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Juvenile Metachromatic Leukodystrophy: A Case Report from Bangladesh

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Abstract

Metachromatic leukodystrophy (MLD) is the neurometabolic disease caused by deficiency of enzyme arylsulfatase a resulting in deficiency of sulfatide degradation. The responsible gene is arylsulfatase A gene and is inherited in an autosomal recessive manner. MLD is characterized by three clinical subtypes, defined primarily by age at presentation such as late infantile MLD, juvenile MLD, adult onset MLD. Here we report a case of Juvenile form of MLD that was identified by means of typical history, clinical findings and supported by nerve conduction study, typical MRI of brain findings and confirmed by enzyme assay. *[Journal of National Institute of Neurosciences Bangladesh, 2018;4(2): 154-157]*

Keywords: Metachromatic leukodystrophy; Arylsulfatase A; ARSA gene; MRI brain; White matter

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Introduction

Metachromatic Leukodystrophy (MLD, also called arylsulfatase a deficiency) is a lysosomal storage disease which is commonly listed in the family of leukodystrophies as well as among the sphingolipidoses as it affects the metabolism of sphingolipids. It is caused by mutations in the ARSA gene encoding Arylsulfatase A on chr.22q13.31 and is inherited in an autosomal recessive manner[2]. It is one of the most prevalent inherited white matter disorders[2]. The enzyme Arylsulfatase A is necessary for the normal metabolism of sulfatides which are important constituents of the myelin sheath[3,4]. The accumulation of sulfatide triggers leukodystrophy[1]. This accumulation occurs not only in the central nervous system but also in various other tissues including peripheral nervous system[3,4]. 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 Asia[1,4,5].

The most common symptom of a leukodystrophy disease is the 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[6]. Clinically MLD shows a wide range of spectrum with respect to the age of onset, the rate of progression and the initial symptoms. It is characterized by three clinical subtypes, defined primarily by age at presentation such as late infantile MLD, juvenile MLD and adult onset MLD. Late infantile MLD patients usually present by age 30 months, after a period of apparently normal development. Juvenile MLD patients present between age 30 months and 16 years (12 to 14 years). Patients presenting after this age are classified as having adult onset MLD[1,2,3,7]. There rarely has been case report of MLD in Bangladesh. So we report a case of Juvenile form of MLD that was confirmed by enzyme assay.

Case Presentation

A 7-year old female child of non-consanguineous parents presented with the history of weakness of both upper and lower limb for last one year with progressive impairment and clumsiness of gait for last 6 months; furthermore, deterioration of school performance was noted for last 6 months with incontinence of bowel and bladder for last 4 months. The vision and hearing of the patient were seemed to be normal. She had no history of seizure, dysarthria, altered sensorium, headache and vomiting. Her perinatal period was uneventful and developmental milestones were age appropriate prior to this illness. The child was the 4th issue of her non-consanguineous parents. One elder brother and one elder sister of the patient were died of same type of illness at around 11 years of age. One brother was alive and he was healthy. On examination, the child was looked apathetic with poor facial expression; she had a somewhat mask like appearance; furthermore there was no facial dysmorphism and there were no neurocutaneous markers. Head circumference (47 cm) was at the 3rd centile. Vision, hearing and speech were

