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LONG-TERM FOLLOW-UP OF A CHILD WITH HYPERMANGANESEMIA WITH DYSTONIA, POLYCYTHEMIA AND CIRRHOSIS

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ABSTRACT

Hypermanganesemia with dystonia, polycythemia and cirrhosis (HMDPC) is a rare but treatable inherited metal deposition syndrome, which occurs due to mutation in SLC30A10 gene. This leads to increase in manganese (Mn) levels in the blood and its deposition in the brain, muscles and liver which results in extrapyramidal symptoms, polycythemia and/or liver cirrhosis. This case report describes a five-year follow-up of a child with HMDPC treated with ethylenediaminetetraacetic acid (EDTA) as chelation therapy. This case also highlights the importance of early recognition and initiation of treatment for children with HMDPC and emphasizes the need for screening of siblings for early detection. The use of EDTA as chelation showed significant improvement of symptoms in this case, however, literature is yet to report the best treatment option for HMDPC. There is a need for more such case reports to help assess the gold standard of management of HMDPC cases.

Keywords: HMDPC, Manganese, EDTA, SLC30A10

INTRODUCTION

Manganese (Mn) is an essential trace element, used in various metabolic pathways.[1] It is an important cofactor for enzymes used in the metabolism for several neurotransmitters and hormones.[2] Although an important cofactor, the elevated levels of Mn in the body are highly toxic to multiple organs. Mn competes with ions for protein binding, therefore its excess in the body can lead to oxidative stress, mitochondrial dysfunction, DNA replication disturbances and apoptosis.[3] Hypermanganesemia imparts its effects more commonly in the brain by depositing in the basal ganglia and disrupting several neurotransmitter pathways, including dopaminergic ones, thereby causing extrapyramidal side effects.[4,5]

To date, there are three Mn related inborn errors of metabolism that have been reported and hypermanganesemia with dystonia, polycythemia and cirrhosis (HMDPC) is one of them.6 HMDPC is a rare disorder that results from the mutation in SLC30A10 gene. The SLC30A10 gene encodes for Mn transporter protein in the intestinal and biliary tract.[4] A mutation in this gene leads to increase in Mn levels in the liver, muscle, blood stream, and brain, particularly the basal ganglia, resulting in extrapyramidal manifestations, dystonia, polycythemia, and liver cirrhosis. However, liver involvement ranges from entirely normal liver function to elevated liver enzymes, hepatomegaly, and fibrosis before progressing to irreversible liver cirrhosis.[7–10]

The diagnosis of the disease is based on the presence of hypermanganesemia, dystonia, polycythemia and cirrhosis. The characteristic findings of HMDPC on magnetic resonance imaging (MRI) is the presence of hyperintense signals in the basal ganglia on T1-weighted and hypointense signals on T2-weighted images.[6] Treatment of HMDPC requires Mn chelation, which is achieved through different chelators, however the optimal treatment has not been identified in literature. Therefore, we describe a five-year follow-up case of a child with autosomal recessive HMDPC treated with chelation therapy using ethylenediaminetetraacetic acid (EDTA).

CASE PRESENTATION

This is a five-year follow-up case report of a girl who had initially presented to our tertiary care center at the age of two, with the complain of progressive lower limb weakness and increased difficulty in walking for six months. The child was born at term, with an immediate cry, to parents with consanguineous marriage. She had an uneventful past medical history and had achieved her developmental milestones timely up to two years of age. Her parents reported normal gait initially but observed frequent falls, which progressed with age and worried the parents. She was therefore brought to our outpatient clinic in 2018 for further management.

On the first clinical encounter, child had appeared to be restless and dystonic. Her anthropometric indices were as follows: Height-for-age between 10th and

25th centiles and weight-for-age at 3rd centile. Neurological examination revealed lower limb weakness with power 4 out of 5, normal deep tendon reflexes, no muscle wasting and presence of an ataxic gait. Child could walk with support but had difficulty in sitting without back support and would topple over to one side. The overall complexion of the patient was darker than that of her parents, and the darkening of the skin was more apparent on the hands and feet as compared to the trunk. The rest of the systemic examination was unremarkable.

