SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medicine

Late Infantile Metachromatic Leukodystrophy: Arylsulfatase A and Saposin B Deficiency

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DOI: 10.36347/sasjm.2024.v10i02.013 | **Received:** 12.10.2023 | **Accepted:** 19.11.2023 | **Published:** 19.02.2024

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Abstract **Case Report**

Metachromatic leukodystrophy is a genetic neurodegenerative disease with autosomal recessive transmission. It is characterized by an accumulation of sulfatides. We report a case of leukodystrophy related to a deficiency in saposin B. The diagnosis was suspected based on the initial clinical presentation, the progressive nature of the symptoms, involvement of both the central and peripheral nervous systems, and the typical radiological appearance on cerebral MRI. The normal arylsulfatase A levels led us to consider performing thin-layer chromatography of glycosphingolipids in urinary sediment to investigate a saposin B deficiency. The substantial excretion of sulfatides in our patient is virtually pathognomonic for metachromatic leukodystrophy due to saposin B activator deficiency. The diagnosis was definitively confirmed through molecular biology, which revealed the IVS+1 g>a mutation.

Keywords: Metachromatic leukodystrophy, accumulation of sulfatides, saposin B deficiency, molecular biology.

INTRODUCTION

Metachromatic leukodystrophy is a recessively inherited genetic neurodegenerative disease resulting from the accumulation of sulfatides in brain tissue due to a deficiency of the catabolic enzyme arylsulfatase A. The most common late infantile form typically begins around the time of walking. Neurological deterioration occurs over a few years, leading to motor and intellectual regression. The deficient enzyme is arylsulfatase A. However, there are rare forms of metachromatic leukodystrophies with normal arylsulfatase A activity and sulfatide overload. This form is caused by a deficiency in the enzyme necessary for the hydrolysis of these lipids: saposin B. Deficiency of this enzyme, called saposin B, is believed to be the cause of rare cases of metachromatic leukodystrophies with a normal arylsulfatase level. We report a new case of late infantile metachromatic leukodystrophy secondary to a saposin B deficiency.

OBSERVATION 1

A two-year-old girl, born to consanguineous parents, from a closely monitored pregnancy, carried to full term, and delivered vaginally. Her psychomotor development was normal until the age of 14 months, after which it began to regress. This regression manifested as a decrease in the quality of her walking, with increasingly frequent falls that eventually made walking impossible. Subsequently, there was a loss of the ability to stand, a progressive deterioration of language, voluntary motor skills, and muscle tone.

Clinical examination revealed a bedridden child with reduced overall muscle strength, predominantly in the lower limbs, and spasticity. Osteotendinous reflexes were diminished, with preserved sensitivity. The rest of the physical examination was unremarkable.

Routine diagnostic tests, including lactate and pyruvate levels, liver function tests, muscle enzymes, ammonia levels, amino acid chromatography in blood and urine, and organic acid chromatography in urine, did not reveal any abnormalities.

Cerebrospinal fluid analysis showed elevated protein levels at 1.16 g/l. The karyotype was normal: 46 XX. An electroencephalogram displayed a subtle slowing of background activity with bi-hemispheric irritative anomalies.

Neurophysiological examination identified peripheral neuropathy (reduced motor and sensory conduction velocities). A brain CT scan showed a generalized increase in white matter hypodensity. Brain MRI revealed bilateral and nearly symmetrical white

matter signal abnormalities, with hypo-intensity on T1 and hyper-intensity on T2, involving almost the entire white matter.

Based on the clinical and radiological findings, the diagnosis of metachromatic leukodystrophy was strongly suspected. Thin-layer chromatography of glycosphingolipids in urinary sediment demonstrated a massive excretion of sulfatides, dihexosylceramide-sulfate, globotriaosylceramide, and dihexosylceramide. The normal arylsulfatase A activity strongly indicated the possibility of a deficiency in its activator, saposine B. The diagnosis was confirmed through molecular biology, which revealed the IVS+1 g>a mutation, apparently in a homozygous state. Currently, our patient is 4 years old, and she has become quadriplegic, bedridden, epileptic, and non-responsive.

OBSERVATION 2

The eldest of three siblings, Adam is born to consanguineous parents, from a closely monitored pregnancy carried to full term, and delivered vaginally with good adaptation to extra-uterine life. This child exhibited a regression in psychomotor acquisitions, with gait disturbances, loss of balance, frequent falls, and intellectual developmental decline.

Clinical examination revealed macrocephaly, delayed growth and weight gain, the ability to stand with assistance and an expanded support base, unsteady walking with a compensated pivot, normal muscle tone, reduced muscle strength, absent osteotendinous reflexes, coordination abnormalities, multidirectional nystagmus, dysarthria, and dysgraphia.

Additional tests, including lactates, pyruvates, liver function tests, muscle enzymes, ammonia levels, amino acid chromatography in blood and urine, and organic acid chromatography in urine, did not reveal any abnormalities. Brain MRI showed some signal abnormalities affecting subcortical gray matter in the parasagittal parietal region, especially on the left, the dentate nuclei bilaterally and symmetrically, suggestive of metabolic origin lesions.

