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Case Report

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Hypermanganesemia with Polycythemia and Dystonia in an 8-year-old: A Case Study

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Abstract

Among the essential trace elements, manganese (Mn) is vital due to its antioxidant property and is necessary in several diverse metabolic processes and generation of neurotransmitters. However, high levels of serum Mn levels are toxic to the central nervous system. In addition to the inherited form of Mn intoxication caused by mutations in the autosomal-recessive SLC30A10 gene, which codes for a protein associated with Mn transportation, there is also evidence of acquired Mn intoxication. Hypermanganesemia with dystonia type 1 is a rare autosomal recessive neurodegenerative condition. High serum Mn levels with dystonia's are associated with syndromes which are hypermanganesemia with dystonia type 1 and type 2. Hypermanganesemia with dystonia type 1 is also called hypermanganesemia with dystonia, polycythemia, and cirrhosis (HMDPC). These inherited disorders are distinguished by the genetic causes and different presentations. Mutations in SLC30A10 are associated with HMDPC, and mutations of SLC39A14 are associated with hypermanganesemia with dystonia type 2. HMDPC is characterized by loss of acquired milestones, dystonia, and Parkinsonian features associated with higher serum Mn levels. MRI (Magnetic Resonance Imaging) findings are characteristic such as bilateral and symmetrical T-1 hyperintensity, and T-2/ fluid - attenuated inversion recovery signal intensity in basal ganglia.

Keywords

Hypermanganesemia, Manganese

Introduction

Manganese (Mn) is an important trace element with antioxidant properties as well as being necessary for several metabolic pathways [1]. Additionally, Mn contests for protein binding with other ions, and excess levels of it, especially in the brain, can cause DNA replication disruption, mitochondrial dysfunction, and oxidative stress leading to apoptosis. Additionally, Mn buildup in the basal ganglia may directly harm the metabolic processes of various neurotransmitters, which include dopamine. Through the physiological management of its biliary excretion and intestinal absorption by a SLC30A10 gene encoded protein associated with Mn transportation, the body's amount of Mn is strictly regulated [2]. Mn can be stored in the brain, liver, and other peripheral organs due to substantial Mn excretion failure caused by autosomal-recessive mutations in the SLC30A10 gene and significant extrapyramidal signs, with parkinsonism and dystonia [1, 3]. Overexposure to the environment (such as in smelters and miners), acquired hepatocerebral degeneration, usage of the potassium permanganate-containing drug ephedrone, and patients receiving parenteral nourishment have all been linked to hypermanganesemia with brain Mn accumulation [4].

Case Report

An 8-year-old boy came to hospital with chief complaints of difficulty to walk since past few months. Patient was apparently asymptomatic till the age of 3 and half years, when the parents initially observed toe walking in right lower limb, 1 month later observed toe walking in left lower limb associated with frequent falls. 6 months later proximal weakness was noticed in the form of difficulty getting up from sitting position. Patients had a history of slurring of speech which is progressive in nature. Neurologic examination showed toe walking with bilateral ankle deformity in plantar flexion. Cock walking gait was observed. Hypertonia of all 4 limbs was present. The ocular examination was normal. The patient had polycythemia with hemoglobin of 18 g/dl. Higher blood serum Mn levels (2322 nmol/L) were found. The total iron (Fe) binding capacity was normal. MRI brain showed signals with hyperintensity from dentate, lentiform, caudate, and cerebellar white matter in T1 sequence with normal T2 sequence. Genetic sequencing showed Homozygous SLC30A10 mutations involving exon 1. Chelation therapy with calcium edetate was given which showed clinical improvement. The patient was given pacitane for dystonia.