Workup revealed polycythemia (Hb: 17.3 mg/dl), normal SGPT levels and raised Mn levels (14.3ug/dl). MRI scan reported abnormal T1 weighted hyper intense signals and T2 weighted hypo-intense signals noted in the basal ganglia (Figure 1A and 1B), midbrain and the dentate nuclei of the cerebellum in a bilateral symmetrical fashion. Ultrasound abdomen was done to assess the liver for Mn deposition, but it was reported normal with normal liver size, regular margins and no parenchymal abnormalities. A clinical diagnosis of HMDPC was made and the child was admitted electively for chelation therapy with EDTA. Genetic testing was carried out five years after the clinical diagnosis due to unavailability of funds to carry out the test. Once available, genetic testing was performed on the child and her siblings (a brother and a sister). Results revealed the mutations in the SLC30A10 gene in our case. Genetic test of the siblings revealed the brother (four years) to be heterozygous for SLC30A10 gene mutation and the sister (three years) to have normal SLC30A10 variant genes (Table 1).

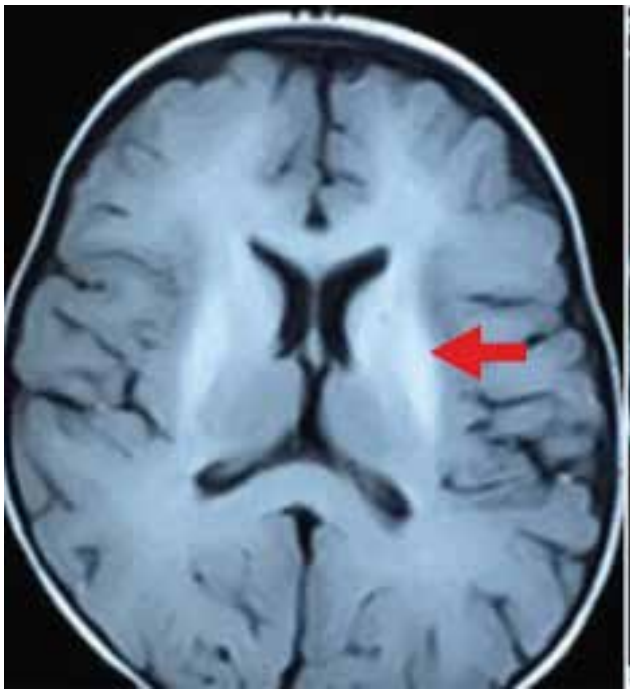


Figure 1A Basal ganglia on T1 weighted image showing intense signals



Figure 1B Basal ganglia on T2 weighted image showing hypointense signals

Table 1: Lab investigation trends over a course of five years and Genetic testing report.

	Baseline	After treatment								Normal Range
Test	Mar'18	Oct'18	Apr'19	Nov'19	Jan'20	Sept'20	Apr'21	Oct'21	Jun'22	
HB (gm/dl) *	17.3	16.9	11	12.5	12.1	12.3	13.1	13.2	13.1	11-14
HCT (%) *	51.6	51.2	32.8	37.6	35.2	38.1	38.7	39.5	38.7	34-40
PLT*(10E9/L)	373	420	440	339	300		359	393	236	150-400
MN (ug/dL) *	14.5	4.71	0.19		0.99	8.7	2.43		2.43	<1.07

*HB Hemoglobin, HCT Hematocrit, PLT Platelets, MN Manganese

Genetic testing

Gene Analysis		Zygosity	Variant classification
Case	SLC30A10	Homozygous	pathogenic
Sibling I	SLC30A10	Heterozygous	pathogenic
Sibling II	SLC30A10	Heterozygous	pathogenic

