Case Report

Atypical presentation of *SLC30A10* gene mutation with hypermanganesemia, seizures and polycythemia

Spoorthi Jagadish *, Lillian Howard, Sreenath Thati Ganganna

Department of Pediatric Neurology, University of Iowa, United States

A B S T R A C T

Manganese is an essential element that is ubiquitously present in our diet and water supply. It is a cofactor for several critical physiological processes. Elevated blood levels of Manganese secondary to *SLC30A10* gene mutation presents distinctly with dystonia, polycythemia, chronic liver disease and a characteristic high T1 signal in basal ganglia on brain MRI. The primary treatment for this condition is chelation along with iron therapy. We report a previously healthy boy with compound heterozygous *SLC30A10* gene mutations who had a unique clinical presentation with prominent seizures, polycythemia, and characteristic T1 hyperintensity in basal ganglia. Seizures have not been previously reported to be associated with this specific mutation.

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1. Introduction

Manganese (Mn) is an essential heavy metal required for normal growth and metabolism. However, excess Mn levels in blood can result in toxic accumulation in liver and brain, particularly in basal ganglia, thereby causing a distinct constellation of clinical features. Hepatic impairment can range from transaminitis, unconjugated hyperbilirubinemia to complicated cirrhosis [1]. Injury to basal ganglia from Mn accumulation results in classic extrapyramidal syndrome with rigidity, dystonia and 'cock walk' gait [2]. Hypermanganesemia usually occurs in the context of occupational exposure to Mn in welders and miners or in patients receiving prolonged total parenteral nutrition [3,4]. Less commonly, hypermanganesemia can occur in pateints with an inherited disorder of Mn metabolism due to SLC30A10 gene mutation [1,5]. Our patient with hypermanganesemia secondary to compound heterozygous *SLC30A10* mutations had a distinctly novel presentation with only polycythemia and focal seizures, without extrapyramidal syn-

drome or hepatic impairment on presentation. His focal seizures resolved upon initiation of chelation therapy.

2. Clinical presentation, diagnosis and treatment

An 8-year-old boy was incidentally noted to have elevated hemoglobin and hematocrit of 16.9 g/dl and 51% respectively without any clinical symptoms or complications at the age of 4 years by his PCP during a regular annual health check, which however, did not initiate further diagnostic evaluation. Subsequently, he started having daily seizures at the age of 5 years. The seizure semiology was most likely consistent with focal to bilateral tonic-clonic seizures. The seizures were characterized by numbness in bilateral hands at onset followed by staring, loss of awareness, and stiffening of bilateral fingers and at times accompanied by tonic flexion or rhythmic jerking of bilateral upper extremities and urinary incontinence. The seizures were unprovoked and would last for about 45 seconds to 2 minutes in duration followed by a post-ictal period of mental confusion and drowsiness lasting for several minutes before returning to his normal baseline mental status. He did not have any identifiable risk factors for epilepsy. His past medical history was significant for obesity, asthma, intermittent abdominal pain and recurrent otitis media needing tympanostomy tubes. He was born preterm at 36 weeks gestation with a birth weight of 7 pounds 5 ounces without any perinatal complications. His early developmental milestones were normal. There was no concern

for cognitive delay prior to onset of seizures. At the time of our initial evaluation he was in the second grade with IEP (Individualized education plan) for learning difficulty. There was no family history of known liver disease or epilepsy. His sister had febrile seizures and mother and sister have a diagnosis of ADHD (attention deficit hyperactivity disorder). His neurological examination including fundoscopy as well as other system examination was unremarkable. Although there was a clear history of academic difficulty, a formal assessment for learning disability was pending at the time of presentation.

