# MRI diagnosis in Metachromatic leukodystrophy: A case report.

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**Abstract:**

Leukodystrophies encompass a wide spectrum of inherited neurodegenerative disorders affecting white matter of central nervous system. There are distinctive clinical, biochemical, pathologic, and radiologic features of each leukodystrophies. Magnetic resonance imaging is primary imaging modality in the identification of underlying white matter abnormalities, to monitor the progression and the response to therapy. Metachromatic leukodystrophy (MLD) is a rare group of inherited, lysosomal storage disease characterized by intra-lysosomal accumulation of sphingolipid sulfatides due to reduction or complete deficiency of Arylsulfatase-A enzyme necessary for normal myelin sheath formation. Diagnosis is usually suspected on MRI of brain and confirmed by enzyme assays. Hematopoietic stem cell transplantation in infancy has shown to delay the progression of disease, making early diagnosis very imperative. We present a case of 5 years old male child of metachromatic leukodystrophy, presented with regression of milestone and progressive spasticity, who underwent MRI brain and diagnosis was confirmed by enzyme assay.

**Key Words:** Arylsulfatase A deficiency, Magnetic resonance imaging (MRI), Metachromatic leukodystrophy (MLD).

## Introduction:

In metachromatic leukodystrophy, primary abnormality is deficiency of Arylsulfatase-A (ARSA) enzyme. This results in accumulation of sulfatides within multiple tissues. This involves cells responsible for myelin-production (with predominant involvement of white matter in the brain and white matter tracts in spinal cord). There is also involvement of cells of biliary tract & distal renal tubules[1,2]. The sulfatides form granules that are described as metachromatic, which means they pick up color differently than surrounding cellular material when stained for examination.

## Case study:

A five-year, male child presented to paediatric OPD of our hospital by parents with chief complains of gradually progressive generalized weakness, gait disturbances and speech difficulties since last 1 year. Patient also had loss of previously achieved milestones and bladder and bowel control. There was no history of seizure or head trauma. No any significant perinatal or family history was noted. Patient had normal routine blood investigations and chest x-ray.

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On examination, all extremities were hypotonic with power of 2/5, absent deep tendon reflex and Babinski sign was bilaterally flexor. Cranial nerve examination was normal.

Patient was advised MRI brain to detect the cause of his problems. High resolution MR imaging was performed using 1.5T Achieva system (Philips Medical Systems). MR imaging protocols included the following: T2 weighted spin echo sequence in axial, coronal and sagittal planes, FLAIR in axial and coronal planes, Diffusion weighted images and ADC images in axial plane, T1 weighted pre-contrast in axial and sagittal plane, post-contrast T1 weighted 3D images and gradient echo (GRE) image in axial plane. MRI revealed T2/FLAIR confluent, symmetric butterfly shaped hyperintensities involving the periventricular deep white matter, centrum semi-ovale and corpus callosum in its entire extent. Alternate areas of hypointense and hyperintense bands were noted in bilateral periventricular white matter due to sparing of perivascular white matter (tigroid or leopard pattern) (Image 1 and 2).

***Image 1: MRI - T2WI axial (A and B), coronal (C) and sagittal (D) images showing confluent, symmetric, butterfly shaped abnormal hyper intensity in bilateral frontotemporoparietal white matter, centrum semi ovale and in corpus callosum.***