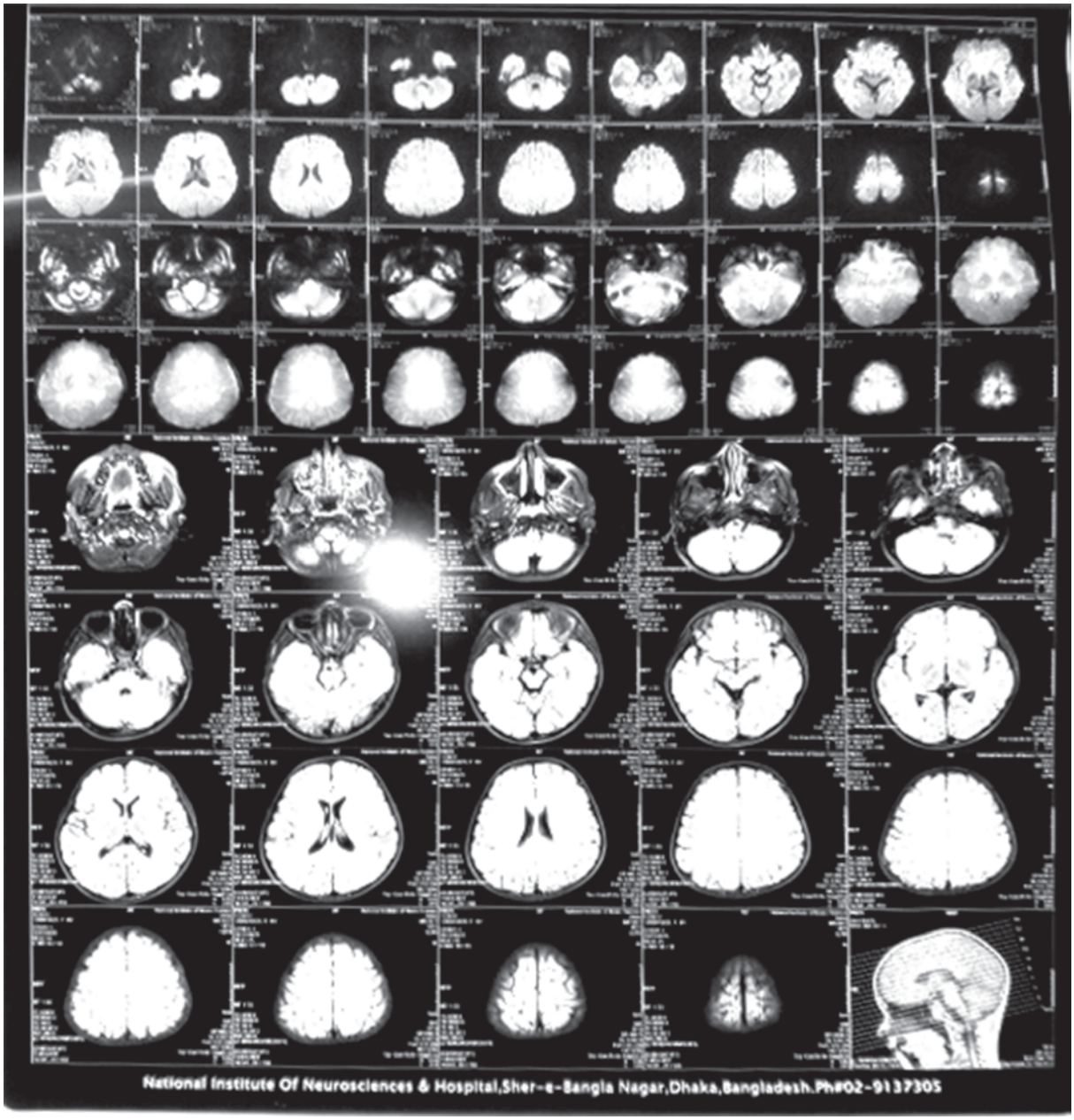

Figure I: MRI of Brain showed diffuse T2WI and FLAIR hyperintense areas seen in the white matter region sparing the subcortical U fiber

normal. Her all extremities were wasted and hypotonic with muscle power of 3/5; deep tendon reflexes were diminished and planter response was bilaterally flexor. There was no sensory impairment and cranial nerves were intact. There was no cerebellar sign. He walked with unsteady gait and clumsiness was seen in all extremities. Nerve conduction study (NCS) of cross limbs was done and the findings were consistent with demyelinating sensory motor polyrneuro-radiculopathy and predominantly sensory. Relative symmetry and absence of definite conduction block was suggestive of hereditary neuropathy (HMSN type-1). Serum vitamin B-12 level was normal. MRI of Brain showed diffuse T2WI and FLAIR hyperintense areas which were seen in the white matter region sparing the subcortical U fiber which was a typical finding of MLD. MRS of Brain showed elevated Lac/Cr and ml/Cr and decrease NAA/Cr ration which was in favor of MLD. Arylsulfatase A enzyme activity in leukocytes was tested and was found to be markedly reduced (patient 9.00 nmol/hr/mg, range in normal subjects: 58-190 nmol/hr/mg; mean value 103.2 nmol/h/mg). Thus the patient was confirmed to have metachromatic leukodystrophy. The patient was treated with supportive care and physiotherapy was advised.

Discussion

MLD is a lysosomal storage disease from the family of leukodystrophies and among the sphingolipidoses it affects the metabolism of sphingolipids. Leukodystrophies affect the growth and/or development of myelin, the fatty covering which acts

