mental regression coupled with the unusual combination of pyramidal dysfunction and peripheral neuropathy.

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