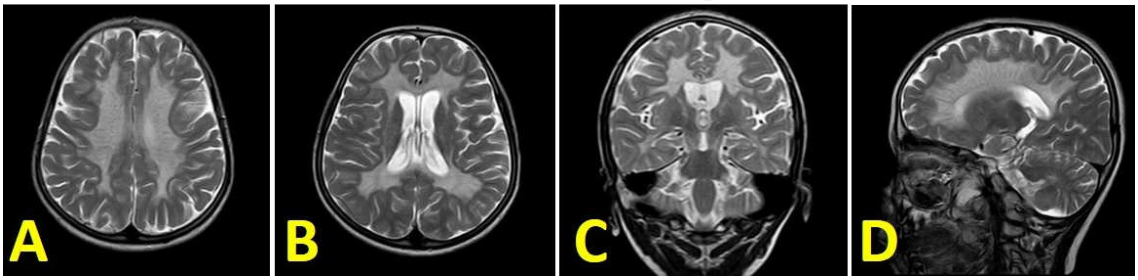



***Image 2: MRI - FLAIR axial (a and b) and coronal (c and d)***

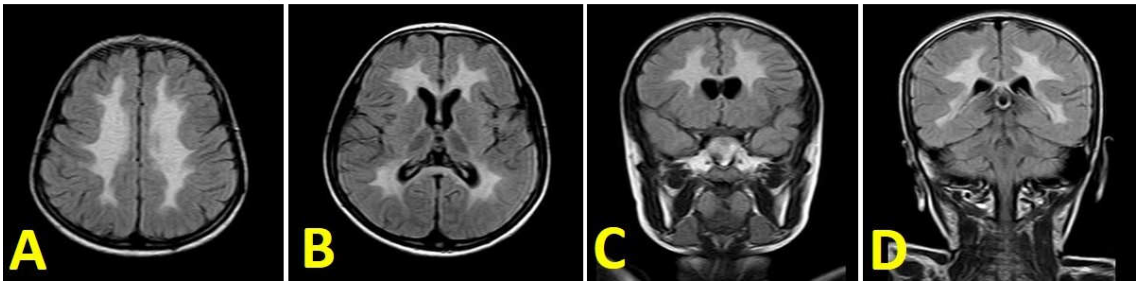
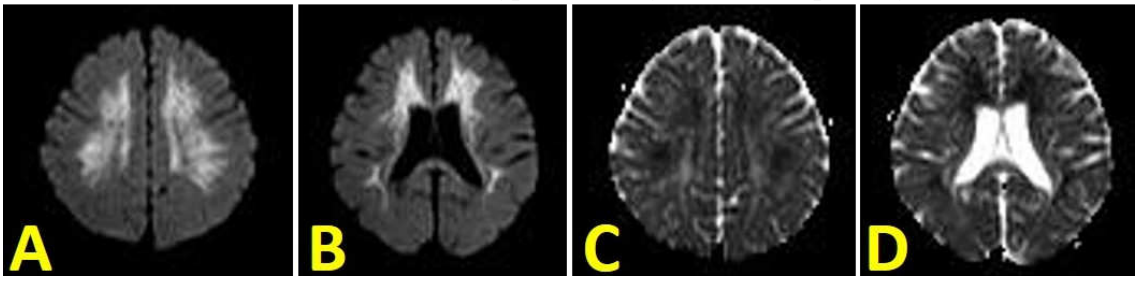


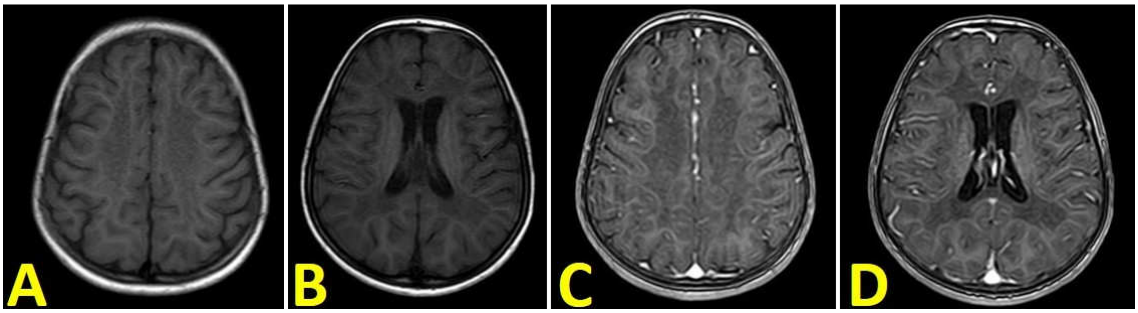

***Image 3: Axial DWI (A and B) shows diffusion restriction; Axial ADC (C and D) shows hypointense signals at corresponding levels***




It showed restriction on DWI images and corresponding hypointense signals on ADC images (Image 3). No evidence of abnormal contrast enhancement was seen (Image 4). There was relative sparing of subcortical white matter. No evidence of internal haemorrhage or

calcification was noted in the white matter.

***Image 4: T1WI axial precontrast (a and b) and post contrast (c and d) images show no significant abnormal contrast enhancement.***




The findings were suggestive of metabolic white matter disease- juvenile form of metachromatic leukodystrophy, which was later confirmed with low levels of arylsulfatase in peripheral white blood cells and urine. Patient was then referred to dedicated paediatric neuro centre for further management.

