Case Report

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Metachromatic leukodystrophy in infant presenting as acute febrile illness: a case report

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Introduction and Importance: Metachromatic leukodystrophy (MLD) is a rare genetic disorder affecting the central and peripheral nervous systems. It results from ARSA enzyme deficiency, causing sulfatide accumulation and myelin damage. Early diagnosis is crucial, and this case highlights the diagnostic challenges and rapid health deterioration associated with MLD.

Case Presentation: A 14-month-old male, initially presenting with fever and crying during micturition, experienced a devastating health decline. Previously, he had achieved developmental milestones but rapidly lost motor and cognitive skills. Extensive investigations led to an MLD diagnosis, complicated by severe malnutrition. Despite medical interventions, his condition worsened, leading to cardiopulmonary arrest and a tragic end.

Clinical Discussion: MLD is an exceedingly rare genetic disease with systemic effects, as illustrated by severe metabolic acidosis in this case. Early diagnosis, through comprehensive investigations like MRI, is critical, but MLD's rapid progression poses challenges in management. Therapeutic options remain limited, emphasizing the importance of a multidisciplinary approach.

Conclusion: This case emphasizes the insidious nature of MLD, highlighting the need for considering rare genetic conditions in unexplained neurological regression. It underscores the urgency of improved awareness, early diagnosis, and comprehensive care for individuals affected by such devastating disorders. Despite the challenges, the medical community's dedication to providing care and support remains unwavering.

Keywords: ARSA enzyme deficiency, case report, metachromatic leukodystrophy, multidisciplinary approach, severe metabolic acidosis

Introduction

Metachromatic leukodystrophy (MLD) was initially diagnosed as a progressive genetic disease affecting both the central and peripheral nervous systems' myelin sheath[1–5]. Over the subsequent two decades, genetic studies and MRI advancements led to the recognition of MLD as a congenital anomaly related to sulfatide metabolism[6].

MLD is a lysosomal storage disease, which is characterized by damage of the myelin sheath that covers most of nerve fibers of the central and peripheral nervous systems. The disease occurs due to a deficiency of the lysosomal enzyme arylsulfatase A (ARSA) or its sphingolipid activator protein B (SapB)[1]. Arylsulfatase enzymes within lysosomes are crucial in sulfatide hydrolysis. The absence of arylsulfatase A (ARSA) enzymes leads to sulfatide accumulation, which damages myelin in the central and peripheral nervous systems, resulting in the loss of motor and cognitive skills.

MLD is one of the most common leukodystrophies and has a prevalence rate of 1 in 40 000–160 000 worldwide. In some isolated populations, the incidence of MLD is much higher. For example, in the group of Habbanite (Jews) it is estimated at 1 in 75, among the Navajo Indian people at 1 in 2500, and among the Arab groups of Israel it is estimated at 1 in 8000[7].

The disease is characterized by the damage of the myelin sheath that covers most of the nerve fibers of the central (CNS) and

HIGHLIGHTS

- Metachromatic leukodystrophy (MLD) is a rare genetic disorder affecting the nervous system due to ARSA enzyme deficiency, leading to sulfatide accumulation and myelin damage.
- Early diagnosis is crucial, but MLD's rapid progression poses challenges, as highlighted by a 14-month-old male's tragic health decline.
- This case underscores the need for considering rare genetic conditions like MLD in unexplained neurological regression and emphasizes the importance of early diagnosis and a multidisciplinary approach.
- Despite the challenges, the medical community's commitment to providing care and support for MLD patients remains unwavering.

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peripheral nervous systems (PNS), resulting in progressive motor and cognitive impairment as clinical manifestations[5].

MLD takes its name from the presence of metachromatic granules in the affected cells, formed as a result of the accumulation of sulfatides and sphingolipids presented in myelin. With MLD, sulfatides accumulate in oligodendrocytes, microglia, some CNS neurons, Schwann cells, PNS macrophages[2,8]. MLD causes demyelination to occur, leading to impaired motor function, spastic tetraparesis, ataxia, spasms, optic atrophy, and cognitive impairment[3].

In most cases, MLD is not included in the fetus and newborn genetic screening tests given that MLD is a rare disease. Commonly, the disease is diagnosed after birth, depending on the form of MLD. Only in cases where the parents know that their family carries the mutation (family history, development of the disease in previous children), diagnosis, and treatment can begin. However, early diagnosis is critically important. The introduction of prenatal diagnosis and newborn screening could increase therapy efficacy, since the effectiveness of the treatment is significantly reduced after the onset of symptoms[9]. Prenatal diagnostics can be performed by measuring the activity of ARSA in amniotic fluid cells and evaluating the accumulation of sulfatides to exclude ARSA pseudo-deficiency[10].

The work has been reported in line with the Surgical CAse REport (SCARE) criteria[11].