The patient was hence, continued on six-weekly EDTA therapy, along with iron supplements and anti-spastic (baclofen) medications. After the sixth cycle her Mn level came down from 14.5 to 0.19 ug/dl (normal range for this age < 1.07 ug/dl) and Hb from 17.3 to 11 gm/dl. The patient was closely followed throughout the treatment due to regular chelation therapy and signs for improvement and/or possible side effects of treatment were assessed at each visit. The patient was lost to follow-up for four months after two and a half years of chelation therapy initiation, during which her symptoms recurred and worsened. Her Mn levels at the time were reported to be 8.7ug/dl. EDTA therapy was restarted and thereon the parents remained compliant to therapy for their child. Marked improvement was seen in the patient at five-year follow-up; she was more playful and cheerful, had started speaking and interacting with the people around her. The parents reported that the patient was able to stand and now started walking without any support. She has joined a regular school and is doing well in her studies. Her laboratory test results had also drastically improved with treatment (Table 1). Her calcium levels varied between 8.3-9.6 mg/dl, and SGPT levels ranged between 33-44 IU/L throughout the treatment. The parents were educated about the disease and were advised to continue follow-up as the treatment was proven to be beneficial for the patient.

DISCUSSION

This is a case report of a child, who initially presented with difficulty in walking at two years of age and was noted to have elevated hemoglobin and manganese levels, along with significant MRI findings suggestive of HMDPC. Chelation therapy and iron supplementation was started based on clinical diagnosis, and marked improvement at five-year follow-up was observed. Genetic testing for the patient's siblings was also run for early identification of disease.

Gospe, S.M et al (2000) were the first to report a case of hypermanganesemia, dystonia, polycythemia and cirrhosis.[11] Tuschl, K (2012) et al, were the first to identify the genetic basis of the inborn error of Mn homeostasis involved in HMDPC, leading to Mn accumulation in the liver and basal ganglia, and linked the disease to mutations in the SLC30A10 gene.[9]

Literature reports dystonic movement disorder to be the most common neurologic manifestation of HMDPC. This was also reported by the first reporters of HMDPC, Gospe et al, as spastic paresis in their first description

of the disease.[11] Tavasoli, A (2019) et al, reporting dystonia and rigidity in children leading to walking difficulty and high stepping gait.[12] In our case, the presenting symptom was also difficulty in walking followed by regression of milestones.

The treatment used for our patient was six-weekly EDTA chelation therapy and supplemental iron, with a significant improvement in symptoms over five years. Literature has previously reported treatment with EDTA, DMSA and Penicillinamine, with greater treatment failures observed with Penicillinamine and overall improvements have been reported with DMSA and EDTA. Although, no concensus on the best treatment option for HMDPC management has yet been identified, the need for lifelong chelation therapy with iron supplementation has been ascertained.[3,9,13]

HMDPC is a treatable inborn error of manganese metabolism, however it is important that it is diagnosed at an early stage and the proper treatment regimens are given routinely. Children left untreated may die from cirrhosis or become severely disabled, and as HMDPC is a preventable disease, it is important to screen siblings for it, either with genetic testing or regular monitoring of hemoglobin and serum manganese levels.[5,12] As in our case, disruption in treatment due to loss to follow-up, led to worsening of symptoms, and resuming treatment led to betterment.

CONCLUSION

This case presented a patient with HMDPC who showed good response to EDTA therapy. HMDPC, apart from Wilson disease, is the only treatable inherited metal deposition syndrome. Therefore, proper identification in symptomatic children based on clinical assessment and their timely treatment can help prevent disability and even mortality.

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Durray Shahwar; Case management, manuscript writing
Jay Kumari; Case management, manuscript writing
Prem Chand; Concept, case management, manuscript revision
All the authors have approved the final version of the article and agree to be accountable for all aspects of the work.

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