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A Rare Case of Late Infantile Metachromatic Leukodystrophy

Jayvardhan Lade[1], Aastha Jain[2], Pawan Nimbhorkar[3], Arunava Bharati[4], Rakesh Thamke[5]

[1]Junior Resident, Department of Family Medicine, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India
E-mail ID: jayvardhanlade77[at]gmail.com
Contact No: 9689465578/9284719794

[2]Junior Resident, Department of Pediatrics, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India
E-mail ID: aastha27_jain[at]yahoo. co. in

[3]Junior Resident, Department of Family Medicine, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India
E-mail ID: pawannimbhorkar95[at]gmail.com

[4]Senior resident, Department of Pediatrics, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India
E-mail ID: arunavabharati55[at]gmail.com

[5]Associate Professor & Head, Department of Family Medicine, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India
E-mail ID: rakeshthamke68[at]gmail.com

Correspondence Address: Dr. Jayvardhan Lade, Department of Family Medicine,
MGM Medical College and Hospital, Kamothe - 410209, Navi Mumbai, Maharashtra, India

Abstract: ***Metachromatic leukodystrophy is a type of lysosomal storage disorders with autosomal recessive inheritance caused by the deficiency of the arylsulfatase an enzyme which leads to the accumulation of cerebroside sulfatides, which result in the dysfunction and destruction of the central nervous system and peripheral nervous system myelin sheaths. Amongst its forms the one presenting in late childhood has the bad prognosis. MLD has a prevalence rate of 1 in 40, 000-160, 000 worldwide. Magnetic resonance imaging and genetic study has key role in diagnosis. Magnetic resonance imaging can rule out other clinical conditions and can give clue to diagnosis and confirmed by genetic study. Early and accurate diagnosis is key to start palliative management and genetic counselling. A 2 years 9 months old female presented with a episode of convulsion and loss of attained milestones. MRI and genetic study confirmed a diagnosis of late infantile metachromatic leukodystrophy.***

Key words: Lysosomal storage disorder, Metachromatic, Leukodystrophies, Arylsulfatase A, PSAP

1.Introduction

Metachromatic leukodystrophy is a demyelinating, autosomal recessive genetic leukodystrophy and Lysosomal storage disease caused by an inborn error of metabolism in the arylsulfatase A lysosomal enzyme. This leads to the accumulation of sulfatides, which result in the dysfunction and destruction of the Central nervous system and peripheral nervous system myelin sheaths [1]. Mutations in the Arylsulfatase A (ARSA) gene which encodes on chr.22q13.31 is the main pathogenesis of this disease. Among white matter disorders it is one of the most common disease [2]. Sphingolipid activator protein B (SapB or saposin B) enzyme deficiency also led to Metachromatic leukodystrophy as a consequence of PSAP gene mutation located on chromosome 10q21.1 MLD is one of the most common leukodystrophies leading to progressive focal or generalized white matter disorders. MLD has a prevalence rate of 1 in 40, 000-160, 000 worldwide [3].

2.Case Presentation

A 2-year 9-month-old female child, second by order of birth, born out of 3rd degree consanguineous marriage, residing in Panvel, hailing from Kolhapur, belonging to Buddhist community came to MGM Hospital, Kamothe, Navi Mumbai with Severe developmental delay. According to father, child was apparently alright till 18 months of age when she developed one episode of fever spike followed by one episode of involuntary body movements for which she was admitted and discharged as a case of Febrile Convulsion and went home without any neurological deficit.10 days after this episode, parents noticed that child was unable to do regular activities that she was doing before a month. Childs pace while walking decreased, child started having frequent falls, child could not stand up from sitting and then could not sit with or without support suggestive of loss of attained milestones.

A significant family history of deceased elder sibling who also had loss of attained milestones and multiple episodes of convulsions and succumbed due to some respiratory illness was present.

On examination child was conscious but was not oriented to time place and person. Presenting with lower limbs extended and upper limbs flexed at the elbow, scissoring of lower limb noticed. Vitals were stable. On systemic examination UMN type of motor weakness and progressive spasticity in bilateral upper and lower limbs with normal sensory sensation seen. Tone was bilaterally increased, spasticity present, bilateral Babinski reflex positive, deep tendon reflex bilaterally exaggerated, Clonus present. Posture of the child - lower limbs

extended and upper limbs flexed at the elbow (Figure 1). On Axillary suspension test scissoring of the lower limb noticed (Figure 2).