Case presentation

A 14-month-old male child, born into a family with a history of second-degree consanguinity marriage, was brought to the hospital with an initial presentation of fever, accompanied by a recorded temperature of 101.8°F, and crying during micturition. Little did his parents know that this febrile episode would mark the onset of a tragic transformation in their child's health. Before this illness, the infant's developmental history had been entirely normal. He had achieved crucial milestones at appropriate ages, including standing with support at 11 months and standing without support at 12 months; he could speak meaningful words, feed himself with hands or utensils, and drink from a glass without spilling.

However, this febrile illness brought about a rapid decline. Initially, his gross motor movements, which were unaffected, began to deteriorate. He lost his ability to walk independently and his capacity to speak. His health further deteriorated, impacting his ability to sit and maintain head control. As his condition worsened, multiple investigations were conducted. At the Primary Hospital, normal hematological parameters and CRP within the normal range provided no immediate answers. Urine R/E and M/E also showed normal findings, adding to the complexity of his case. To address the febrile illness, he received medications:

Syrup cefpodoxime proxetil (50 mg/5 ml) 3 ml po bid for 5 days.

Drop paracetamol 0.7 ml po six hourly for 5 days.

Syrup mefenamic acid 2.5 ml po sos

However, his fever persisted, leading to his transfer to a Tertiary Hospital for further evaluation. There, his condition was diagnosed with 'Acute Febrile Illness (cause)' and 'Global Developmental Delay (secondary to ? MLD)'. Additionally, severe acute malnutrition was identified. The infant's birth history indicated a normal vaginal delivery, with a birth weight of 2.3 kg. He cried immediately after birth, requiring no NICU admission.

During clinical examination, vital signs showed an elevated pulse rate, and his temperature was 101°F. He appeared ill-looking and irritable. Anthropometric measurements indicated severe malnutrition. Laboratory results, including hemoglobin, hematocrit, platelet count, calcitonin, and serum sodium, were documented. Blood culture showed no organism detected, and urinalysis indicated ketones at 2+, with other findings within normal limits. An MRI revealed concerning results, including diffuse white matter hyperintensity in bilateral fronto-temporo-parieto-occipital lobes, periventricular location, and bilateral external capsules affected in T2 (Fig. 1) and FLAIR (Fig. 2) sequences with diffusion restriction. This prompted consideration of differentials, including demyelinating disease compatible with MLD and hypoxic-ischemic encephalopathy (Fig. 3 and Fig. 4).

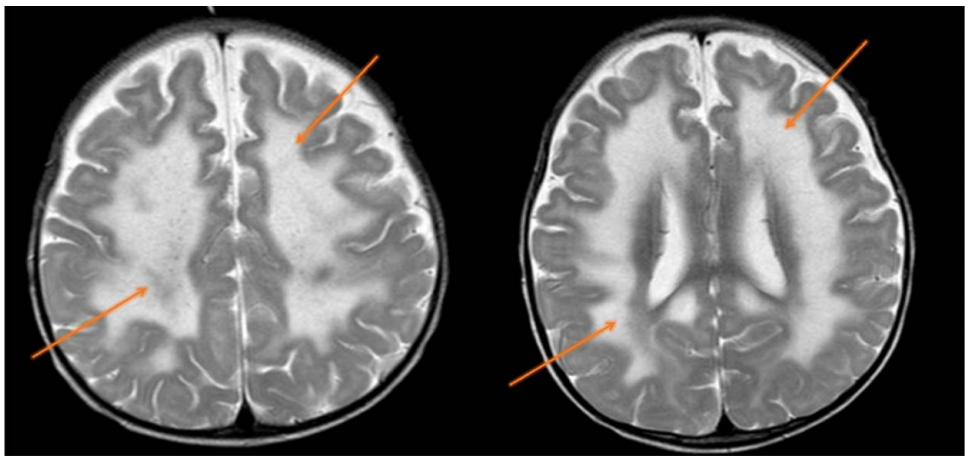

Figure 1. Red arrows in both images a. and b. are of MLD of periventricular white matter. These T2-weighted MRI images show symmetrical hyperintensities in bilateral deep white matter and periventricular white matter is suggestive of Metachromatic leukodystrophy (MLD).