His initial EEG at 5 years old was abnormal with right occipital sharp waves. He underwent a brain MRI (magnetic resonance imaging) with and without contrast which demonstrated T1 hyperintense signal in basal ganglia (particularly globus pallidus), cerebral peduncles, midbrain, dorsal pons, superior cerebellar peduncles, dentate nuclei and cerebellar white matter (Fig. 1). Classic T1 MRI abnormalities prompted a diagnosis of hypermanganesemia. His CBC at the time of referral to Hematology, showed an elevated hemoglobin of 17.1 g/dl (normal 11.9–15), elevated hematocrit 54% (normal 35–44) with elevated RBC count 7.23 m/mm^3 (normal 4.3–5.5), low MCV 74 fL (77–90), low MCH 24 pg (25–33), MCHC 32 g/dL (32–36), increased RDW 16.7 % (9–14.5), WBC count 9.3*10^3, platelets 356*10^3. Other labs included normal ferritin 109.2 ng/ml (30–400), iron 115 mcg/dl (53–119), transferrin 364 mg/dl (200–360), and iron saturation 22% (22–39) while total iron binding capacity (TIBC) was high at 521 mcg/dl (250–425). Whole blood manganese level was markedly elevated at 118 mcg/L (normal 4.2–16.5), with normal levels of copper 135 mcg/dl (75–153), Zinc 90 mcg/dl (60–120) and selenium 127 mcg/L (23–190). Liver function tests showed a mildly elevated ALT 52 U/L (5–20) and a normal AST 28 U/L (10–45). Abdominal ultrasound revealed a normal liver.

The characteristic T1 hyperintensities in combination with elevated blood Mn levels confirmed the diagnosis of hypermanganesemia. The clinical presentation and lab investigations did not favor the diagnoses that can cause basal ganglia T1 hyperintensities such as, Wilson's disease, carbon monoxide poisoning, nonketotic hyperglycemia, Japanese encephalitis or hemorrhagic lesions. In
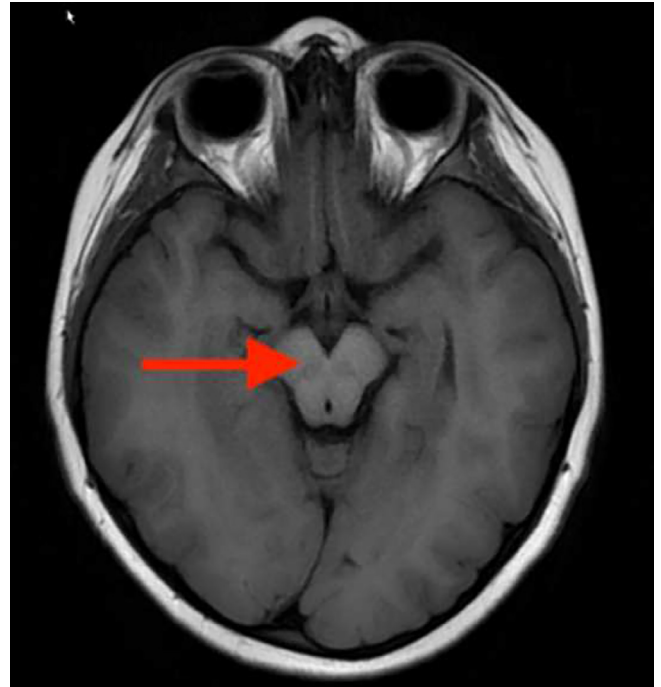

Fig. 1 (*continued*)

the absence of obvious etiology for elevated manganese in the patient like TPN (total parenteral nutrition) or environmental exposure, single gene analysis of the *SLC30A10* gene was completed. Single gene sequencing revealed two variants in *SLC30A10* gene assumed to be in trans; NM_018713.2:c.496del (p.Ala166Leufs*26) and c.275 T>G (p.Leu92Arg). Both variants were novel at the time of testing. However, given the high degree of clinical correlation, this result was consistent with a diagnosis of hereditary syndrome of hypermanganesemia with polycythemia. Both parents and 9-
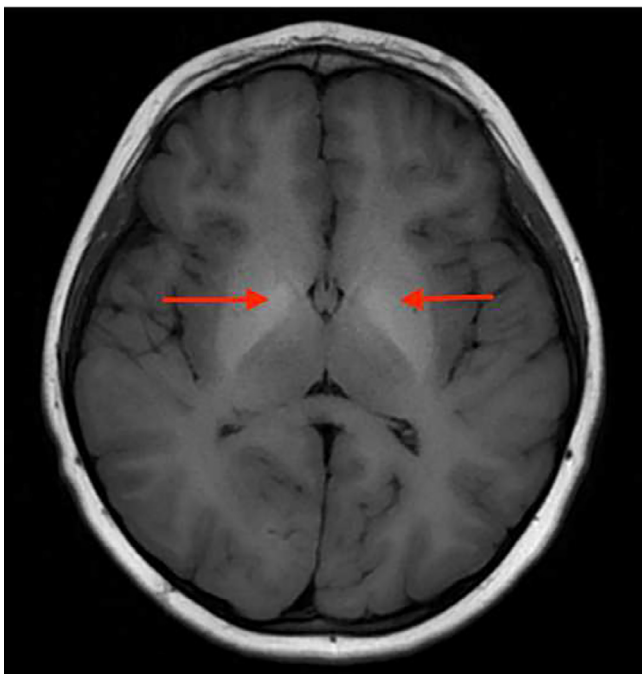

