# Inherited Manganese Disorders and the Brain: What Neurologists Need to Know

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## Abstract

Although acquired manganese neurotoxicity has been widely reported since its first description in 1837 and is popularly referred to as "manganism," inherited disorders of manganese homeostasis have received the first genetic signature as recently as 2012. These disorders, predominantly described in children and adolescents, involve mutations in three manganese transporter genes, i.e., *SLC30A10* and *SLC39A14* which lead to manganese overload, and *SLC39A8*, which leads to manganese deficiency. Both disorders of inherited hypermanganesemia typically exhibit dystonia and parkinsonism with relatively preserved cognition and are differentiated by the occurrence of polycythemia and liver involvement in the *SLC30A10*-associated condition. Mutations in *SLC39A8* lead to a congenital disorder of glycosylation which presents with developmental delay, failure to thrive, intellectual impairment, and seizures due to manganese deficiency. Chelation with iron supplementation is the treatment of choice in inherited hypermanganesemia. In this review, we highlight the pathognomonic clinical, laboratory, imaging features and treatment modalities for these rare disorders.

**Keywords:** Inherited hypermanganesemia, manganese transport, SLC30A10, SLC39A14, SLC39A8

## Introduction

Manganese (Mn) transport disorders or transportopathies are inherited disorders leading to excess or deficiency of Mn and have been reported to occur as a result of mutations in *SLC30A10*, *SLC39A14*, and *SLC39A8* genes, This review highlights pathogenesis, clinical presentation, and treatment of Mn transporter defects [Table 1]. We also intend to sensitize the treating clinicians and neurologists so as when to suspect and investigate for these disorders, including genetic testing, in order to initiate appropriate therapy before there is a profound progression of the disease process.

### Manganese in health and disease

Mn is a naturally occurring essential trace metal which serves as a cofactor for multiple enzymes including transferases, lyases, hydrolases, ligases, isomerases, and oxidoreductases, thereby catalyzing numerous physiological processes, including regulation of immune function, blood sugar and cellular energy, reproduction, digestion, bone growth, blood coagulation and homeostasis, defense against reactive oxygen species, and neuronal and glial cell function such as neurotransmitter synthesis.[1-5] Foods rich in Mn include legumes, seafood, leafy green vegetables, rice, nuts, whole grain, seeds, chocolate, tea, spices, soybean, and some fruits such as pineapple and acai.[4] Most dietary supplements and multivitamin preparations contain Mn. Occupational exposure to Mn occurs in activities involving mining, welding, battery manufacture, and with the use of fungicides containing the metal in its composition, such as maneb and mancozeb.[3,6-10] The levels of Mn in the environment may also increase secondary to the use of the gasoline additive methylcyclopentadienyl manganese tricarbonyl (MMT).[11] Drug abuse of the injectable drug methcathinone may lead to Mn toxicity due to the use of potassium permanganate in the synthesis process.[12] Mn is also present in significant concentrations in both neonatal and infant formulas and total parenteral nutrition (TPN), which may cause Mn accumulation when given for prolonged periods of time.[13-15] Patients with liver failure or hepatic encephalopathy can develop Mn toxicity as it is excreted in the bile.[14] Iron (Fe) deficiency, one of the most common nutritional deficiencies, can also hypothetically result in Mn toxicity as Fe and Mn compete for similar transport protein and decreased Fe levels might lead to an accumulation of Mn to toxic levels over time.[16-18]

### Search methodology

We have conducted a narrative review using PubMed database which was searched and all published data available on

