



MRI Diagnosis in Classical Metachromatic Leukodystrophy

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Abstract

Metachromatic leukodystrophy (MLD) is a rare group of genetically-transmitted, autosomal-recessive, lipid-storage disorders characterised by accumulation of glycosphingolipids caused by deficiency of Arylsulfatase-A enzyme in lysosomes of cells necessary for formation of normal myelin sheath. The disease can present anytime from infancy to adulthood and is characterised by progressive deterioration of motor & neurocognitive functions with variable prognosis. Though till date, there is no definitive treatment / cure for the disease yet bone marrow transplantation in infancy has shown to delay the progression of disease & gene therapy in animal experiments has shown promising future, making early diagnosis very imperative. Diagnosis is usually suspected on magnetic resonance imaging (MRI) of brain and confirmed by enzyme assays. Hence, in this article we are describing the classical brain MRI and clinical features to make the readers aware of this uncommon but important neurological entity.

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Introduction

Deficiency of Arylsulfatase-A (ARSA) enzyme in patients suffering from metachromatic leukodystrophy (MLD) results in accumulation of sulfatides within the human cells affecting their function including cells responsible for myelin-production (with predominant involvement of white matter in the brain and white matter tracts in spinal cord) and cells of biliary tract & distal renal tubules^[1,2]. Microscopically, these sulfatides appears as colored granules during staining with specific dyes, hence the term *metachromatic*. Presence of these granules in the white matter / nerves justifies the term *metachromatic leukodystrophy*. This article discusses the characteristic clinico-pathological and MRI features of MLD with slight emphasis on management.

Case Report

A four-year, female child presented to pediatric outpatient department of our hospital with history of gradually pro-

gressive generalized weakness and gait disturbances since last 6 - 12 months. She recently had an episode of generalized seizure. Though there was no complaint related to speech yet it was incoherent at the time of presentation. There was no history of fever or significant parental history. The child was given some local treatment off & on for weakness in the village for which no medical records was available. No family history of similar symptoms / disease was noted. Routine laboratory investigations and radiograph of the chest were unremarkable.

Patient was advised MRI brain to detect the cause of her problems. It revealed near-symmetrical, bilateral, confluent, periventricular white matter, hyperintensity on T2W & T2FLAIR images at the level of centrum semiovale region with hypointense transverse striations & dots on transaxial images and corresponding hypointensity on T1W images without significant post contrast enhancement or mass effect (Figures 1- 4). No obvious signal alteration was noted on diffusion-weighted (DW) images. No obvious sign of internal hemorrhage or calcification was noted in the white matter.



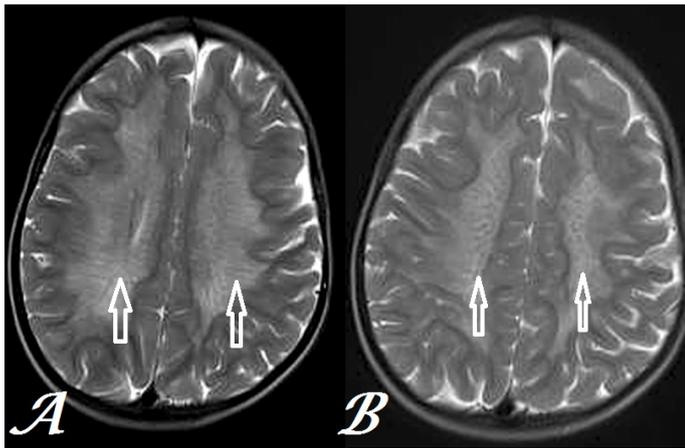


Figure 1a-b: Transaxial, T2W MR Brain images at inferior (a) & superior (b) centrum semiovale levels show *tigroid and leopard skin pattern* respectively (arrows) in a case of MLD.

