

Metachromatic Leucodystrophy: A Case Report

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Abstract

Metachromatic leukodystrophy (MLD) is an autosomal recessive neurodegenerative disorder characterized by deficient activity of the enzyme arylsulfatase-A. Deficiency of this enzyme results in intralysosomal storage of sphingolipid cerebroside 3-sulfates (sulfatides), which are abundant in myelin and neurons. A pathological hallmark of MLD is demyelination and neurodegeneration, causing various and ultimately lethal neurological symptoms. Its frequency is estimated to be 1/40,000 live births. The disease encompasses three clinical subtypes: late infantile (40% of the patients with MLD), juvenile (40%), and adult (20%).

The Case

A four years old male, presented with a three month history of a progressively unsteady gait and deterioration of speech for the same duration. He was apparently well three months back when he started having frequent fall with gradual impairment of walking. Since one and half months back, he was unable to walk even with support. In addition, also had progressive deterioration in his speech. Initially, speech was slurred and dysarthric and then he could speak only a few words with difficulty. However, hearing and vision seemed to be normal. There was no history of unconsciousness, seizure, bowel and bladder incontinence or head injury. Detailed history revealed that he was born full term at home. Antenatal, perinatal and postnatal history was not significant. His developmental milestones were within normal limits for age prior to the illness. The family history was however significant; Among the four siblings, one sister had similar type of progressive deterioration of motor as well as intellectual function and had died at age of 5 years. Another sister who was eleven years old also had mental sub normality. However, there was no history of consanguinity. On examination, there was no obvious facial dysmorphism. His head circumference was 49.5 cm (10th percentile NCHS) and weight was below 5th percentile (HCHS) with normal height. He appeared dull and emotionally labile. All cranial nerves were clinically normal. On motor system examination, all extremities were hypotonic with

power of 3/5 and absence of deep tendon reflexes. Planters were flexure in response bilaterally. There were no sensory involvement; however cortical sensation and coordination could not be assessed. Rest of the general and systemic examinations was found to be normal. MRI revealed periventricular and deep white matter high signal areas (T2, NC, and axial view) and Leopard sign in contrast enhancement. CSF finding was normal. A diagnosis of MLD was suggested by the family history and clinical presentation. Further, neuroimaging abnormalities were well characterized and consisted of confluent periventricular white matter abnormalities sparing the arcuate fibers which have helped to confirm the diagnosis of MLD. The patient was advised for physiotherapy and regular follow up.

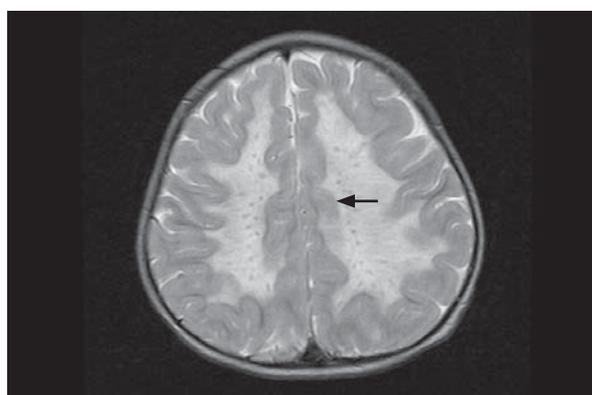


Fig 1: Deep white matter high signal areas in T2 weighted image.

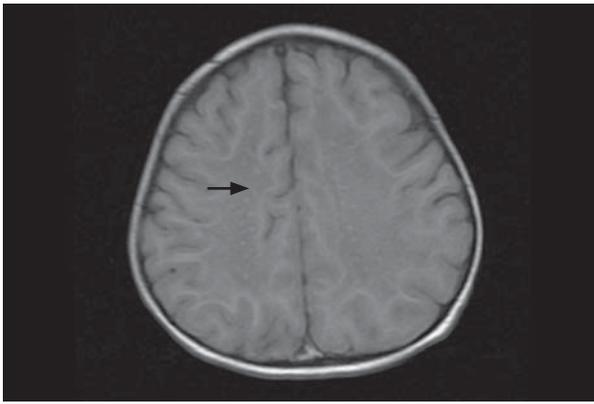


Fig 2: "leopard skin" patterns of demyelination, which suggest sparing of the perivascular white matter.