Blood investigations were within normal limits. CSF examination was within normal limits. On neuroimaging MRI Brain plain was done which showed white matter replaced by CSF (Figure 3). White matter was diffusely involved extending from periventricular white matter to subcortical arcuate fibers (Figure 4). Atrophy of splenium of corpus callosum noted (Figure 5). Minimal Cerebellar atrophy is also present. Findings are suggestive of white matter disease (late stage Metachromatic Leukodystrophy**).** Fundus Examination was done which was suggestive of evidence of early optic atrophy with generalized retinal thinning. Genetic testing showed a homozygous missense variation in exon 3 of the EIF2B5 gene (chr: g.183855494G>A; Depth: 94x) that results in the amino acid substitution of Histidine for Arginine at codon 136 (p. Arg136His; ENST00000273783.3).

Treatment: Child was started on Levetiracetam at 20 mg per kg per day and supportive treatment. Physiotherapy and rehabilitation were started within days of admission. Poor prognosis was explained. After days on medical management, the patient was discharged on Levetiracetam. Genetic counselling was given and prevention strategies implemented.

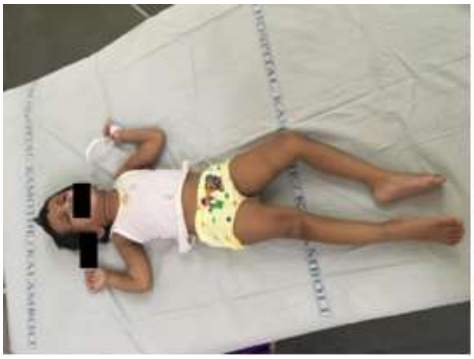

Figure 1

Figure 2

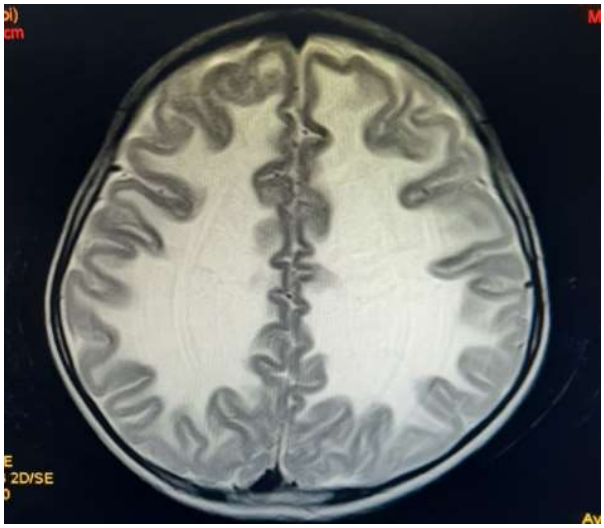

Figure 3

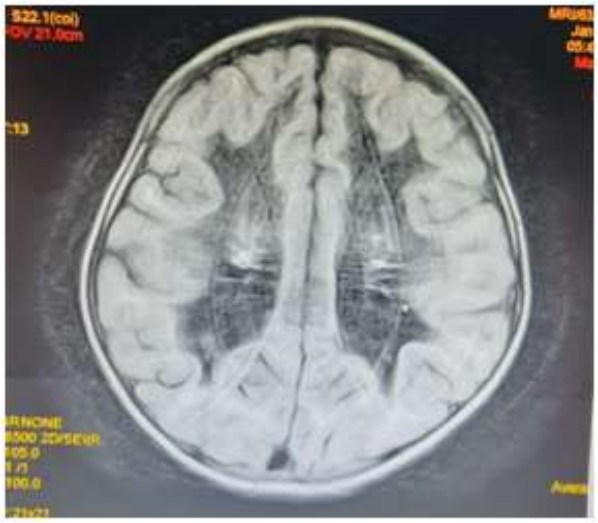

Figure 4

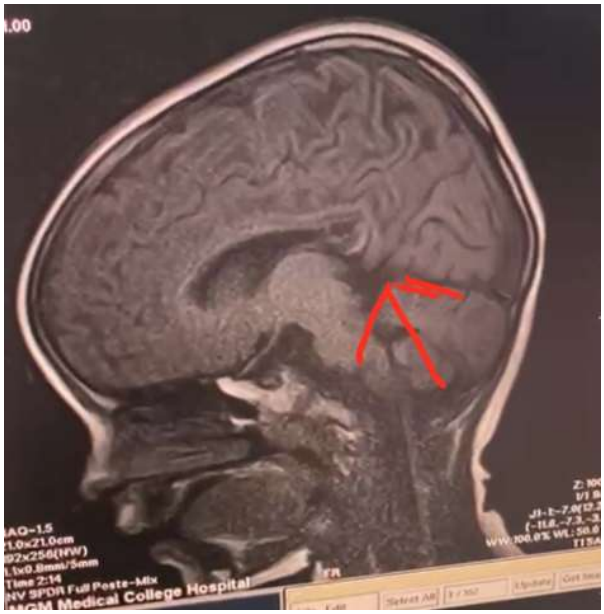

Figure 5

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3.Discussion

Metachromatic leukodystrophy is a lysosomal storage disease characterized by the inability to degrade sulfated glycolipids, mainly the galactosyl-3-sulfate ceramides. During the process, the sulfated glycolipids are degraded into galactocerebroside by the enzyme Arylsulfatase A [1]. Classical type MLD results from arylsulfataseA enzyme deficiency which leads to accumulation of sulfatide in central and peripheral nervous system causing progressive demyelination, motor and cognitive dysfunction. Sulfatide accumulation in cells appears as granules that are colored differently than other cellular material (metachromatic) when viewed under a microscope [4].

