CASE REPORT

Hypermanganesaemia with dystonia polycythemia and cirrhosis

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Abstract

Hypermanganesaemia with dystonia, polycythemia, and cirrhosis (HMDPC) is a rare genetic and autosomal recessive disorder that occurs due to mutation of the SLC3A10 gene, which encodes the manganese (Mn) transporter in the body; as a result, Mn accumulates in the brain, liver and muscles. This accumulation leads to symptoms of generalized dystonia, polycythemia, and hypermanganesaemia. In this report, we present the case of a 2½-year-old baby girl (patient) with complaints of lower limb weakness and increased difficulty in walking for six months. Her laboratory test results showed deranged values with increased Mn levels in the body. The patient was put on six cycles of EDTA therapy, which showed an improvement in her condition. This case report is presented to create awareness about a rare genetic disorder with an effective treatment in some cases. Thus, more work and research is required to understand and develop better treatment options for this disease.

Keywords: Hypermanganesemia, Dystonia and polycythemia.

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Introduction

Hypermanganesaemia with dystonia, polycythemia, and cirrhosis (HMDPC), also known as Familial Manganese induced toxicity,[1] is a rare genetic disorder. Its cases have been reported among Pakistani,[2,3] Canadian,[3] American,[3] Philippine,[3] Portuguese,[3] Indian,[3] Italian,[4] Irani (Baloochi),[5] Dutch,[4] and Arab[3,6,7] children. HMDPC has two modes of onset; early or childhood onset (ages 2 to 15) and adult onset.[5] This autosomal recessive disorder occurs due to a mutation in the SLC30A10 gene, which encodes a Manganese (Mn) transporter; as a result of this mutation, Mn accumulation takes place primarily in the brain (basal ganglia and cerebellum in particular), liver and muscles.[2,4] The accumulation of this element in the body leads to the early onset of generalized HMDPC.[4,6] The dystonia is specifically seen in arms and legs, often accompanied by a high stepping gait, also known as "the cock-walk gait".[1] Other neurologic symptoms include tremors, dysarthria, and bradykinesia.[1] However, the adult onset form of this disorder has a pattern of abnormalities such as Parkinsonism, in which the patient suffers from bradykinesia, tremors, muscle rigidity, and postural instability.[1,4]

Mn is an essential requirement for several metabolic pathways and cellular homeostasis. In normal amounts, Mn plays a substantial role in bodily functions, however in excess, it can be harmful to human health.[4] Normally Mn is absorbed from dietary intake in the intestines and then excreted in the biliary system by the liver.[4] Mn toxicity is seen in environmentally exposed professionals such as miners, smelters, and welders[10] and in patients with chronic liver disease, prolonged total parenteral nutrition, and drug addicts.[2] Excessive amount of Mn in the liver and brain leads to neurological disturbances and hepatic cirrhosis, characterized by behavioural problems.

The diagnosis of HMDPC is based on elevated blood manganese levels, MRI brain showing hyper intense signals in the basal ganglia on T1 weighted and hypo-intense signals on the T2 weighted images.[2] Mutation in (the) SLC30A10 gene is strongly associated with it and is currently used to diagnose HMDPC. The treatment modalities applied presently, include the use of chelating agents and penicillin therapy.[2] But these treatments are not definitive, and research showed that their effects vary amongst patients depending on their age of presentation and time lapsed from the onset of symptoms to the presentation.[2] Here we report a case of a 2½-year-old baby girl with HMDPC and typical brain findings on MRI.

Case Report

The case of a 2½-year-old baby girl who was born full-term with no immediate post-natal complications, is presented. Her parents were consanguinity related, having two healthy children, and there was no history of genetic or metabolic disorder in the family. This case first reported at the Aga Khan University Hospital (AKUH), Karachi, Pakistan, in May 2018 with complaints of progressive lower limb weakness along with increased difficulty in walking for the past six months. Her parents

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Table-1: Laboratory findings after treatment.

Test	26/05/18	17/07/18	01/10/18	27/11/18	28/01/19	29/01/19	08/04/19	17/07/19	16/09/19	20/11/19	28/01/20	21/07/20	Ranges
Hb (gm/dl)	-	-	16.9	13.8	12.2	-	11.0	12.9	12.7	12.5	-	-	11- 14
HCT(%)	-	-	51.2	39.9	36.4	-	32.8	38.7	37.4	37.6	-	-	34 - 40
RBC (million cell/mcl)	-	-	6.05	4.89	4.21	-	3.88	4.63	4.48	4.31	-	-	3.9-5.3
Plt 10E9/L	-	-	420	449	319	-	440	447	408	339	-	-	150-400
Mn (µg/dL)	14.52	4.71	-	-	-	8.4	0.19	-	-	-	0.99	8.7	< 1.07 µg/d)

Hb: Haemoglobin; HCT; haematocrit; RBC: red blood cell; Plt: platelets; Mn: manganese.

reported normal gait initially but observed frequent falls while walking, running, and playing. This was at first considered normal by the parents for the child of her age but the increase in the frequency of falls concerned the parents, due to which they paid a visit to a physician in Quetta where a non-specified treatment was given. However, when no improvement was observed in the child's condition, the parents brought her to AKUH for the best possible treatment.