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**Table 1: Prominent characteristics of inherited defects of manganese transport**

| Inherited disorder | Hypermanganesemia with Dystonia 1 (HMNDYT 1) | Hypermanganesemia with Dystonia 2 (HMNDYT 2) | Congenital Disorder of Glycosylation 2N (CDG 2N) |
|---|---|---|---|
| Affected gene | *SLC30A10* | *SLC39A14* | *SLC39A8* |
| Inheritance | Autosomal recessive | Autosomal recessive | Autosomal recessive |
| Blood Mn level | Increased | Increased | Decreased |
| Manifestations of neurological involvement | Dystonia, "cock walk" gait, spasticity, pyramidal signs. | Early onset, progressive dystonia, spasticity, bulbar dysfunction. | Pronounced developmental delay, seizures, dystonia |
| | Cognition relatively spared | Cognition relatively spared | |
| Manifestations of systemic involvement | Liver disease | Absent | Short stature |
| | Polycythemia | | Hearing impairment |
| | Depletion of iron stores | | |
| Brain MRI changes | T1-hyperintensity of the globus pallidus and white matter, pathognomonic sparing of the ventral pons | T1-hyperintensity of the globus pallidus and white matter, pathognomonic sparing of the ventral pons | Variable and nonspecific T2 hyperintensity of the basal ganglia |
| | T2-hypointensity of the globus pallidus | T2-hypointensity of the globus pallidus | Cerebral/cerebellar atrophy |
| Management | Chelation therapy with EDTA-CaNa2 | Chelation therapy with EDTA-CaNa2 | Mn supplementation |
| | Iron supplementation | "Mn free" days | Galactose |

inherited disorders of Manganese transport up to June 2020 was reviewed, using the search terms "manganese transport," "inherited hypermanganesemia," "manganese homeostasis," "manganese transportopathies," and "hereditary manganese diseases." All types of studies including reviews, case series, and case reports were included in the review. The abstracts were screened for relevance to the review topic.

## Determinants of Mn homeostasis

The homeostasis of Mn levels in our body is crucially regulated through intestinal absorption and hepatobiliary secretion of the metal into the gastrointestinal tract.[19] The nervous system is the primary target for excessive Mn. Normal physiological Mn concentration of Mn in the human brain is estimated to be 5.32–14.03 ng Mn/mg protein and 15.96–42.09 ng Mn/mg protein is the estimated pathophysiological threshold.[20,21] Excessive levels of Mn are toxic causing oxidative stress, impaired mitochondrial function, impaired autophagy, and neuronal apoptosis.[22]

Understanding of *in vivo* Mn homeostasis has dramatically expanded over the past decade with the recognition of inherited disorders of Mn transport. The uptake of $Mn^{2+}$ into the cells is facilitated by a number of membrane transporters such as the divalent metal transporter 1 (DMT1/SLC11A2), ZRT/IRT-like proteins ZIP8 (SLC39A8) and ZIP14 (SLC39A14), the dopamine transporter (DAT), and calcium channels' choline and citrate transporters. $Mn^{2+}$ is oxidized in the blood by ceruloplasmin to $Mn^{3+}$ which binds to transferrin (Tf) and is subsequently internalized through transferrin/transferrin receptor (Tf/TfR)-mediated endocytosis. Within the endosome, $Mn^{3+}$ is again reduced to $Mn^{2+}$ and uptake into the cytoplasm occurs via the DMT1 transporter. Manganese efflux and export from the cytosol is mediated by the membrane-localized transporters ferroportin (Fpn or SLC40A1) and the solute carrier family 30 member 10 (SLC30A10).[23,22,24] Within the cell cytosol, Mn gets shuttled via a number of organelle-specific transporters.[25-28] Iron (Fe) competes with Mn for binding and uptake at a number of transporters including the Tf/TfR complex, DMT1, and ferroportin.[29] Recently mutations in several transporter proteins with affinity to Mn (i.e., ATP13A2, ATP13A1, DMT-1 and Fpn) have been described and might have implications on Mn homeostasis on subcellular level; however, blood manganese levels tend to remain unaffected with no evidence of excessive Mn deposition.[30-32]

## Pathophysiology

Excess Mn shows predilection to accumulate in the basal ganglia, especially in the striatum (caudate nucleus, putamen and nucleus accumbens), globus pallidus (GP), and the substantia nigra (SN), an intricate network of neurotransmitters.[33,34] Exposure to excessive Mn can lead to disruption of harmony among various neurotransmitter functions, causing behavioral alterations including hypoactivity, cognitive impairments, and altered sensorimotor function. These complex physiological imbalances lead to a distinct neurodegenerative extrapyramidal syndrome known as manganism. The symptoms include initial cognitive and psychiatric disturbances followed by a movement disorder resembling Parkinson's disease with limb rigidity, dystonia, and a characteristic high-stepping gait.[23,22] Mn, being a paramagnetic metal, leads to characteristic deposition and MRI brain appearances with pronounced hyperintensity of the globus pallidus on T1-weighted and hypointensity on T2-weighted images[35] [Figure 1].