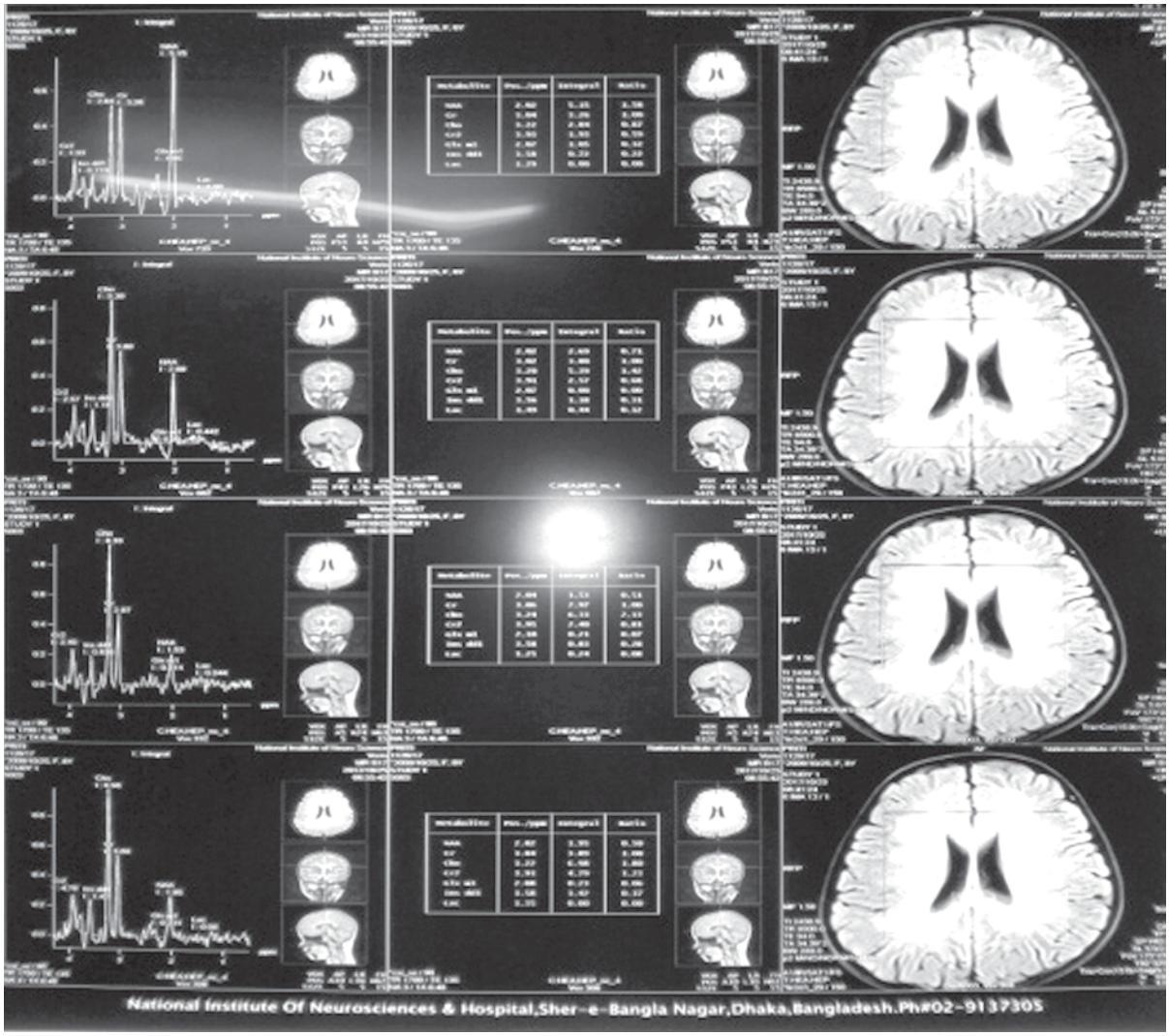

Figure II: MRS of Brain showed elevated Lac/Cr and ml/Cr and decrease NAA/Cr ration which goes in favor of MLD

as an insulator around nerve fibers throughout the central and peripheral nervous systems. MLD involves cerebroside sulfate accumulation. MLD has an autosomal recessive inheritance pattern[1,8].

Depending on the age of presentation, Metachromatic Leukodystrophy has been classified as late infantile type, Juvenile type, Adult type[2]. Rapid motor decline is typical for the late infantile and also the juvenile types[13]. Juvenile MLD patients present between age 30 months and 16 years (12 to 14 years)[2]. Patients often present with cognitive and behavioral difficulties. Younger onset patients often show early motor involvement and may also show rapid decline. Clumsiness, gait problems, dysarthria, incontinence and worsening behavioral problems occur later in the course. Patients may have seizures, most often complex partial seizures. Juvenile MLD has a slower course than infantile MLD[2]. The age of onset and clinical presentation was suggestive of Juvenile variant of MLD in our patient.

The various methods are used to confirm metachromatic leukodystrophy which are aryl sulfatase A enzyme activity, molecular genetic testing of aryl sulfatase A[9], estimation of urinary sulfatides and finding metachromatic lipid deposits in the nervous system tissue[10]. ARSA gene sequence analysis aids in prenatal diagnosis[13].

Metachromatic leukodystrophy is a progressive degenerative disease and does not have a definitive mode of treatment till date. Bone marrow transplantation, stem cell transplantation, and genetic engineering are possible options to halt the progression of neurologic dysfunction[11,12]. However Bone Marrow Transplantation which is a new mode of treatment is not feasible for this patient. Administration of recombinant human aryl sulfatase A is an experimental tool; however, it lacks universal recommendation and adaptation[13].

Conclusion

Metachromatic Leukodystrophy is to be strongly suspected in a child when present with features of developmental regression coupled with the unusual combination of pyramidal dysfunction and peripheral neuropathy, consanguinity and positive family history.

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