



## Misdiagnosed Late Infantile Metachromatic Leukodystrophy in a 2-Year-Old Male: A Case Report

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### Abstract

Metachromatic Leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder that is classed as a demyelinating disorder of the nervous system along with other leukodystrophies. The disease is characterized by a genetic deficiency of *Arylsulfatase A (ARSA)*, or the deficiency of *Saposin B* (which activates *ARSA* and is a non-enzymatic protein co-factor). *ARSA* has the function of breaking down and removing sulfatides from the body, and is toxic to myelin when built up in the CNS or PNS, causing pathological demyelination of the nerves. Cerebroside sulfate, which is normally broken down by *ARSA*, consequently accumulates, and is what causes the toxicity to myelin. We present a 2-year-old male who presented with recurring seizures and drop attacks beginning 18 months of age. He then recently began to regress with regard to milestones and subsequently progressed to quadriplegia. The case was investigated with an MRI and confirmatory biochemical testing for MLD. The MR imaging showed areas of elevated signal intensity of periventricular white matter, and the contrast MR shows early signs of demyelination on the basis of the lack of enhancement.

**Keywords:** Metachromatic leukodystrophy; Lysosomal storage disorders; Leukodystrophies; Demyelinating disorder; Seizures; Developmental delay

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### Case Presentation

A 2-year-old male presented to the outpatient pediatric neurology department of a large tertiary care center for further evaluation of persistent deterioration of gross motor skills as well as regression of his developmental milestones. He began experiencing paroxysmal drop attacks starting around 18 months of age, described as sudden loss of motor tone and consciousness that would result in him falling to the floor during normal everyday activities. Although previously meeting all developmental milestones, including walking unsupported, his motor functions deteriorated to the point that on presentation he was unable to sit up unsupported. He was previously misdiagnosed with Doose's syndrome, which is a seizure disorder characterized by frequent myoclonic and myoclonic-atonic seizures, owing in part to the limited availability of MR imaging studies in the rural areas of which the patient was a resident. The patient had no family history for seizure disorders. No other significant past medical or surgical history was reported, and he was delivered at term, *via* normal vaginal delivery, with an uncomplicated post-partum course. On initial examination the patient was a non-dysmorphic male who appeared his stated age. Vital signs were within normal limits. Neurologic examination was pertinent for generalized weakness in all muscle groups, with muscle power being 2/5. Reflexes were exaggerated, and bilateral plantar reflexes were up going. A generalized increase in body tone was also noted. Basic investigations including a complete blood count and basic metabolic panel were unremarkable. Further imaging was sought with an MRI of the brain, which showed bilateral symmetrical confluent areas of periventricular deep white matter signal change, in particular around the atria and frontal horns with sparing of subcortical U fibers leading to a "butterfly pattern" on T2 weighted imaging, along with the 'tigroid' pattern on the axial section and the 'leopard' pattern on sagittal sections which were classic for a diagnosis of metachromatic leukodystrophy [1-3]. A contrast enhanced MRI showed lack of enhancement in areas of demyelination, a finding which also indicative of MLD (Figure 1). Biochemical testing also confirmed deficient *ARSA* activity in leukocytes. The patient was managed with injectable levetiracetam and divalproex sodium syrup for seizure control, along-with muscle relaxants for



**Figure 1:** Metachromatic leukodystrophy. a) T2-weighted Sagittal magnetic resonance image showing the beginnings of confluent areas of hyperintensity in the periventricular white matter. b) Contrast enhanced MRI shows lack of enhancement in areas of demyelination, a finding that is indicative of metachromatic leukodystrophy.

symptom control. Physical therapy rehabilitation services were offered. Although allogeneic hematopoietic stem cell transplantation is the standard of care for management of early or no MLD disease, the parents of the patient refused to provide consent for the procedure in view of the risks and complications of the procedure.

## Discussion

The pathogenesis of MLD revolves around the fact that deficiency of arylsulfatase A disrupts the normal metabolism of sulfate compounds, which are the most important components myelin. This defect leads to the accumulation of lipid material (e.g., cerebroside sulfate), which stains metachromatic in the white matter of the CNS and PNS, as well as in other organs like the gallbladder and kidney [1-4]. When the accumulation occurs in glial cells and neurons, it causes a pathological demyelination. The clinical course is progressive, characterized for symptoms such as paralysis, tremors, stiffness, dysphagia, seizures, ataxia, optic atrophy, speech alterations, and deterioration of mental abilities, dementia and deterioration of the peripheral nervous system. In a growing child, this is characterized by a regression of milestones [5]. This pathology is classified on the basis of age of onset of symptoms, and there are three recognized variants: Late infantile, between 6 and 24 months; juvenile, between 3 and 16 years old, and adult MLD which begins at any age after puberty [5]. In the early-onset variant, there is a predominant motor loss that comes before the mental deficit; in later-onset variants, the deterioration is reversed with neuropsychiatric symptoms preceding the motor. The progression of the disease is unstoppable and typically patients tend to die around a decade after symptoms present. The brain changes can be evidenced in magnetic resonance images, in T2 sequences, FLAIR and diffusion studies [6-8]. The classic findings, notably the aforementioned "butterfly pattern", as well as the classic 'tigroid' pattern on axial or 'leopard' pattern on sagittal sections with relative sparing of sub-cortical U fibers were well described in our patient, and with progression can lead to cortical and subcortical atrophy. The gene that encodes *Arylsulfatase A* is on Chromosome 22p13.33. Treatment options currently available include bone marrow transplantation, enzyme replacement therapy, and gene therapy. However, their effectiveness in improving the long-term prognosis of the disease has not yet been proven. Bone Marrow Transplantation has been implemented to curb CNS effects [9], and the best clinical results are obtained when it is done before the symptoms present. Other treatment aspects include physical rehabilitation and pharmacological treatment of symptoms.

## Conclusion

Since the clinical course of metachromatic leukodystrophy is fatal, it is necessary for early recognition of this disease. As our case demonstrates, it is important to limit misdiagnosis, which can delay appropriate care. The almost crucial role of MRI for accurate diagnosis is also highlighted here. The disease has an autosomal recessive inheritance pattern, and therefore carrier screening and genetic counseling are important aspects of the management.

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