Fig. 1. MRI brain prior to starting chelation showing high T1 signal sequentially in basal ganglia, especially globus pallidus (A) and midbrain (B).
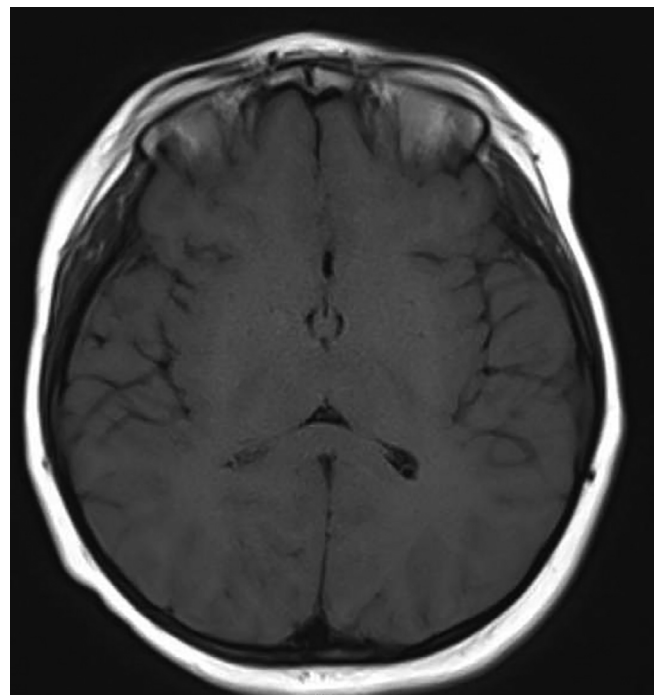
Fig. 2. MRI brain obtained 9 months after starting chelation showing resolution of T1 signal sequentially in globus pallidus (A) and midbrain (B).
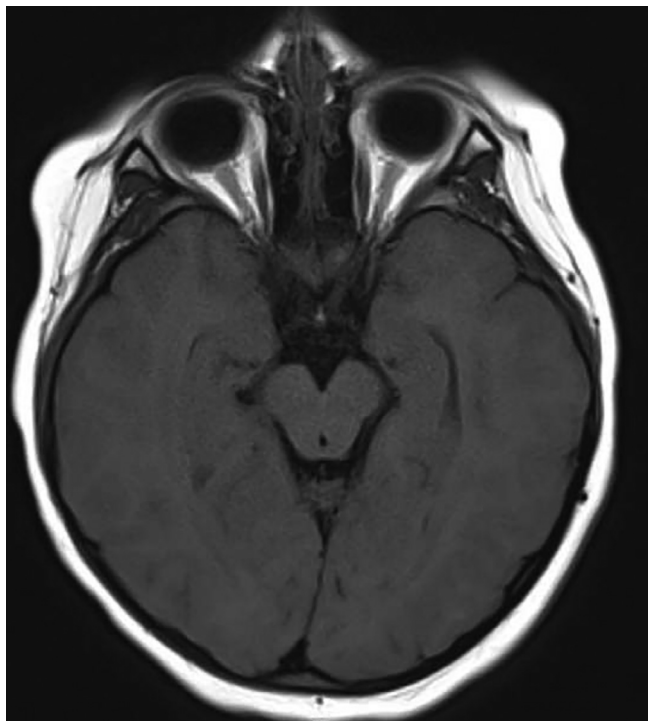
Fig. 2 (*continued*)

year-old sister were asymptomatic and tested negative for both *SLC30A10* variants supporting pathogenicity of the novel variants.

