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Research Article

Navigating Molybdenum Cofactor Deficiency: A Multifaceted Case Study on Diagnosis, Clinical Presentation, and Therapeutic Strategies

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Abstract

The abstract discusses a case study of a 3-year-old and 7-month-old male patient with Molybdenum Cofactor Deficiency (MoCD), a rare and severe autosomal recessive metabolic disorder characterized by impaired biosynthesis of the molybdenum cofactor (MoCo), essential for several enzymes involved in sulfur metabolism. The patient presented with lethargy, hypotonia, and delayed milestones from infancy. Despite early intervention involving various therapies, the patient continued to experience severe motor, psychomotor, and speech delays. Brain MRI showed specific abnormalities consistent with MoCD, and genetic testing identified a homozygous mutation in the MOCS2 gene. The case underscores the challenges in managing MoCD and the need for comprehensive care strategies. MoCD's diverse clinical presentation and genetic underpinnings are explored, highlighting the importance of raising diagnostic suspicion, particularly in consanguineous contexts, and providing informed family guidance. Current management focuses on supportive care and monitoring, but the lack of a definitive cure underscores the necessity for further research in this field.

Keywords: Cofactor Deficiency; Diagnosis; Clinical Presentation; Therapeutic

Case Presentation

The patient, a 3 years and 7 months old male, was admitted to the hospital at 6 months of age due to presenting with lethargy, hypotonia, and delayed milestones. Born full-term through a normal vaginal delivery with a negative neonatal history, the patient had a past medical history of hyperactive airway disease requiring nebulizers as needed. On physical examination, the patient exhibited lag, central, and axial hypotonia, being unable to sit with support and showing poor eye fixation gaze. Deep tendon reflexes were elicited and found to be +2 in all extremities. Comprehensive infectious workup yielded negative results, and routine metabolic evaluations, including serum amino acids, urine organic acids, ammonia, lactate, and pyruvate, were also unremarkable. An MRI of the brain revealed periventricular high T2 and flair bilaterally in the frontal lobes, as well as a small cerebellum.

During an ophthalmologic examination, no abnormalities were noted. It is pertinent to note that the patient's parents share first-degree consanguinity. Whole exome sequencing revealed a homozygous mutation in the MOCS2 gene: ENST00000361377.8: c.3G > A, ENSP00000355160.4: p. Met1?. In response to the diagnosis, the patient commenced physiotherapy, psychomotor therapy, and feeding and speech therapy. At present, the patient, now 3 years and 7 months old, continues to experience severe motor, psychomotor, and speech delays, with non-verbal communication and absence of speech thus far. Careful and comprehensive management remains essential to address the patient's unique

needs and support their ongoing development. The diagnosis is Molybdenum Cofactor Deficiency.

Discussion

Molybdenum Cofactor Deficiency (MoCD) is an extremely rare and severe autosomal recessive metabolic disorder. It is mainly characterized by impaired biosynthesis of the molybdenum cofactor (MoCo), an essential molecule required for the proper functioning of many enzymes involved in sulfur metabolism. MoCo acts as a cofactor for three main enzymes that play a vital role in catalytic reactions crucial for the elimination of compounds containing toxic sulfur: sulfite oxidase (SUOX), xanthine dehydrogenase (XDH), and aldehyde oxidase (AOX). MoCo biosynthesis is a multistep process that converts precursor molecules into the active form known as molybdenum pyranopterin cytosine dinucleotide (Mo-PCD).

MoCD is caused by biallelic pathogenic variants in genes involved in different steps of MoCo biosynthesis, namely MOCS1, MOCS2, MOCS3, or GPHN. Pathogenic variants in these genes lead to the disruption of MoCo synthesis, resulting in loss of enzymatic activity and subsequent accumulation of toxic metabolites. The MOCS2 gene consists of two distinct subunits, MOCS2A and MOCS2B, which together form a complex responsible for MoCo synthesis. Some patients with Molybdenum Cofactor Deficiency of complementation group B (MOCODB) carry biallelic mutations in MOCS2. These mutations, including a 2-bp deletion and missense variations, directly impact the functioning of MOCS2's two overlapping ORFs, highlighting their essential roles.