On examination, the patient appeared to be restless and dystonic. She had a head circumference of 48 cm with a normal back examination. She had lower limb weakness with power 4/5 with deep tendon reflexes ++ without any muscle wasting and could only walk with support. She also had difficulty in sitting without a back support and would topple over to one side. The overall complexion of the patient was darker than the parents, and the darkening of the skin was more apparent on the hands and feet as compared to the trunk (Figures-1A-D). Abdominal and rest of examination was (were) normal.

Ultrasound abdomen showed normal liver size without parenchymal abnormalities with regular margins. MRI showed abnormal T1 weighted hyper intense signals and T2 weighted hypointense signals were noted in the basal ganglia, mid brain and the dentate nuclei of the cerebellum in a bilateral symmetrical manner (Figure-1E and 1F).

Based on the clinical presentation, history, examination, laboratory and radiological findings, the patient was diagnosed with HMDPC. The MRI brain findings were consistent with HMDPC; thus, (a) workup for Wilson's disease was not conducted, and liver function tests were also normal. The patient was hence, started on ethylenediaminetetraacetic acid (EDTA) every six weeks apart; after the sixth cycle her Mn level came down from 14.5 to 0.19 ug/dl (normal range for this age < 1.07 µg/d) and Hb from17.3 - 11 gm/dl. The limitation of this case study is that we were unable to conduct genetic testing of the patient due to its unavailability in our country. Moreover, the patient's family was not financially stable to get genetic testing from abroad. Therefore, the best available treatment was provided to the patient.

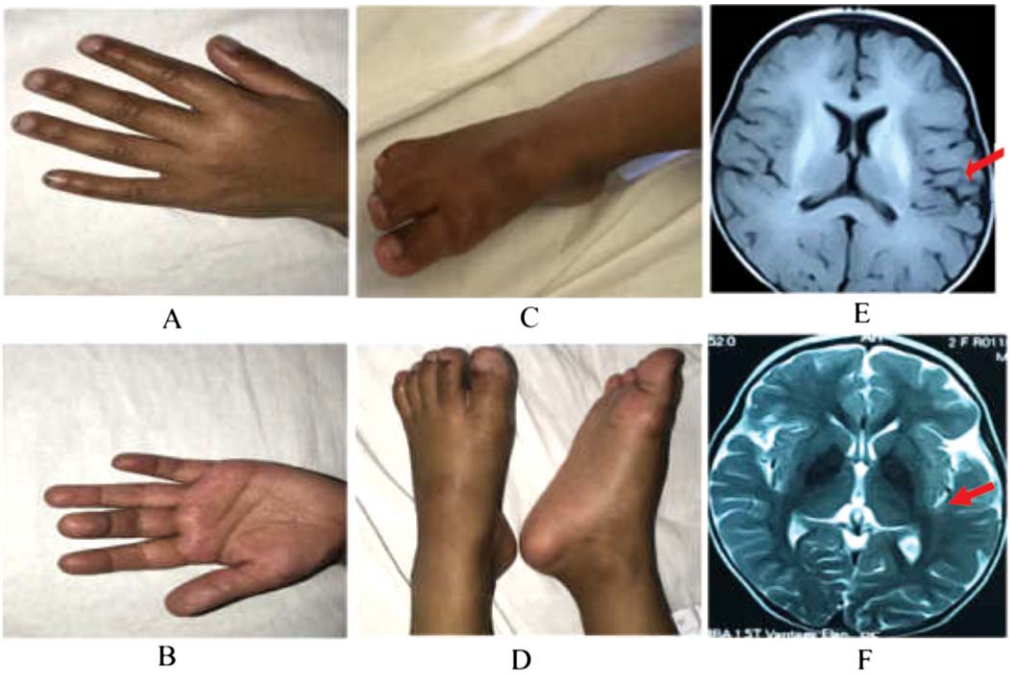

Figure-1: All the figures (1A-D) showing the complexion of the hands and feet which appears to be slightly darker than the trunk region Figure 1A shows the dorsal aspect of the hand, Figure 1B shows the palmer aspect of the hand, Figure 1C shows the dorsal aspect of the foot, and Figure 1D shows the dorsal and planter aspect of the foot. Figure 1E shows Basal ganglia on T1 weighted image showing hyperintense signals and Figure 1F: Basal ganglia on T2 weighted image showing hypointense signals.

The patient was closely followed-up throughout the treatment due to

ongoing chelation therapy and for signs of improvement and to observe any possible side effects of treatment. The Family was also counselled for genetic workup. However, as the treatment progressed, a marked improvement was seen in the patient; 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. 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 advised to complete the entire treatment as it was beneficial for (the) patient.