The patient was initially treated with levetiracetam for his seizures, which was discontinued due to behavioral and mood side effects. He was then started on valproic acid and eventually lamotrigine both of which caused weight gain, subsequently requiring a switch to topiramate therapy. The seizure frequency reduced to every other day with initiation of antiseizure medication. He was started on ferrous sulfate supplementation and IV disodium calcium edetate chelation therapy for 5 days every 4 weeks with strict monitoring of other essential heavy metals like zinc, copper and selenium. He did not have any seizures after chelation was started. A repeat brain MRI obtained 9 months after starting chelation, showed nearly complete resolution of the hyperintense signal in the globus pallidus and other aforementioned regions related to manganese deposition (Fig. 2). When he was last seen in Neurology Clinic, he had been seizure-free for 2 years on low dose topiramate. A follow-up EEG was obtained which was normal in awake and asleep states and therefore, topiramate was gradually weaned. He has been seizure-free so far. He is currently in fourth grade and is doing well academically, no longer needing IEP. His most recent whole blood Mn level was mildly elevated at 39.5 mcg/L (normal 4.2–16.5). He was started on oral succimer chelation, but this was stopped due to renal calculi.

3. Discussion

Manganese is an important micronutrient necessary for several metabolic pathways and cellular homeostasis [6]. Manganese becomes toxic when present in excessive amounts resulting in a distinct clinical syndrome with polycythemia, hepatic dysfunction, cirrhosis, motor neurodegeneration with extrapyramidal features and neuropsychiatric symptoms [7,8]. Accumulation of excessive amounts of Mn resulting in toxic manifestations has been mostly reported in literature in patients on chronic TPN or liver cirrhosis where the regulatory mechanisms are impaired [9,10]. Addition-

ally, genetic mutations affecting Mn transport protein have been identified in patients with toxic levels of Mn, including mutations in genes *SLC30A10* [1,5] and *SLC39A14* [11]. Neither of these genetic mutations have been reported to have seizures.

The typical clinical syndrome associated with biallelic pathogenic mutations in *SLC30A10* gene consists of hypermanganesemia with dystonia, polycythemia and chronic liver disease, also referred to as hypermanganesemia with dystonia 1 (HMNDYT1) [1,5]. The etiology of hypermanganesemia in our patient was confirmed to be due to an underlying pathogenic mutation in *SLC30A10* gene. To our knowledge, seizures have never been reported as a neurological manifestation of this rare metabolic disorder of manganese metabolism associated with *SLC30A10* mutation. In sharp contrast to the typical phenotypic presentation of this genetic mutation, our patient had seizures as the sole neurological manifestation and also, he did not have any extrapyramidal or pyramidal abnormalities such as dystonia, rigidity, spasticity or gait disturbance during his clinical course. This novel neurological phenotype due to *SLC30A10* mutations has not been reported before. Seizures dramatically resolved after starting chelation therapy which also suggests that his seizures were most likely secondary to hypermanganesemia and not due to any other etiology.

There have been few reports of seizures secondary to hypermanganesemia due to accidental manganese poisoning from welding fumes [12] and TPN use in children [13,14]. The exact pathogenesis of seizures in hypermanganesemia is still unclear. Hsieh reported hypermanganesemia in a 10 year old girl on TPN who presented with seizures and altered mental status in the setting of septic shock. It was unclear if the seizures were primarily due to hypermanganesemia or secondary to septic shock [14].

Although basal ganglia is not directly involved in the generation of seizures, animal studies have demonstrated the key role of basal ganglia in the epileptic networks involved in seizure propagation [15]. Due to the interaction of basal ganglia with prefrontal cortex and inferotemporal lobe, damage to the basal ganglia has been known to be associated with cognitive and learning impairment and impaired visual working memory [16]. This correlates with the learning and cognitive disability in our patient which improved with treatment of hypermanganesemia.

As seizures have not been typically associated with this condition and in order to exclude other genetic etiologies of epilepsy, we obtained a comprehensive epilepsy gene panel of 186 genes related to syndromic and non-syndromic genetic epilepsies. Three variants of unknown significance were identified: SCN3A c.5589G>C (p.Glu1863Asp); ALDH5A1 c.794A>C (p.Lys265Thr), and JMJD1C c.3386C>T (p.Ala1129Val). ALDH5A1 is associated with a recessive condition for which a single variant is not sufficient to cause disease. JMJD1C currently has no well-established disease associations. Neither were considered likely to be the cause of this patient's seizure history. However, further investigation was warranted to determine the pathogenicity of the SCN3A variant as this gene is associated with autosomal dominant childhood onset epilepsy. Parental testing was completed and revealed the SCN3A variant was maternally inherited. There is no maternal family history of childhood onset epilepsy, supporting a benign effect of this variant. Overall, this targeted gene panel ruled out the most common genetic causes of epilepsy for this patient.