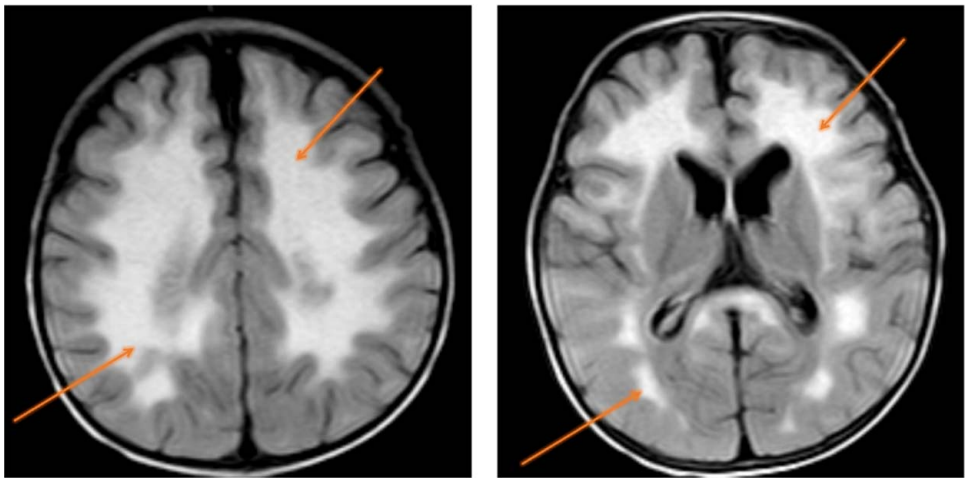

Figure 2. FLAIR Sequence showing symmetric high signal intensity in both bilateral deep white matter (left) and bilateral periventricular white matter which is suggestive of Metachromatic Leukodystrophy (MLD).

During his stay at the hospital, he received treatments, including NG feeding, multivitamin supplements, mitochondrial cocktail regimens, and medications such as Ceftriaxone and Acyclovir. He was also prescribed Tab Pacitane (Trihexyphenidyl) at 1 mg thrice daily.

Upon discharge, the infant was hemodynamically stable and euglycemic. His heart and respiratory rates had improved, but he still experienced intermittent fever spikes. Dystonia was present in his bilateral upper and lower limbs, and his Glasgow Coma Scale (GCS) was 14/15 with irritability.

However, the infant's health took a critical turn, leading to his admission to Child Hospital. He presented with a high fever and decreased feeding. His vital signs, including pulse and respiratory rates, were severely abnormal. He was diagnosed with severe acute malnutrition and gestational diabetes mellitus secondary to MLD. His condition deteriorated rapidly, and he was intubated. When he was transferred to another hospital due to the unavailability of a bed in the PICU, his respiratory efforts were grasping. He was connected to a ventilator due to respiratory distress. Noradrenaline was administered to maintain blood pressure. Arterial blood gas results indicated severe metabolic acidosis and sodium bicarbonate was administered. Despite all medical interventions, within 30 min of presentation, the infant experienced cardiopulmonary arrest, respiratory failure on mechanical ventilation, and severe metabolic acidosis; an emergency cardiopulmonary resuscitation was done, and despite all effects, there occurred a tragic and sudden end to his battle against the devastating MLD.

Discussion

MLD is a rare genetic disease with a prevalence rate of ~1 in 40 000–160 000 worldwide[1]. This devastating condition results from the absence of ARSA enzymes, leading to elevated sulfatide levels and gradual damage to the myelin in the central and peripheral nervous systems. Patients typically experience a progressive loss of motor function and cognitive decline. The presented case report sheds light on the tragic journey of an

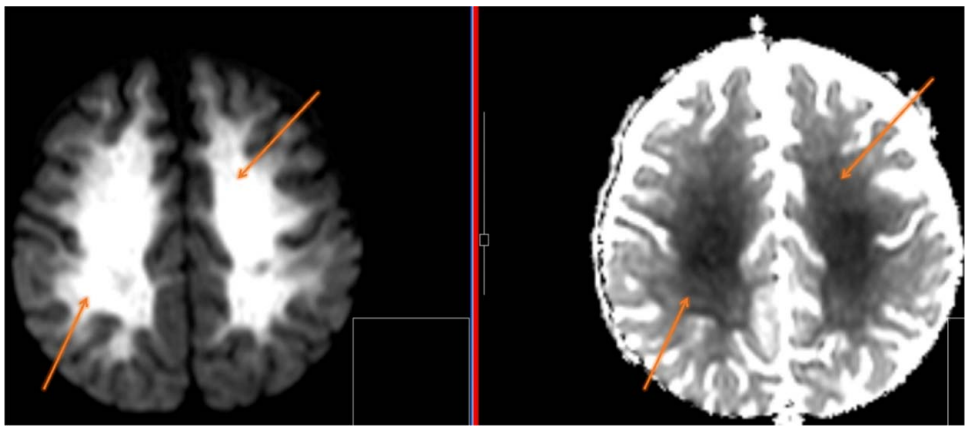

Figure 3. Images showing diffusion restriction in bilateral frontoparietal periventricular white matter which is suggestive of Metachromatic leukodystrophy (MLD) Right: Diffusion weighted imaging of bilateral periventricular white matter showing high signal intensity Left: ADC map of bilateral periventricular white matter showing corresponding low signal on ADC map.

