Infantile metachromatic leukodystrophy in an 18 month old girl
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Abstract
Metachromatic leukodystrophy is a rarely occurring neurodegenerative metabolic disorder with an incidence of 1-9 individuals out of 1,000,000. We present a similar case in an eighteen month old child which was extremely challenging to diagnose. Clinical symptoms suggested motor regression and developmental delay which gave rise to suspicion of a neurodegenerative disorder. An MRI scan of the brain revealed cortical demyelination with tigroid appearance which confirmed the diagnosis of Metachromatic leukodystrophy. Due to the lack of availability of a treatment option like bone marrow transplant, the patient could only be given physiotherapy to help with the musculoskeletal manifestations of the disorder. The purpose of this case report is to identify clinical presentation and classical MRI findings to diagnose MLD in absence of enzyme assay and gene mutation analysis.

Keywords: Metachromatic leukodystrophy, Motor regression, Tigroid.

Introduction
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.1 MLD is a rare neurodegenerative metabolic disorder, occurs with an incidence of 1 in 40,000 to 1,60,000 individuals, worldwide.2 A rare, serious and progressive disease, MLD currently is incurable. But treatment may help defer the disease’s progress and research is exploring new treatment possibilities for MLD.

Herein, we report a case of an eighteen month old female child presenting with increased motor tone and failure to achieve developmental milestones after 11 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 in future.

Case Report
An eighteen month old female child, born of consanguinity, presented to the Paediatric Department in November 2015 at Civil Hospital Karachi with decreased mental function and generalized rigidity for 12 days. She could not hold her neck and was unable to sit (with or without support) since 15 days. There was no history of fits. 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. She developed social smile at 2nd month and had attained neck holding at fifth month. She was able to sit with support by 6th month and sitting without support was attained by the end of 7th month. She showed stranger anxiety by 11th month. After one year of age, her mother felt a developmental halt in the following months and brought her to the hospital. 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.

On examination, the child was irritable with high-pitched crying and inflexed postures at the elbows. Child’s anthropometric measurements were within normal ranges. 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.
Prenatal history was unremarkable. There were no antenatal or postnatal complications and the child was fully vaccinated.

Initial differential diagnoses of neurodegenerative disorder, infantile stroke and spastic cerebral palsy or post meningitic 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 atria and frontal horns with sparing of subcortical U fibers (Figure-1). T1: affected areas were low signaled while T2: affected areas were high signaled sparing along the venules, with some tigroid pattern (suggestive of metachromatic leukodystrophy) (Figure-2). There was increased extra axial CSF space along both cerebral hemisphere with mildly dilated ventricular system representing mild cerebral atrophy (Figure-3).

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 newest modalities of treatment for MLD, was not performed as her parents could not bear the expense of the procedure. The parents did not bring the child back for follow up.

Discussion
Metachromatic Leukodystrophy gets its name from the metachromatic granules which are formed as a result of the accumulation of galactosyl and lactosyl sulfatide substrate deposits. These deposits are found as a result of the enzyme arylsulfatase-A (ARSA) deficiency. Metachromatic granules can accumulate in macrophages, oligodendrocytes, in visceral organs such as liver, kidney, pancreas, gallbladder, sweat glands, adrenal cortex, testes and rectal tissue, and in macrophages and Schwann cells in the peripheral nervous system.
Metachromatic leukodystrophy is generally classified under four separate forms based on the age at onset of symptoms. These are late infantile, early and late juvenile and adult forms. Manifestation of symptoms during the second year of life represents the late infantile variant. Onset of symptoms between 4 and 6 years represents the early juvenile, while an onset between 6 and 15 years represents the late juvenile form. An onset of symptoms after the age of 15 is classified under the adult form.

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. 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, 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 such as multiple sclerosis and MLD. MRI is considered far superior to Computed Tomography (CT) and the imaging modality of choice in white matter diseases. The multiplanar imaging capability and very high sensitivity for demyelinating foci due to its excellent gray white matter resolution make MRI imaging the modality of choice.

Brain magnetic resonance shows a diffuse symmetric hyperintense signal in both the periventricular and subcortical supratentorial white matter on FLAIR (fluid-attenuated 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 which is also present in the index case (Figure-2).

Tae Sung kim et al conducted a study on seven children with late infantile MLD with their MR imaging findings which are similar to the findings in our case. An increased extra axial CSF space along both cerebral hemispheres with mildly dilated ventricular system representing mild cerebral atrophy was also seen in the index case. These findings of mild ventriculomegaly, as well as mild to moderate atrophic ventriculomegaly (in those who had developed diffuse brain atrophy) have been previously documented in other cases of late infantile MLD as well.

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 entire coding region of an ARSA gene often requires sequencing owing to the absence of three of the most commonly screen mutations (459 þ 1G4A, P426L and I179S) in more than 50% of the patients. The aforementioned tests were not performed because of the lack of availability of these diagnostic modalities and financial constraints of the family.

There are no treatment options available to us at present and therapeutic strategy is generally supportive. The idea of Haematopoietic Stem Cell Transplantation is to restore an important scavenger function by repopulating recipient haematopoietic and lymphoid compartments with normal cells which have the potential to express a functional hydrolase and replace macrophages and microglia as the major components of the catabolism of storage product. Enzyme replacement therapy and gene therapy are also being considered as therapeutic options for MLD.

**Conclusion**
MLD 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 underdeveloped countries like Pakistan where expensive procedures like enzyme assays and genetic testing are generally unaffordable and also not widely performed across hospitals due to lack of resources.

**Consent:** Informed consent was obtained from the parents of the patient to reproduce her case in this report.

**Conflict of Interests:** The authors declare that they have no conflict of interests.

**Disclaimer:** The manuscript has not been published previously and is not under consideration for publication in any other journal.

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