The first reported hereditary disorder of Mn metabolism with associated neurotoxicity was found to be due to *SLC30A10* mutation [1,5]. This is a rare disorder and the exact prevalence is unknown although there are few case reports and case series [1,5,8,17]. The function of the *SLC30A10* gene is to encode an important Mn transporter protein which responsible for Manganese efflux from the Cytosol. In humans, it has been found that *SLC30A10* is expressed in liver, central nervous system, and other organs in fetal as well as adult life [18]. In the human brain, the

areas that maximally express *SLC30A10* are the globus pallidus, subthalamic nucleus, and deep cerebellar nuclei and to a lesser extent, in the putamen, diencephalic and cortical areas, with the cerebellum and hippocampus having the lowest expression [5]. The distinct MRI brain abnormality in hypermanganesmia consists of hyperintensities on T1-weighted images, of the globus pallidus and striatum, and the white matter of the cerebrum, cerebellum, midbrain, dorsal pons and medulla, with typical sparing of ventral pons [1,5]. These classic neuroimaging abnormalities were seen in our patient as well.

Clinically, most patients present with childhood-onset dystonia, with a peculiar high-stepping gait, described as "cock walk gait" by Von Jaksch in 1901 due to lower limb dystonia. White matter involvement also leads to spasticity and pyramidal tract signs [19]. There have also been reports of a late onset form of this disorder, that presents with adult onset parkinsonism unresponsive to levodopa treatment [5]. Most of the patients have normal cognition. Excess Mn in liver leads to hepatic dysfunction ranging from mild steatosis to fatal cirrhosis [19]. Polycythemia is found in all patients which can be present prior to clinical symptoms like in our patient. Mn and iron mutually compete for binding at several transporters, and hence, individuals with *SLC30A10* mutations have low iron stores, increased total iron-binding capacity and a low ferritin [1,5]. Our patient was noted to have a high total iron binding capacity.

Treatment of Mn toxicity consists of eliminating the source of Mn exposure if it is due to total parental nutrition or environmental exposure. Early initiation of chelation with disodium calcium edetate has been effectively used to enhance urinary Mn excretion in patients with *SLC30A10* gene mutation leading to hypermanganesmia. Chelation reduces Mn accumulation, promotes resolution of neurological symptoms, hepatic dysfunction, polycythemia, normalization of iron parameters and stabilization of blood Mn levels. However, it is not unusual for Mn levels to remain mildly to moderately elevated even after chelation as was the case with our patient [8]. Additionally, in our patient, contributory factor could be inconsistent IV chelation therapy due to financial and social issues and discontinuation of oral succimer chelation therapy due to occurrence of renal calculi. Disodium calcium edetate is typically administered intravenously as a 5 day course every 4 weeks and needs to be continued lifelong [20]. Close monitoring of calcium and other trace metal levels such as zinc, copper and selenium is required to avoid adverse effects [21]. Chelation with oral dimercaptosuccinic acid has been found to helpful in a set of siblings [1]. Another important treatment in addition to chelation therapy, is oral iron supplementation as iron competes with Manganese for common transport proteins and decreases Mn absorption [22]. Treatment leads to reduction of the Mn load as evidenced by reduction of T1 hyperintensity on brain MRI [19].

4. Conclusion

The unique neurological presentation with isolated seizures in the absence of associated pyramidal or extra- pyramidal signs, adds to our understanding of the phenotypic spectrum evolving in this rare genetic disorder involving Mn metabolism due to a *SLC30A10* gene mutation. Identifying more patients with this inherited disorder will probably shed light on varied phenotypic presentations.

Ethical statement

- All authors mentioned in the manuscript have read and approved the manuscript prior to submission.

- Our research has not been submitted or published elsewhere.
- No patient identifiers have been used in the case report

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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