Electromyography (EMG) indicated a sensory-motor axonal polyneuropathy. Based on the clinical and radiological findings, the diagnosis of metachromatic leukodystrophy was considered. Enzymatic assays showed an Arylsulfatase A level of 27 IU/ml, consistent with a partial heterozygous deficiency.

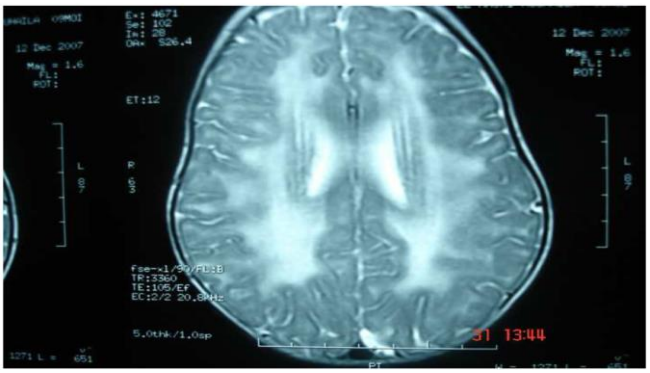

Figure 1

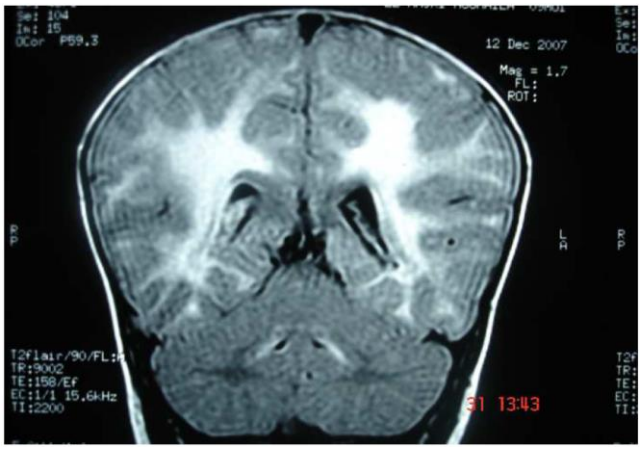

Figure 2

Figure 1 and 2: Brain spectro-MRI images showing bilateral and nearly symmetrical white matter signal abnormalities, hypointense in T1, hyperintense in T2, involving almost the entire white matter.

DISCUSSION

While metachromatic leukodystrophy due to arylsulfatase A deficiency is the most common form (incidence between 1/50,000 and 1/100,000; late infantile form 60%; juvenile form 20-30%; adult form 10-20%), metachromatic leukodystrophy related to saposin B deficiency has only been described in a few cases.

This protein, "sphingoglycolipid activator protein," was first described in 1964 by Mehl and Jatzkewitz as a cofactor that stimulates the degradation of sulfatides by arylsulfatase A. Saposin B is encoded by the PSAP gene, located on chromosome 10q21, and is produced as a precursor (prosaposin) transported to lysosomes, where it gives rise to four types of saposins: A, B, C, and D.

Saposin B deficiency is inherited in an autosomal recessive manner. The clinical symptoms are identical to those described in metachromatic leukodystrophy due to arylsulfatase A deficiency. Approximately ten cases have been reported, corresponding to late infantile, juvenile, or adult forms.

The metabolic abnormality underlying metachromatic leukodystrophy involves an enzymatic block in the lysosomal degradation pathway of cerebroside sulfate. The deficient enzyme is cerebroside sulfate sulfatase, or arylsulfatase A. This deficiency applies to the majority of metachromatic leukodystrophy cases, except for short-chain sphingoglycolipids, for which catabolism requires an additional low molecular weight enzyme called "SAP" (sphingolipid activator protein).

This disease is classified into four clinical forms based on the age of onset: late infantile, early or late juvenile, and adult forms. The late infantile form, also known as Scholz-Greenfield disease, accounts for 60-80% of cases of metachromatic leukodystrophy due to saposin B deficiency and typically starts between 12 and 24 months. It begins with irritability, hypotonia, gait disturbances with segmental hypertonia contrasting with weak or absent osteotendinous reflexes. These children exhibit a pyramidal syndrome, loss of the ability to stand, sphincter issues, and intellectual decline. The child becomes quadriplegic, bedridden, unresponsive, and experiences epileptic seizures, with death usually occurring 2 to 6 years after the onset of symptoms.

The juvenile form begins between 4 and 12 years with a decline in intellectual performance and behavioral issues, followed by the rapid onset of gait disturbances and a pyramidal syndrome with reduced reflexes. Language difficulties, extrapyramidal signs, dystonic movements, progressive spastic quadriplegia, and optic atrophy mark the disease's progression.

In terms of treatment, it is primarily symptomatic and focuses on managing neurological complications, swallowing difficulties, malnutrition, epileptic seizures, and pain. This symptomatic treatment is crucial for the patients' quality of life. Death typically occurs 7 to 10 years after the onset of symptoms.

CONCLUSION

A normal level of arylsulfatase A, in the presence of a typical clinical and radiological presentation of metachromatic leukodystrophy, should raise suspicion of saposin B deficiency and lead to the performance of thin-layer chromatography of glycosphingolipids in urinary sediment. Prenatal diagnosis is possible by identifying mutations or by studying the in-situ hydrolysis of sulfatides labeled with cultured fetal cells.

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