**Discussion:**

White matter diseases in children are traditionally divided into three categories:

Dysmyelinating diseases, demyelinating diseases and hypomyelinating disease [3, 4]. Dysmyelinating diseases, also known as leukodystrophies, result from an inherited enzyme deficiency that causes abnormal structure and function of myelin. Demyelinating diseases involve destruction of previously normal myelin. In hypomyelinating disease, there is reduction in amount of otherwise normal myelin.

MLD, also known as sulfatide lipidosis is one of the most common of all inherited white matter disorders with reported occurrence of up to one in 1.7 lakh worldwide. It has high incidence in Jew group of Israel and in Navajo Indians [5].

MLD is caused by mutation in ARSA gene in lysosomes, leading to reduction or complete absence of arylsulfatase A. This enzyme is necessary for the normal metabolism of sulfatides, which are important constituents of the myelin sheath. In metachromatic leukodystrophy, sulfatides accumulate in various tissues, including the brain, peripheral nerves, kidneys, liver, and gallbladder.

ARSA gene is located on chromosome 22q13 and is transmitted in autosomal recessive pattern. Earlier onset is associated with greater reduction in ARSA[6].

White matter damage due to abnormal myelin sheath causes progressive deterioration of intellectual functions and motor skills, such as the ability to walk. Affected individuals also develop loss of sensation in the extremities (peripheral neuropathy), incontinence, seizures, paralysis, loss of ability of speech, blindness, and hearing loss. Eventually they lose awareness of their surroundings and become unresponsive.

Initial signs of MLD may appear at any age, depending on which three distinct clinical forms are currently recognized.

***Late-Infantile form (LIF):*** Onset earlier than 3 years of age. It is the most common form and

presents with visuomotor impairment, gait disturbance and convulsion. Rapid-progression to non-responsiveness or death during childhood mainly due to aspiration or bronchopneumonia and respiratory failure [(1)].

***Juvenile-form (JF):*** Onset earlier than 16 years. Can have similar features as in late infantile form, but with slower progression. Cases presenting in form of behavioural disturbances or poor school performance. Survival beyond 20 years is rare.

***Adult form (AF):*** Characterized by psychiatric disturbances like delusions / hallucinations, gradual cognitive decline and dementia, multiple sclerosis like symptoms, and progressive cerebellar signs. Survival may extend up to 2-3 decades after diagnosis.

Involvement of gall bladder can be seen in the form of cholecystitis.

CT scan shows bilateral symmetrical, confluent hypodense areas in periventricular white matter. Brain MRI is investigation of choice. It reveals bilaterally, symmetrical& confluent hyperintensity on both T2 weighted & T2FLAIR images involving primarily periventricular white matter involving all cerebral lobes in posteroanterior pattern & relative sparing of subcortical white matter and cerebellum in early stages[(7)]. Serial MRI studies show centrifugal spread of abnormal confluent T2/FLAIR hyperintensity. Eventually it may involve subcortical U fibres. Corpus callosum, corticospinal tracts and internal capsule are additional sites of involvement in late stage of disease. Island of normal myelin around medullary vein in white matter may produce tigroid or leopard pattern with linear hypointensity in confluent white matter hyperintensity.

Diffusion -weighted images may show hyperintensities in the corresponding region in the active stage of demyelination, however regions of chronic demyelination demonstrate increased diffusivity. Contrast enhanced T1WI shows no enhancement, however in some cases punctate enhancement can be seen. Proton MR-Spectroscopy in the areas of hyperintensity shows increased Cho/Cr & Cho/NAA ratio and decreased NAA/Cr ratio along with myoinositol peak [(8)].

The important diagnostic modalities used to confirm this degenerative disorder are arylsulfatase A enzyme activity in leukocyte, molecular genetic testing of arylsulfatase A, estimation of urinary sulfatide and detecting metachromatic lipid deposits in the nervous tissue.

MLD progresses with age and the neurodegeneration worsens with time. There is no definitive treatment till date. Newer treatment modalities include stem cell transplantation, bone marrow transplantation along with genetic engineering and these might halt the progression of neurologic dysfunction[(9)]. Recombinant human ARSA administration, an experimental treatment can be a promising option in future, although it lacks universal recommendation and adaptation.

**Conclusion:**

In conclusion, the presence of neurological symptoms with characteristic imaging findings on MRI helps in early possible diagnosis of MLD, which can then be confirmed by ARSA activity in blood leukocytes.

**Declaration of patient consent:**

Written informed consent was obtained from the parents of patient for the publication of this report, along with the MRI images.

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**Conflict of interest**: Nil

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