Discussion

Mn is a critical trace element which is involved in numerous metabolic pathways which include protein, carbohydrate, and lipid metabolism. Mn is also required for proper immune system functioning, ATP production and energy production. Mn acts as a Co-factor for many enzymes, some of these enzymes are required in neurotransmitter synthesis. Several mechanisms come into play to maintain intracellular levels of Mn. When these homeostasis mechanisms are disrupted inherited hypermanganesemia occur. The membranes enclosing cells and the membranes of cellular structures both contain the proteins SLC30A10 and SLC39A14 [5]. According to studies, when the blood Mn level rises, the SLC30A10 protein moves the Mn from the liver (an essential organ in the homeostasis of Mn) cells into the bile, where it is expelled from the body, while the SLC39A14 protein transports the Mn into the liver cells. Additionally, Mn is removed from brain cells by the SLC30A10 protein in order to prevent a build-up of the element [4]. Mutations in the SLC30A10 gene prevent Mn from leaving brain and liver cells, which leads to its build-up in the brain and blood resulting in Parkinsonian characteristics such as polycythaemia and liver diseases. In HMDPC, Mn accumulates in the liver, brain, and blood [1]. Mn stimulates the expression of the erythropoietin gene, which may be the mechanism causing polycythemia [4]. Hypermanganesemia increases the release of Fe from intracellular storage, enhances Fe intake, and lowers Fe utilization, which can be used to explain the depleted Fe stores [4].

Early-onset HMDPC symptoms often appear in the age range of 2 to 15 in children, but they can also appear in adults (adult-onset) [2]. Children who have the early-onset HMDPC show dystonia in their arms and legs, which causes them to walk with the distinctive cock-walk gait. Cock Walk Gait has a characteristic high stepping gait [3]. Additionally, slurred speech, bradykinesia, and tremor are other neurological symptoms which can be observed in affected children. On the other hand, HMDPC in adults is characterized by Parkinsonism, which includes postural instability, rigidity in muscles, tremors, and bradykinesia [6]. Individuals diagnosed with HMDPC show relatively lower amounts of Fe in the body and polycythemia. Additionally, liver cirrhosis and hepatomegaly will be observed due to the accumulation of Mn excessively in the liver [7]. MRI findings of hypermangansemia typically include symmetric hyperintensities of dentate nucleus and basal ganglia on T-1 weighted images and near normal changes in T-2 weighted images. These MRI findings were identical in both congenital and acquired hypermanganesemia. Other factors such as Fahr disease, Wilson's disease, end-stage liver illness, and acquired Mn overload from excessive environmental exposure were ruled out as causes of symmetric T1 hyperintensities of the basal ganglia [2].

Other inherited diseases with metal deposition seen on neuroimaging include syndromes of brain calcium storage, which appear as hyperdensities on a Computed Tomography scan, and syndromes of brain Fe accumulation, which result in particular patterns of Fe deposition on T-2 scans. To establish inherited hypermanganesemia and to distinguish it from acquired hypermanganesemia and other inherited metal deposition syndromes, several laboratory tests are used. In contrast to acquired hypermanganesemia, these patients have a mean serum Mn level that is higher than 2000 nmol/L [1].

Polycythemia is a common finding in SLC30A10 mutations and polycythemia may occur prior to neurological manifestations sometimes. Upregulation of erythropoetin due to Mn was considered as a probable cause. Transporters such as ferroportin, transferrin/transferrin receptor complex, and the divalent metal transporter 1 are shared between Mn and Fe metals, as both this metal homeostasis are interdependent [2]. Chelation therapy or Fe supplementation are used to correct polycythemia. Lifelong chelation therapy along with Fe-supplementation is the first line treatment [8]. IV disodium calcium edetate is the first line chelating agent used as it increases urinary excretion of Mn. Oral Fe-supplementation causes reduced absorption of Mn due to competitive inhibition in intestinal tract because same transporters are needed for their absorption and increases urinary excretion of Mn [3, 4]. As HMDPC induces neurodegeneration, it is remarkable that treatment with either chelator or Fe improves neurological disease in people with severe disease progression. This shows that metal toxicity also irreversibly impairs neuronal function, as shown in Wilson's disease, in addition to neuronal death [2].

Conclusion

In conclusion, like Wilsons disease, HMDPC is a treatable condition. With early diagnosis and genetic testing and with early treatment, improvement in symptoms and prevention of progression of this fatal disease can be achieved. Finally, additional chelating drugs, preferably oral in administration and long-term monitoring of various therapy outcomes are required.

Conflict of Interest

The authors declare there is no conflict of interest.

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