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CASE STUDY

METACHROMATIC LEUKODYSTROPHY

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ABSTRACT

Metachromatic leukodystrophy (MLD) is an in heritedneurometabolic disease caused by deficiency of enzyme arylsulfatase A resulting in deficiency of sulfatide degradation. The responsible gene is arylsulfatase A(ARSA) gene. Sulfatide accumulation in myelin-producing cells causes progressive destruction of white matter (leukodystrophy) throughout the nervous system, including in the brain and spinal cord (the central nervous system) and the nerves connecting the brain and spinal cord to muscles and sensory cells that detect sensations such as touch, pain, heat, and sound (the peripheral nervous system). A pathological hallmark of MLD is demyelination and neurodegeneration. In people with metachromatic leukodystrophy, white matter damage causes progressive deterioration of intellectual functions and motor skills. We report a case of the lateinfantile MLD that was diagnosed by means of clinical history and typical MRI of brain findings.

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INTRODUCTION

Leukodystrophy is defined as a group of genetic disorders which are characterized by the imperfect growth/development of the myelin sheath that covers nerve fibers in the brain. The disorder may be inherited in a recessive, dominant or X-linked manner, depending on the type of leukodystrophy. Specific leukodystrophies include metachromatic leukodystrophy, Krabbe disease, adrenoleukodystrophy, Pelizaeus-Merzbacher disease, Canavan disease, Childhood Ataxia with Central Nervous System Hypomyelination or CACH (also known as Vanishing White Matter Disease), Alexander disease, Refsum disease and cerebrotendinous xanthomatosis. (Mallikarjun *et al*., 2011) Metachromatic leukodystrophy [MLD] is an autosomal recessive inherited lysosomal disorder, characterized by deficiency of the enzyme arylsulfatase-A (ARSA), or more rarely, of its activator protein saposin-B. (Biffi *et al*., 2008) Due to arylsulfatase A enzyme deficiency, chemicals called sulfatides build up in and damage the nervous system, kidneys, gallbladder and other organs. In particular, the chemicals damage the protective sheaths that surround nerve cells. MLD is a rare neurodegenerative metabolic disorder, occurs with an incidence of 1 in 40, 000 to 1, 60 000 individuals, worldwide. (National Library of Medicine (US) Genetics Home Reference [updated February 2013)) Clinically, MLD shows a wide range of spectrum with respect to age of onset, the rate of progression and the initial symptoms. The most common and lethal form is the late□infantile form, which begins before 4 years of age typically presenting between 12 and 18 months of age, and patients die by the end of the first decade. The juvenile form of MLD comprises age onset between 4 and 16 years, whereas symptoms of adult MLD begin after puberty. The patients usually present with signs and symptoms of peripheral neuropathy and alterations in intelligence, speech, and coordination. The disorder is progressive with gait disturbance, quadriplegia, decerebration, and mortality by the age of 6 months to 4 years. (Singh and Kaur, 2016) Here in, were by report a case of a three year old female child presenting with increased motortone and failure to achieve developmental milestones after 12 months of age. She was diagnosed as a case of Metachromatic Leukodystrophy based on MRI findings. This report presents this infrequent form of disease in its initial presentation, diagnosis and treatment administered which can provide useful information for medical representatives in paediatrics to deal with this condition infuture.

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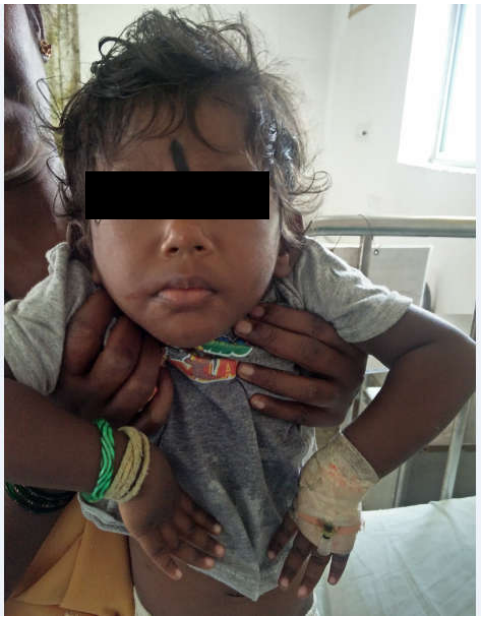
Case report

A3-year-old female child, born of consanguinity, presented to the Paediatric Department of Sri DevarajUrs Medical College, Kolar with chief complaints of developmental delay and generalized tightness which started developing from the age of 1 year. She showed normal pattern of development before the onset of symptoms. The developmental regression progressed continuously. There was no history of seizures. After one year of age, her mother felt a developmental delay in the following

months. She developed a progressive inability to walk and sit without support. She was not able to crawl and stand on her own with feet spared apart by 15 months of age. She could not articulate any real words by 18 months which made her speech unintelligible. She was also not able to feed herself from a spoon or drink from a cup with both hands. An unusual finding included head nodding with fever at 6 months of age which wasn't associated with up rolling of eyes, twisting of limb, frothing from mouth or urinary incontinence. Child's developmental landmarks were normal until the onset of symptoms. Child's anthropometric measurements were less than 3rd centiles. Head circumference was 43 cm (less than 3rd centile). Child also had hypertelorism. Vital signs were within normal limits and no abnormal skin pigmentation was noted. Cardiovascular system and respiratory system were unremarkable. There was no sign of meningeal irritation. Frontal and parietal bossing along with presence of oral thrush were the only characteristic findings from head and neck region. Chest examination revealed prominent rib cage with rachitic rosary. Central nervous system examination revealed increased muscle tone, decreased bulk of muscle (thin extremities) and brisk deep tendon reflexes.



