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Case Report

# A Case of Late Infantile Metachromatic Leukodystrophy Presenting with Gradually-onset Paraplegia

**Seyed Ahmad Hosseini1[1], Sara Rahafard[1*], Alireza Kia[2]**

1. Neonatal & Children's Health Research Center , Golestan University of Medical Sciences, Gorgan , Iran
2. Mehregan Imaging Centre , Gorgan , Iran

*Correspondence: Sara Rahafard, Neonatal & Children's Health Research Center, Golestan University of Medical Sciences, Gorgan, Iran

Email: dr.rahafard@gmail.com

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## ABSTRACT

**Background and objectives:** Metachromatic leukodystrophy (MLD) is an autosomal recessive neurodegenerative disease, with an estimated prevalence rate of 1 per 40,000 to 160,000 worldwide. Progressive alteration in motor and cognitive functions is the most common clinical presentation. Late infantile MLD is the most common form of the disease that presents with a progressive decrease in visual acuity, impaired swallowing, muscle rigidity, seizures, and developmental delays. We herein present a rare case of late infantile MLD in a four-and-half-year-old male patient presenting with gradually-onset paraplegia.

**Case description:** The patient had normal growth and neurodevelopmental pattern until 15 months of age. Afterward, he had a gradually increasing abnormality in gate and finally became paralyzed since the age of three years. The patient was also suffering from dysphagia, bilateral ptosis, and bad temperament. Normal metabolic test, myopathies, and brain MRI findings led to the diagnosis of MLD with gradually-onset paraplegia.

**Conclusion:** Generally, early diagnosis of MLD may increase the chance of recovery from the disease. We suggest considering MLD in patients suffering from behavioral, visual, and motor regressions, especially those with normal metabolic tests.

**Keywords:** Lysosomal storage diseases; Metachromatic leukodystrophy; Demyelinating disease; Neurodegenerative disease; Late infantile MLD

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## INTRODUCTION

Metachromatic leukodystrophy (MLD) is a lysosomal storage disease with an estimated prevalence of 1 per 40,000 to 160,000 around the world (1). This hereditary autosomal recessive, neurodegenerative disease affects the myelin sheath of the nerve fibers of central (CNS) and peripheral nervous systems, a pathophysiology similar to multiple sclerosis (2). Progressive alteration in motor and cognitive functions are the most common clinical presentation (2), while, muscle spasms, spastic tetraparesis, optic atrophy, and ataxia are other important clinical manifestations (3). The age of onset of MLD varies from 18 months to adulthood. The disease has a poor prognosis with a majority of cases ending up with vegetative state or death (2). Late infantile MLD is the most common form of the disease that accounts for about 50% of all cases of MLD. It usually presents with progressive decrease in visual acuity, impaired swallowing, muscle rigidity, seizures, and developmental delays (4). Juvenile variant has a worldwide prevalence of 23% and occurs at age of 4 to 12 years. It is marked as early juvenile MLD if presented before age of 6 (2, 5).

In this case report, we present a rare case of late infantile MLD in a four-and-half-year-old male patient presenting with gradually-onset Paraplegia.

## CASE PRESENTATION

We hereby present a four-and-half-year-old male patient with chief complaint of gradually-onset disability in walking. The patient had been conceived from a term pregnancy by natural vaginal delivery and had a birth Apgar score of 9 out of 10 from cousin parents. He had a normal growth and neurodevelopmental pattern until the 15th month of life. Afterward, he had a gradually increasing abnormality in gate and finally has become paralyzed since the 3rd year of life. The patient was also suffering from dysphagia, and the barium swallow test was normal. Parents reported complaint of bilateral ptosis in the patient as well as a bad temperament. The patient also had a left side undescended testis.

First, we assessed the patient in terms of metabolic syndromes and myopathies by measuring aldolase (7.5 units/l), creatine kinase (238 units/ l), anti-acetylcholine receptor antibodies, and anti-muscle specific kinase antibodies, which were all within the normal range. The patient underwent brain MRI without contrast (Figure 1), which indicated symmetric, high signal intensities in the parietal-occipital central white matter and frontal central white matter, with spreads to periventricular white matters in T2-weighted sequence. Upon these findings and according to the clinical manifestations, we had a high suspicion toward MLD. Whole exome sequencing revealed the possibly of pathogenic variant chr22:51064623C>G;c.938G>C(p.Arg313Pro) in exon 5 of Arylsulfatase A (ARSA) gene, which is compatible with autosomal recessive MLD. Thus, the diagnosis of late-infantile MLD was confirmed for the patient.