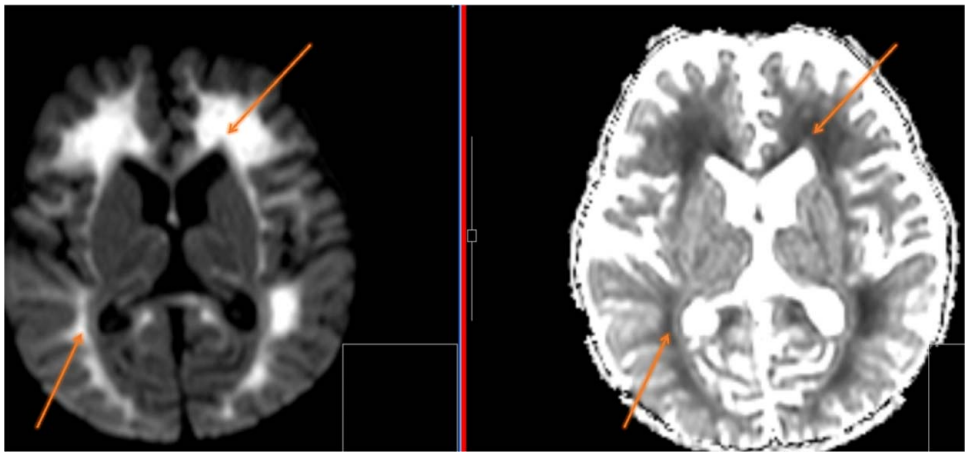

Figure 4. Images showing diffusion restriction in bilateral frontoparietal periventricular white matter which is suggestive of Metachromatic leukodystrophy (MLD) Right: Diffusion weighted imaging of bilateral periventricular white matter showing high signal intensity Left: ADC map of bilateral periventricular white matter showing corresponding low signal on ADC map.

infant, a 14-month-old male child, initially admitted with an acute febrile illness and many symptoms. Ultimately, the diagnosis revealed MLD. This case merits significant attention and discussion due to its rarity, diagnostic complexities, and rapid patient health deterioration. This case report underscores the intricate nature of seemingly benign symptoms like fever and decreased feeding in pediatric patients.

Early diagnosis plays a pivotal role in managing MLD. In this instance, the initial presentation could have easily been misinterpreted as an infectious ailment. Nevertheless, thorough investigations, including an MRI that unveiled white matter abnormalities, facilitated a timely diagnosis[12]. This underscores the importance of considering rare diseases in cases of unexplained neurological regression in children.

This case report also delineates severe metabolic acidosis, likely stemming from MLD. This underscores the systemic impact of the disease, affecting not only the central nervous system but other organ systems. The swift progression of the disease, even after diagnosis, serves as a challenge associated with managing MLD. Regrettably, this case highlights the dearth of effective treatments for MLD. Therapeutic interventions primarily center around supportive care, nutritional support, and symptom management. Despite these efforts, the infant's condition continued to deteriorate alarmingly.

There are no fully curative therapies for MLD, but early MLD is a treatable disease. Allogeneic hematopoietic cell transplantation (HSCT) is the first-line treatment option offered for eligible patients. Ex vivo HSCT gene therapy has also been associated with benefit and is approved for treatment in some region like European union. Hematopoietic stem cell transplantation — Allogeneic HSCT is the standard of care for eligible patients with no or early MLD disease involvement.

Managing a case like these demand a multidisciplinary approach involving pediatricians, neurologists, radiologists, and intensive care specialists. This collaborative effort is crucial in addressing the complex issues MLD poses, which affects various organ systems. This case report is a poignant illustration of the challenges of rare genetic diseases like MLD. It emphasizes the need for early diagnosis, genetic testing, and a multidisciplinary approach to managing these devastating conditions.

Conclusions

The case of this infant unfolds as a challenging medical journey, marked by an initial presentation of acute febrile illness, which later unraveled into a far more complex and dire diagnosis. The progression of his condition, from a healthy toddler to a state of profound disease, showcases the insidious nature of MLD, a rare and devastating neurodegenerative disorder.

This case underscores the importance of considering rare genetic conditions like MLD in unexplained neurological regression, even when initially presented as an acute febrile illness. This report serves as a poignant reminder of the urgent need for improved awareness, early diagnosis, and comprehensive care for individuals affected by such devastating disorders. Despite the challenges, the medical community's dedication to providing care and support for this infant remained unwavering throughout this heartrending journey.

Ethical approval

This is case report; therefore, it did not require ethical approval from ethics committee.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

S.A.: conceptualization, methodology, writing – original draft, and writing – review and editing; B.U.R.: data curation, investigation, revising, and editing manuscript; Y.A.: data curation,

methodology, revising, and editing manuscript; P.T., B.P., and D.B.: data curation and visualization. All authors were involved in manuscript drafting and revising and approved the final version

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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Not applicable.

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Data those included are publicly available.

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