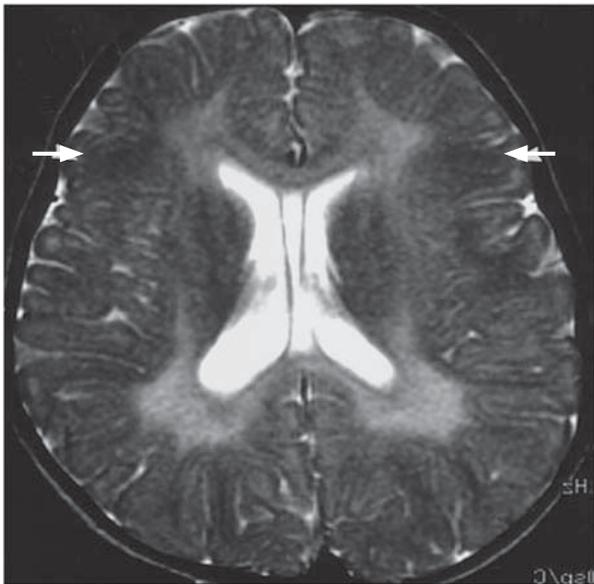


Fig 3: T2-weighted MR image demonstrates bilateral confluent areas of high signal intensity in the periventricular white matter. Note the classic sparing of the sub-cortical U fibers (arrowheads).

Discussion

Metachromatic leukodystrophy is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme arylsulfatase A. This enzyme is necessary for the normal metabolism of sulfatides, which are important constituents of the myelin sheath. The accumulation of sulfatides occurs not only in the central nervous system, but also in various other tissues, including the peripheral nervous system¹. The excessive cerebroside sulfate is thought to cause myelin breakdown and destruction of oligodendroglia.

Three different types of metachromatic leukodystrophy are recognized according to patient age at onset: late infantile, juvenile, and adult². The most common type is late infantile metachromatic

leukodystrophy, which usually manifests in children between 12 and 18 months of age and is characterized by motor signs of peripheral neuropathy followed by deterioration in intellect, speech, and coordination. Within two years of on-set; gait disturbance, quadriplegia, blindness, and decerebrate posturing may be seen. Disease progression is inexorable, and death occurs six months to four years after onset of symptoms³. The extremities are hypotonic, and the deep tendon reflexes are absent or diminished⁴.

In juvenile MLD, the onset of symptoms is delayed to 5–10 yr of age. Deterioration in school performance and alterations in personality may herald the onset of the disease. This is followed by incoordination of gait, urinary incontinence, and dysarthria. In the terminal stages, generalized tonic-clonic convulsions are prominent and are difficult to control. Adult MLD occurs from the 2nd to 6th decade. Abnormalities in memory, psychiatric disturbances, and personality changes are prominent features⁴.

However, extrapyramidal signs are not a commonly described feature of MLD. Both juvenile and adult types of MLD may present with extra pyramidal and cerebellar signs⁵.

Neurophysiologic evaluation shows progressive changes in the VEPs, ABRs, and somatosensory-evoked potentials (SSEPs), and the nerve conduction velocities (NCVs) of the peripheral nerves are significantly reduced⁴. Prenatal diagnosis by amniocentesis is possible in the first trimester of pregnancy⁶. Since prenatal diagnosis is possible, the disease can be prevented, by first trimester diagnosis of MLD by assaying ASA in chorionic villi or cultured fibroblasts and possible intervention thereafter⁷.

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 and "leopard skin" patterns of demyelination, which suggest sparing of the perivascular white matter, can be seen in the periventricular white matter and centrum semiovale⁸. In the later stage of metachromatic leukodystrophy, corticosubcortical atrophy often occurs, particularly when the subcortical white matter is involved⁸. Magnetic resonance (MR) imaging has become the primary imaging modality in patients with leukodystrophy and plays an important role in the identification, localization, and characterization of underlying white matter abnormalities in affected

patients. MR imaging has also been extensively used to monitor the natural progression of various white matter disorders and the response to therapy⁸.

Treatment

Bone marrow transplantation is a promising experimental therapy for the management of late infantile MLD⁴. Prenatal diagnosis of MLD is made by assay of arylsulfatase A in chorionic villi or cultured amniotic fluid cells. Reports of hematopoietic cell transplantation (with or without mesenchymal stromal cells) for MLD have yielded a wide range of results^{9, 10}. Umbilical cord blood transplantation may be a better option than bone marrow transplantation because stored and cataloged umbilical blood can be rapidly identified and transplanted, producing a shorter period between diagnosis and transplantation, an important characteristic to consider in neurodegenerative diseases¹¹.

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