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Infantile Metachromatic Leukodystrophy: Case Report

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ABSTRACT

Metachromatic Leukodystrophy (MLD) is typically characterized by the accumulation of sulfatide in various organs, including the central nervous system. This accumulation leads to neurological and mental symptoms. A case of a two-year-old male patient with a history of psychomotor retardation, developmental delay, and poor overall performance is reported. The patient's imaging findings are compatible with Leukodystrophy. The aim of this case report is to identify the clinical presentation and typical MRI features that can help diagnose MLD, even in the absence of an enzyme assay or gene mutation investigation.

Introduction

Metachromatic Leukodystrophy (MLD) is a rare, hereditary, demyelinating, autosomal recessive illness. It is a typical white matter disease characterized by a deficit in the lysosomal arylsulfatase A (ARSA) enzyme. This condition results from a mutation in the ARSA gene located on chromosome 22q13, leading to the accumulation of sulfatide in the nervous system [1,2]. The prevalence of this disease is estimated to be between 1/40000 and 1/160000 [3]. MLD is divided into three forms based on the patient's age. The most prevalent is the late infantile type, which has a poor prognosis due to rapid development and high mortality just a few years after symptoms appear. The disease is categorized based on the age of onset: the late Infantile form, which most commonly occurs between 6 months to 4 years of age; the early juvenile form, diagnosed between 4 to 6 years of age; the late juvenile form, diagnosed between 6 to 16 years of age; and the adult form, diagnosed beyond 16 years of age [4].

Only a few cases of MLD have been confirmed worldwide. This paper presents a case of MLD of the late infantile variety.

Case Presentation

The case involves a two-year-old male child, born

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to parents with a second degree of consanguinity. The child suffered from a progressive developmental inability to walk and speak, which started at one and a half years of age. Until one year of age, the child's developmental milestones were normal. However, the child exhibited muscular atrophy that began at one year and a gradual inability to walk and communicate over one to four months.

The child was born healthy via vaginal delivery, weighing 2,800 grams after a 40-week uneventful pregnancy. He received all his vaccinations from birth until he was one and a half years old. He was once hospitalized for a chest infection, where he was treated with antibiotics, rest, and increased fluids. The family history was found to be negative.

Regarding developmental milestones, from the age of one to one and a half years, the child could grovel, move his hands, and babble. However, at the age of two, his movement had declined to the point where he couldn't move at all and couldn't make any sound. His eye reflexes had begun to deteriorate. Breathing and swallowing became difficult due to muscle weakness, and he was unable to support his neck and head or crawl or walk. Cyanosis, newborn spasms, or neonatal jaundice were not observed.

Laboratory findings did not reveal any abnormalities. However, due to persisting worsening symptoms (developmental delay), an MRI scan was ordered for investigation. The scan indicated high signal intensity in the white matter of both cerebral hemispheres.

In the MRI, there is extensive abnormal signal intensity, which was hyperintense on T2 (Figure A) and FLAIR (Figure C) images. This abnormality is distributed in the periventricular white matter and extends into the subcallosal region, sparing the subcortical U-Fibers, leading to a butterfly pattern. This pattern is more predominant in both parietal regions, without evidence of any mass effect or midline shift with FLAIR imaging.

There is no indication of restricted diffusion or accompanying brain tissue volume loss or ventricular dilatation, and there is a similar intensity affecting the corpus callosum. Otherwise, the brain, brain stem, and cerebellum all appear normal. There are no signs of cerebral bleeding or acute infarction, and the craniocervical junction appears normal. The mastoid air cells and paranasal sinuses are effectively aerated.

Given these findings, Metachromatic Leukodystrophy without concomitant brain shrinkage or hydrocephalus is the most likely diagnosis.

Discussion

Metachromatic Leukodystrophy (MLD) is named after the metachromatic granules that form due to the buildup of sulfatide substrate deposits. This buildup is caused by a lack of the enzyme arylsulfatase-A (ARSA). Metachromatic granules can accumulate in various cells and organs such as oligodendrocytes, macrophages, visceral organs like the liver, pancreas, kidneys, rectal tissue, peripheral nervous system, Schwann cells, and macrophages. This accumulation leads to several signs and symptoms.

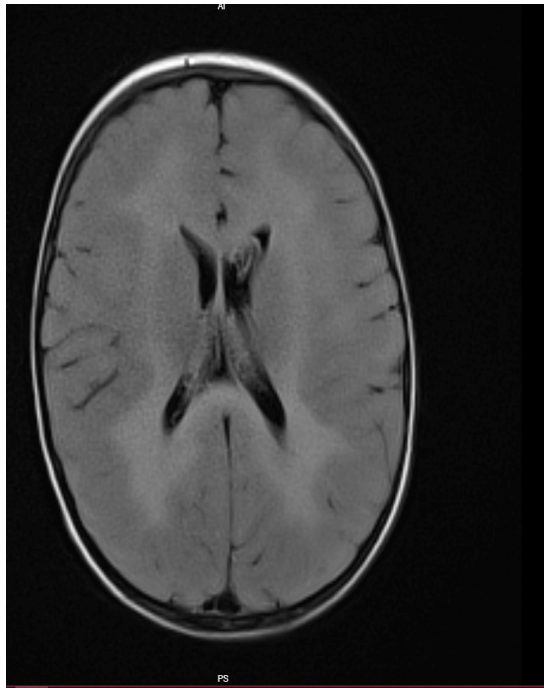
MLD is a progressive neurodegenerative disorder for which there is currently no cure. Halting the progression of neurologic dysfunction may require interventions such as stem cell transplantation, bone marrow transplantation, or genetic engineering [4].