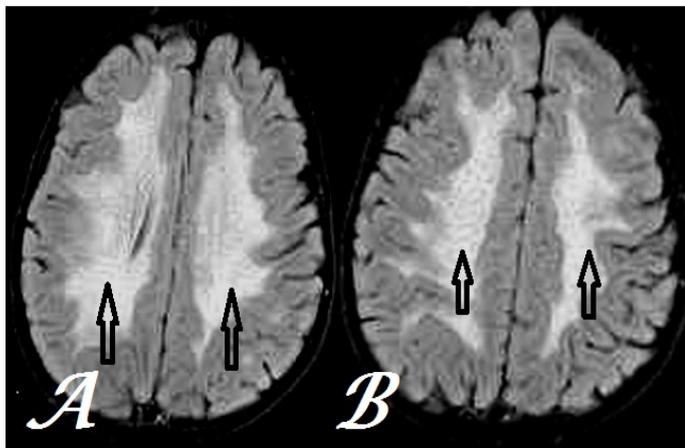


Figure 2a-b: Transaxial, T2FLAIR MR Brain images at inferior (a) & superior (b) centrum semiovale levels show *tigroid and leopard skin pattern* respectively (arrows) less conspicuously than figure 1 in the same case.

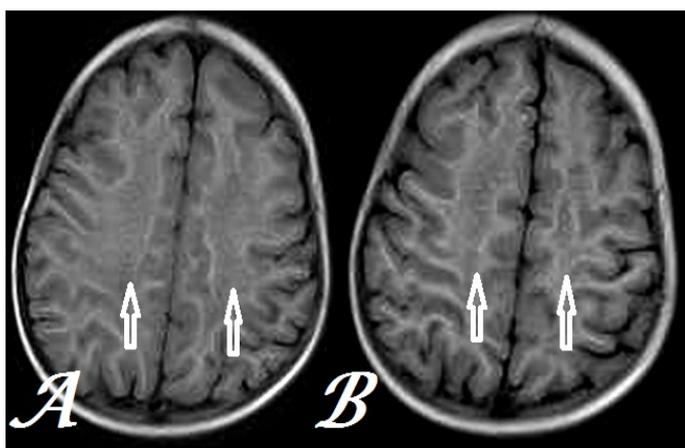


Figure 3a-b: Transaxial, T1W MR Brain images at inferior (a) & superior (b) centrum semiovale levels show hypointensity with indistinct pattern in corresponding areas as in figure 1 (arrows) in a same case.

Based on the above findings, the diagnosis of juvenile-form of MLD was considered and the patient blood was sent for ARSA enzyme activity in leukocytes that revealed markedly low levels (60% lower than controls), thus confirming the diagnosis. Patient was then referred to dedicated pediatric neurocen-

tre for further management.

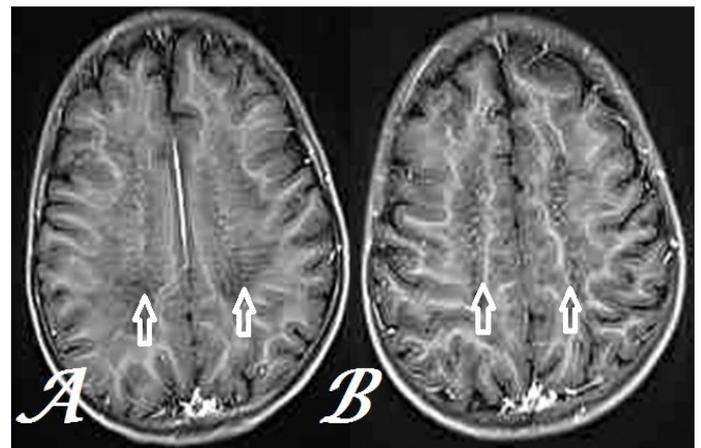


Figure 4a-b: Transaxial, postcontrast T1GRE MR Brain images at inferior (a) & superior (b) centrum semiovale levels show conspicuous *tigroid and leopard skin pattern* respectively (arrows) in the same case.