Discussion

A rare genetic form of disorder, namely hypermangnesaemia has recently been identified.[5] We presented a clinical case with MRI brain and treatment response of a patient with HMDPC due to SLC30A10 gene mutation, which is not a novel disorder and has been previously reported by Tuschl and Tavasoli et al.[3,5]

SLC30A10 gene is a significant Mn efflux transporter that reduces cellular Mn levels and protects from tissue toxicity. It is highly expressed in the liver and contributes to Mn homeostasis. Liver diseases develop with direct hyperbilirubinaemia, increased serum transaminases, and cirrhosis; however, a study has reported SLC30A10 gene mutation with neurologic symptoms but without hepatic manifestation.[11] We did not find any liver mutation with respect to the disease. Two similar case studies reported on HMPDC with no involvement of the liver.[3,5] Of these two, Tavasoli et al.[5] reported a case of a 10-year-old boy with HMPC with pure neurologic manifestation and without liver involvement. The study also showed that early detection and chelation therapy improve the manifestation of the disease. Quadri et al.[11] reported a case of three siblings, of which two of them had no hepatic dysfunction, while the other child died due to liver manifestations.

Moreover, according to many studies' dystonia is the most common neurological manifestation in hypermanganesaemia. Tavasoli and Tuschl et al.[3,5] found that individuals affected in childhood suffer from dystonia, causing motor impairment and walking difficulties. Our case also reports dystonia in a young girl with hypermanganesaemia.

Lifelong chelation therapy has shown improved results in children with HMPC.[3,5,12] Intravenous disodium calcium edetate increases Mn excretion through urine, hence its constant use leads to decreased Mn levels, improving MRI of brain, liver damage and neurological activity. However, patients with acquired hypermangnasemia may show variable results.[5] But untreated patients may die of cirrhosis or may be bound to wheelchair for lifetime. Early detection and treatment can decrease the severity of the disease and may save a child from death. However, the variability of treatment results amongst patients of HMDPC shows that there is a need for better understanding of the precise mechanism of this disorder, and it requires further good quality studies assessing the definitive diagnosis and treatment options.

Conclusion

In conclusion, we have highlighted a case of a baby girl with HMDPC caused by a SLC30A10 gene mutation leading to neurological manifestations. This case report is being presented as an example for better diagnosis and treatment of HMDPC. However, we still need to understand the precise mechanism of this disorder and develop better means of definitive diagnosis and treatment options.

Consent: Consent for publication was provided by the father of the patient.

Disclaimer: None.

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References

1. Hypermanganesemia with dystonia. [Online] [Cited 2020 October 01]. Available from: URL: https://ghr.nlm.nih.gov/condition/hypermanganesemia-with-dystonia#sourcesforpage.
2. Mukhtiar K, Ibrahim S, Tuschl K, Mills P. Hypermanganesemia with Dystonia, Polycythemia and Cirrhosis (HMDPC) due to mutation in the SLC30A10 gene. Brain Dev. 2016; 38:862-5.
3. Tuschl K, Clayton PT, Gospe Jr SM, Gulab S, Ibrahim S, Singhi P, et al. Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a manganese transporter in man. Am J Hum Genet. 2012; 90:457-66.
4. Quadri M, Federico A, Zhao T, Breedveld GJ, Battisti C, Delnooz C, et al. Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. Am J Hum Genet. 2012; 90:467-77.
5. Tavasoli A, Rafsanjani KA, Hemmati S, Mojbafan M, Zarei E, Hosseini S. A case of dystonia with polycythemia and hypermanganesemia caused by SLC30A10 mutation: a treatable inborn error of manganese metabolism. BMC Pediatr. 2019;

19:229.
6. Tuschl K, Mills PB, Parsons H, Malone M, Fowler D, Bitner-Glindzicz M, et al. Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia--a new metabolic disorder. J Inherit Metab Dis. 2008; 31:151-63.
7. Stamelou M, Tuschl K, Chong W, Burroughs AK, Mills PB, Bhatia KP, et al. Dystonia with brain manganese accumulation resulting from SLC30A10 mutations: a new treatable disorder. Move Disord. 2012; 27:1317-22.
8. Tuschl K, Clayton PT, Gospe SM Jr, Mills PB. Dystonia/Parkinsonism, Hypermanganesemia, Polycythemia, and Chronic Liver Disease. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, eds. Seattle WA: Gene Reviews, 2012;
9. Roth JA. Homeostatic and toxic mechanisms regulating manganese uptake, retention, and elimination. Biol Res. 2006; 39:45-57.
10. Huang CC, Chu NS, Lu CS, Wang JD, Tsai JL, Tzeng JL, et al. Chronic manganese intoxication. Arch Neurol. 1989; 46:1104-6.
11. Quadri M, Federico A, Zhao T, Breedveld GJ, Battisti C, Delnooz C, et al. Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. Am J Hum Genet. 2012; 90:467-77.
12. Zulu JM, Goicolea I, Kinsman J, Sandøy IF, Blystad A, Mulubwa C, et al. Community based interventions for strengthening adolescent sexual reproductive health and rights: how can they be integrated and sustained? A realist evaluation protocol from Zambia. Reprod Health. 2018; 15:145.