Behavioral issues are often the earliest symptoms in individuals with juvenile and adult MLD. The insidious nature of cognitive symptoms makes early detection difficult and poses a challenge to physicians across all disciplines. Hematopoietic stem cell transplantation may benefit some MLD patients with juvenile disease if performed early in the disease's development. Adults with MLD have also recently received transplants. Therefore, improved early diagnosis procedures are desperately needed [2].

Given that the first symptoms may lead to psychiatric evaluation, psychiatrists should be aware of their role in early MLD diagnosis. The onset may resemble schizophrenia and other psychotic diseases, despite its low prevalence. Adequate follow-up should increase the likelihood of a timely diagnosis and treatment [4].

Treatment for Metachromatic Leukodystrophy (MLD) is primarily symptomatic and supportive, including physiotherapy, nutrition, nursing care, environmental adaptability, and maintaining a support network and regular activity [4].

The disease derives its name from the metachromatic granules that form in afflicted cells due to the buildup of sulfatides and sphingolipids found in myelin. In MLD, sulfatides accumulate in various cells such as oligodendrocytes, microglia, a few CNS neurons, Schwann cells, and PNS macrophages. They also build up in the cells of internal organs like the gall bladder, raising the possibility of malignant neoplasms of this organ [5–12]. Morphological alterations in the endoplasmic reticulum (EPR) and mitochondria of Schwann cells have also been described [13].



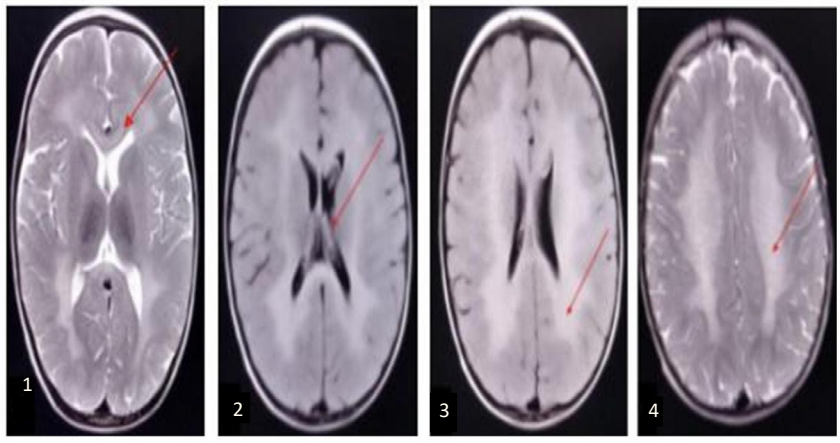


Fig. 1 and 3. Magnetic resonance imaging (MRI) of the brain (T2) showing hyperintensities in bilateral periventricular white matter and corpus callosum. There is sparing of subcortical "U" fibres.
Fig. 2. Showing sulfatide accumulation through lateral ventricles.
Fig. 4. Showing sulfatide accumulation through white matter

Demyelination caused by MLD results in cognitive impairment, ataxia, spasms, reduced motor function, and spastic tetraparesis [14,15]. The precise mechanisms of demyelination in MLD are still unknown. Possible causes include an increase in sulfatides and a decrease in its cleavage products, which cause the myelin sheath to become unstable [16]. Sulfatides also result in calcium buildup in the cytoplasm of cells, altering calcium homeostasis and causing cell stress and apoptosis [10].

The accumulation of sulfatides leads to neuronal degeneration and astrocyte dysfunction and may trigger an inflammatory response. Several studies support the role of inflammation in MLD. For instance, increased levels of monocyte chemoattractant protein 1 (MCP-1), interleukin (IL)-1 receptor antagonist (IL-1Ra), IL-8, macrophage inflammatory protein 1β (MIP-1β), and vascular endothelial growth factor (VEGF) are detected in both plasma and cerebrospinal fluid (CSF) of patients with MLD. These cytokines can function as biomarkers to detect MLD at early stages and to analyze disease progression.

Conclusion

A case of a two-year-old male child born from a consanguineous marriage is presented. The child has a history of psychomotor retardation. Typical MRI findings and low arylsulfatase A activity suggest a

diagnosis of the late infantile variant of Metachromatic Leukodystrophy. This case underscores the importance of early detection and diagnosis in managing this rare condition.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors state that they have no conflicts of interest.

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