Regarding clinical presentation, MoCD is heterogeneous and can vary widely in severity. In early-onset cases, infants typically present with neurological symptoms such as lethargy, hypotonia, seizures, and developmental delay. Acute neurologic decompensation in the setting of infection may be the first sign of MoCD and may prompt an evaluation leading to diagnosis. These features may improve after resolution of the inciting infection or progress gradually or in a stochastic manner over a lifetime [1]. Affected individuals may also exhibit nystagmus, myoclonic jerks, or hyperekplexia (excessive startle reaction to loud noises, touch, or movement), with or without concurrent seizures [2]. All these symptoms result from the accumulation of a toxic metabolite: sulfite, a potent neurotoxin causing brain damage and neurodegeneration. The main culprits for neurodegeneration in MoCD individuals and those with isolated sulfite oxidase deficiency are the toxic metabolites sulfite and S sulfocysteine (the reaction product of sulfite and cystine). Sulfite depletes intracellular ATP in cultured neuronal cell lines and impairs mitochondrial respiration. NMDA receptors are activated by S sulfocysteine, which is stereochemically similar to glutamate. Imaging often reveals delayed myelination, cerebral atrophy, and abnormal white matter on MRI scans. Progressive thinning of the corpus callosum and cerebellar atrophy also develop over time [3].

The true incidence of MoCD is uncertain due to its rarity, but more than 100 individuals with molybdenum cofactor deficiency have been identified [1]. However, this condition is underdiagnosed due to its nonspecific clinical presentation. The disorder exhibits a global distribution, affecting individuals of diverse ethnicities and geographical regions. Raising diagnostic suspicion in young children and infants presenting unexplained neurological symptoms, especially in consanguineous contexts, is crucial.

Prognosis is poor: about 75% of affected individuals succumb in infancy to secondary complications of their neurologic disability [6].

Currently, there is no ultimate cure for MoCD, and disease management primarily focuses on supportive and symptomatic care. Supportive care involves thiamine supplementation, feeding therapy, and tailored symptom treatments. Monitoring neurologic changes, milestones, amino acid levels, and growth is crucial for adjusting treatment effectively. Immediate metabolic treatment is necessary for at-risk relatives. Genetic counseling is highly recommended as it aids in prenatal diagnostics and preimplantation genetic testing. A comprehensive strategy ensures effective MoCD management and informed family guidance.

A case study involves a 3-year-old and 7-month-old male patient presenting with lethargy, hypotonia, and delayed milestones, consistent with the neurological symptoms commonly seen in early-onset MoCD. Additionally, the patient's brain MRI revealed periventricular high T2 and flair bilaterally in the frontal lobes, as well as a small cerebellum, consistent with the neuroimaging findings often associated with MoCD.

Genetic testing in the case revealed a homozygous mutation in the MOCS2 gene, supporting an autosomal recessive inheritance pattern.

Despite early intervention with physiotherapy, psychomotor therapy, and feeding and speech therapy, the patient in the case continues to experience severe motor, psychomotor, and speech delays. This highlights the challenges in managing MoCD and the limited efficacy of current therapies.

Conclusion

Deficiency (MoCD), an exceptionally rare metabolic disorder. The patient's clinical features, coupled with genetic testing confirming a MOCS2 gene mutation, underscore the disorder's intricate nature. MoCD's disruption of molybdenum cofactor biosynthesis leads to toxic metabolite accumulation, resulting in severe neurological symptoms as observed in the patient's motor and psychomotor delays.

Despite interventions, the patient's developmental progress remains limited, highlighting the complex and refractory aspects of MoCD. With a grim prognosis and no definitive cure, current management strategies focus on supportive care and monitoring milestones, amino acid levels, and growth. This case emphasizes the importance of early recognition, genetic insights, and comprehensive management in addressing the unique challenges presented by MoCD.

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