MLD is commonly classified into three clinical subtypes depending on the age of onset: late-infantile, juvenile or adult (< 30 months, 2.5-16 years and > 16 years, respectively). The late-infantile form is generally associated with rapid and severe functional decline, while patients with the juvenile and adult forms tend to experience a slower rate of disease progression. Impairments in gross motor function, such as a failure to develop independent walking, are frequently reported first for patients with late-infantile MLD. For patients with the later-onset forms, cognitive and behavioral signs and symptoms are often the earliest indicators of disease, followed by a more protracted decline in motor function [5].

This case is considered as late infantile Metachromatic Leukodystrophy on the basis of age of onset and clinical presentation. The child presented with one episode of convulsion followed by typical regression of milestones. As in this case generalized seizures are more common in late infantile type, while partial seizures are more common in juvenile type. Older children present with decrease in scholastic performance, behavioral changes, gait abnormalities and seizures [6] [7]. Family history of loss of milestones and multiple episodes of convulsion with mortality due to some respiratory tract infection is significant in this case.

Offspring should get a copy of the defective gene from both parents to have the disease. When two carriers have a child, there is a 25 % chance that the child will get both genes and have MLD. Children who inherit only one defective from one parent will be a carrier but usually will not develop MLD.

For MLD there is no any specific treatment available to reverse the functional loss or to stop the disease progression. For symptomatic treatment muscle relaxants, antiepileptics, psychiatry medications and analgesics can be prescribed. Physiotherapy can be given to maintain joint movement as much as possible. Physiotherapy will to delay joint stiffness or contractures and reduce loss of function or pain that can result from contractures [8]. Bone marrow transplantation, stem cell transplantation, and genetic engineering are possible options to halt the progression of neurologic dysfunction before the development of symptoms [9, 10]. Bone Marrow Transplantation which is a new mode of treatment is not feasible for this patient as diagnosis was made at a progressed stage of disease. Administration of recombinant human aryl sulfatase A is an experimental tool but it lacks universal recommendation and adaptation [11].

4.Conclusion

A 2 years and 9 months old child with convulsion and regression of milestones with characteristic MRI findings and genetic testing suggestive of Late Infantile Metachromatic Leukodystrophy.

5.Future Scope

Various treatment options to halt the disease progression and improvement of quality of life of MLD patients can be studied.

Conflicts of Interest: The Authors have no conflicts of interest.

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Authors Profile

Dr. Jayvardhan Madanraj Lade
M. B. B. S. (Government Medical College, Miraj, Maharashtra) 2016. M. D. Family Medicine (MGM Medical College and Hospital, Navi Mumbai, 3rd year Junior Resident)

E-mail ID: jayvardhanlade77[at]gmail.com

Contact No: 9689465578 / 9284719794

Correspondence Address: Dr. Jayvardhan Madanraj Lade, Department of Family Medicine, MGM Medical College and Hospital, Navi Mumbai - 410209 Maharashtra, India.

Dr. Aastha Jain
M. B. B. S. (MGM Medical College and Hospital, Navi Mumbai) 2018, M. D. Pediatrics (MGM Medical College and Hospital, Navi Mumbai, 3rd year Junior Resident) aastha27_jain[at]yahoo.co.in

Dr. Pawan M. Nimbhorkar
M. B. B. S. (Government Medical College, Nagpur, Maharashtra) 2018, M. D. Family Medicine (MGM Medical College and Hospital, Navi Mumbai, 3rd year Junior Resident)
E-mail ID: pawannimbhorkar95[at]gmail.com

Dr. Arunava Bharati
M. B. B. S. (Calcutta National Medical College)
M. D. Pediatrics (MGM Medical College and Hospital, Navi Mumbai, Senior Resident)
E-mail ID: arunavabharati55[at]gmail.com

Dr. Rakesh Thamke
M. B. B. S., M. D. Pediatrics
Currently working as: Associate Professor & Head, Department of Family Medicine, MGM Medical College and Hospital, Navi Mumbai.
E-mail ID: rthamke[at]yahoo.com