Discussion

MLD is known by multiple names as *arylsulfatase deficiency*, *Greenfields' disease*, *cerebroside sulfatase deficiency disease*, *sulfatide lipidosis*, *sulfatidosis*, etc. MLD has a reported occurrence of up to one in 1.7 lakh worldwide with higher incidence in small population subgroup of Israel (Jews & Arabs) and in Navajo Nation^[3]. MLD occur secondary to mutation in ARSA gene in lysosomes leading to deficiency of ARSA enzyme with consequent accumulation of sulfatides within the cells^[4]. This gene is transmitted in autosomal recessive pattern with carriers being asymptomatic. Some of these patients show mutation in PRAP gene which results in cellular deficiency of protein, *Saposin-B* that works in conjunction with ARSA enzyme. Some individuals with low-ARSA levels (less than 15% of control / normal) do not reveal signs of MLD, hence referred to as *pseudoarylsulfatase deficiency*^[5]. Accumulation of sulfatides in myelin-producing cells results in abnormal myelin-sheath in patients of MLD affecting white matter of brain as well as tracts & nerves of brain & spinal cord, involving cranial as well as peripheral nerves. Hence, these patients often present with pseudobulbar palsies, muscle weakness & neuropathies showing variable progression to seizures, gait disturbances & paralysis before being non-responsive.

MLD may present at different ages with variable clinical features as described below:

Late-Infantile form (LIF): represent more than half the cases with loss of speech that has already developed, loss of muscle tone, development of rigidity, gait disturbance and rapid-progression to non-responsiveness or death during childhood mainly due to aspiration or bronchopneumonia and respiratory failure^[1].

Juvenile-form (JF): represents nearly one-third cases presenting in form of behavioral disturbances or poor school performance during childhood to adolescence with slower progression relative to LIF and survival up to third decade of life.

Adult form (AF): represents less than one-third cases and is characterised by psychiatric disturbances like delusions / hallucinations in addition to features seen in JF with periods of waxing & waning. Survival may extend up to 2 - 3 decades after the diagnosis.

Besides involving nervous system, other organs most commonly gall bladder may be involved with MLD. Few previous case reports have described enlargement of gall bladder with thickened walls, pericholecystic fluid and peripheral calcifications in a case of MLD^[6]. Brain MRI in classical case reveals bilaterally, symmetrical, homogeneous & confluent hyperintensity on both T2 weighted & T2FLAIR images involving primarily periventricular white matter involving all cerebral lobes in posteroanterior pattern with extension in to corpus callosum & relative sparing of subcortical white matter in early stages^[7]. The dysmyelination occurs typically in *tigroid* or *leopard-skin pattern* in the centrum semiovale due to relative sparing of myelin along transmedullary vessels as seen in our index case^[8]. Diffusion-weighted images may also show hyperintensities in the corresponding region in the active stage without significant abnormality on ADC map^[9]. Proton MR-Spectroscopy in the areas of hyperintensity shows increased Cho/Cr & Cho/NAA ratios and decreased NAA/Cr ratio along with myoinositol peak^[10]. Besides, the central nervous system, peripheral nervous system may be involved in form of peripheral neuropathy with reduced motor & sensory nerve conduction velocities leading to gait disturbances^[11]. Secondary to suggestion of MRI diagnosis of MLD, low ARSA enzyme activity in leukocytes or chromosomal analysis for ARSA gene may be used for final confirmation^[12,13].

Till date, there is no definitive treatment for MLD and management is limited to palliative & supportive measures including gastric tube feeding, antibiotic therapy and bone marrow replacement. Hematopoietic stem cell transplant has shown to delay the progress of disease especially in juvenile form^[14,15].

Conclusions

To summarize, though MLD is an uncommon neurological entity yet its characteristic features on MRI brain should prompt us to make an early suggestion of diagnosis so that ARSA activity can be advised in blood leukocytes for final confirmation.

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