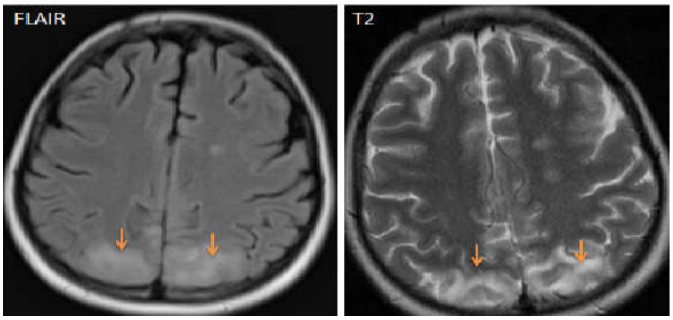


Figure 2. T1: affected areas were low signalled while T2: affected areas were high signalled sparing along the venules, with some tigroid pattern

Prenatal and family history were unremarkable. There were no antenatal or postnatal complications and the child was vaccinated as per schedule. Initial differential diagnoses of neurodegenerative disorder, infantile stroke and spastic cerebral palsy or post meningitis sequel were contemplated and the child was further investigated. MRI scan of the brain was performed which revealed bilateral symmetrical confluent areas of periventricular deep white matter signal change (demyelination), in particular around the frontal horns with sparing of subcortical U fibers. T1: affected areas were low signalled while T2: affected areas were high signalled sparing along the venules, with some tigroid pattern (suggestive of metachromatic leukodystrophy). There was increased extra axial CSF space along both cerebral hemispheres with mildly dilated ventricular system representing mild cerebral atrophy. EEG showed asymmetric sharp and slow wave with predominance over parietal and posterior temporal regions. CBC and urinalysis showed no specific findings. Low socioeconomic status of the patient did not allow for the enzyme assay to be performed. Imaging findings alone proved to be highly diagnostic for the white matter disorder, Metachromatic Leukodystrophy with brain atrophy. The child was treated with supportive care together with physiotherapy. Vitamin D was supplemented to manage the signs of rickets (frontal bossing and rachitic rosary). Bone marrow transplantation, one of the newer modalities of treatment for MLD, was planned and the child was referred to higher centre for the same.

DISCUSSION

Metachromatic leucodystrophy (MLD) is a lysosomal storage disorder characterized by accumulation of sulphated glycolipids, specifically 3-o-sulfogalactosyl-containing glycolipids as a consequence of defects in lysosomal hydrolase. The main site of 3-o-sulfogalactosyl-containing glycolipids is the myelin sheath of central and peripheral neurons. Because of this location the clinical manifestations of MLD are predominantly neurological in nature. The accumulation of sulphated glycolipids in the lysosomes results in the characteristic metachromatic staining of the tissues, hence the derivation of the name of this disease. (Lugowska *et al*., 2005) Based on the age of onset, the index case falls under the late infantile variant of MLD. Regression of milestones is common in infantile variants (as seen in this case), generalized seizures, which are a common feature of the infantile variant were however absent in this case. Spasticity is another feature of the infantile form which were seen in the form of increased muscle tone and brisk deep tendon reflexes in the child. (Mahmood *et al*., 2009) Children suffering from the late infantile variant

have been reported to lose head and trunk control at around 3 years of age as a result of motor function regression, (Liaw *et al*., 2015) these findings can be seen in the index case as early as the 12 month itself. Brain magnetic resonance and electro-neurographic recordings are appropriate diagnostic modalities for white matter diseases. MRI plays an essential role in the early diagnosis of white matter diseases and it is far superior to Computed Tomography (CT). The multiplanar imaging capability and very high sensitivity for demyelinating foci due to its excellent grey white matter resolution make MRI imaging the modality of choice. (Ahsan *et al*., 2008) Brain magnetic resonance shows a diffuse symmetric hyperintense signal in both the periventricular and subcortical supratentorial white matter on FLAIR (fluidattenuated inversion recovery) and T2-weighted images. As the disease progresses, other structures are involved such as corpus callosum, cerebellar white matter, corticospinal tracts, internal capsules and thalami. In the late stages, the U-fibers are involved and atrophy appears. Another common finding is the tigroid pattern of demyelination (Singh and Kaur, 2016) which is also present in the index case. Tae Sung kim *et al* conducted a study on seven children with late infantile MLD with their MR imaging findings (Kim *et al*., 1997) which are similar to the findings in our case. A combination of mutation analysis and biochemical procedures can be used to reach the specific diagnosis. Mutation Analysis is an extremely valuable diagnostic technique. The abovementioned tests were not performed because of the lack of availability of these diagnostic modalities and financial constraints of the family. (Kundu *et al*., 2016) There are no treatment options available to us at present and therapeutic strategy is generally supportive. In individuals with late infantile and early juvenile forms of the disease, bone marrow or cord blood transplantation may stabilize neurocognitive function. In addition to bone marrow transplantation, gene therapy is under experiment as a possible solution to correct the underlying genetic abnormality. (Rao *et al*., 2015)

Conclusion

MLD is to be strongly suspected in infancy and childhood when they present with features of mental regression coupled with combination of pyramidal dysfunction. It is a progressive demyelinating neuropathic disorder that manifests with symptoms similar to other neurodegenerative disorders hence the difficulty to diagnose accurately. This report seeks to indicate that MRI can prove to be an essential diagnostic tool for MLD especially in developing countries like India where expensive procedures like enzyme assays and genetic testing are generally unaffordable and also not widely performed across hospitals due to lack of resources.

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