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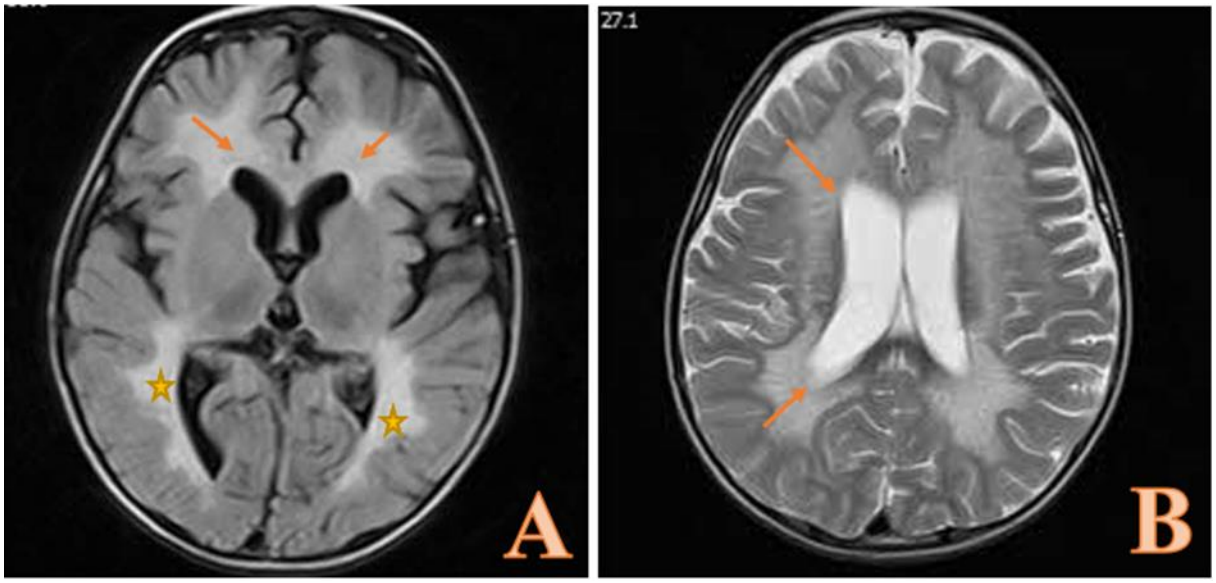


**Figure 1. T2-weighted brain MRI showing symmetric high signal intensities in the parietal-occipital central white matter (★) and frontal central white matter (arrows in A) with spreads to periventricular white matters (arrows in B).**

## DISCUSSION

Metachromatic leukodystrophy is a lipid storage disorder resulting from the ARSA enzyme deficiency. A majority of patients with MLD are from Caucasian ethnicities (6, 7). Deficiency in the ARSA enzyme leads to accumulation of sulfatide (sphingolipid cerebroside 3-sulfate) in neurons of the CNS, thereby causing neuronal dysfunction and degeneration (8). Previous studies have also considered a determining role for inflammatory processes in the pathophysiology of MLD, as there have been elevated levels of interleukin-8, interleukin-1 receptor antagonist, and vascular endothelial growth factor in both plasma and cerebrospinal fluid of MLD patients (1). The disease is divided into three subtypes based on the age of onset; late infantile MLD (occurs before age of 30 months), juvenile MLD (starts at age of 30 months-16 years), and adult-onset MLD (occurs after the age of 16 years) (2). Definite diagnosis of MLD involves a complete evaluation ranging from molecular and biochemical tests to genetic and neuroradiological (MRI) evaluations (2). In early phases, MLD is usually presented with unspecific signs and symptoms including behavioral problems and focal neurological disorders, which make the MLD difficult to diagnose (9). About 75% of cases show the initial symptoms prior to 18 months of age (10). Our patient had a gradually progressive gait problem and motor regression since age of 15th month until he got para-paralyzed at 3 years of age.

According to a nationwide cohort study in Germany, 48% of patients with late infantile MLD develop regression of speech and language, similar to our case (11). In addition, the mean time between early symptoms and diagnosis has been reported be 12 months in patients with late infantile MLD, which is similar to our case. In a case series involving 18 MLD cases (10 male and 8 female) in Iran, 80% of the patients had consanguineous parents, out of which, 45% were first cousins. In addition, 12 patients had late infantile MLD and six patients had juvenile MLD. Electromyography showed demyelinating sensorimotor neuropathy pattern in 96% of the patients (12). These results suggest that MLD should be considered in patients with ataxia, developmental regression, positive family

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history of MLD, and consanguinity marriage.

In another study in Iran, Golchin et al. evaluated three MLD patients from a family and identified a new mutation in the ARSA gene. They reported a homozygous missense mutation c.1070 G > T (p.Gly357Val) in exon 6 of these patients, which was reported for the first time in MLD patients. They concluded that diagnostic strategies should detect both common and rare MLD alleles (13).

Similar to our case, two studies reported periventricular white matter involvement in brain MRI of patients with late infantile MLD (14, 15). Groeschel et al. found almost no brain MRI abnormalities in late infantile MLD patients until the presentation of first clinical symptoms. Thus, it seems that early brain MRI studies may not provide enough diagnostic clues.

Currently, there are no approved treatment for MLD; however, transplantation of hematopoietic stem cells and enzyme replacement therapy are used to postpone disease progression in some patients (2).

## CONCLUSION

Generally, early diagnosis of MLD is of great importance as it may increase the chance of recovery from the disease. Clinical suspicion toward MLD is the key component of early diagnosis, and adequate paraclinical tests can completely confirm the diagnosis. In conclusion, we suggest considering MLD in patients suffering from behavioral, visual, and motor regressions, especially those with normal metabolic tests. Despite absence of a definitive treatment, proper diagnosis helps physicians with better follow-up of patients and managing complications.

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### Ethics approvals and consent to participate

Consent was taken from parents of the patients after ensuring confidentiality of personal information.

### Conflict of interest

The authors declare that there is no conflict of interest regarding publication of this article.

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