## Historical aspects

The first disorder of inherited Mn transport was reported in 2012 leading to Mn neurotoxicity characterized by dystonia, in association with polycythemia and cirrhosis of the liver, attributable to homozygous mutations in the *SLC30A10*

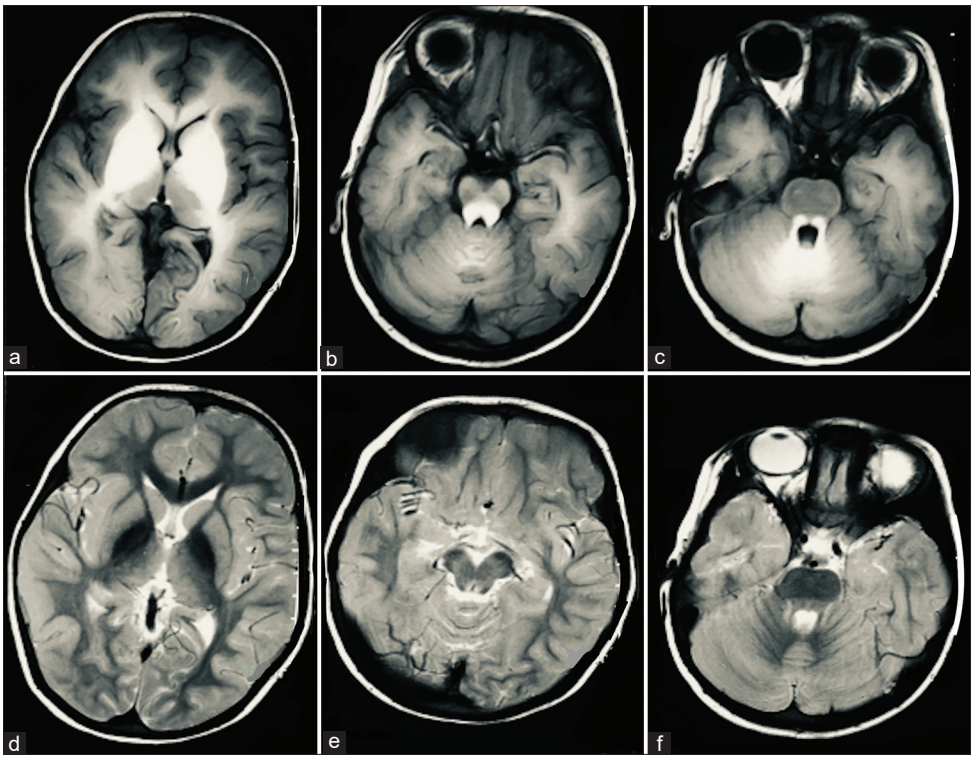


**Figure 1:** (a-c). T1-weighted MRI (axial section) brain showing hyperintensities in bilateral caudate, globus pallidus, and lentiform nucleus (a), dorsal pons with sparing of ventral pons (b), and cerebellar white matter (c). (d-f). T2-weighted MRI (axial section) showing hypointensities in bilateral basal ganglia (d), midbrain (e), and pons (f)

gene.[36,37] Prior to this in 2008, Tuschl *et al*. had described a clinical study of a patient who was later shown to harbor *SLC30A10* mutations. This was a 12-year-old female born to consanguineous parentage who developed gait abnormality and dystonia. MRI revealed Mn deposition in the basal ganglia, anterior pituitary, and cerebellar white matter. Liver biopsy revealed the presence of cirrhosis and elevated Mn levels. Preceding even these descriptions, Gospe *et al*. in 2000 described a similar case. In 2016, another inherited disorder leading to hypermanganesemia was described attributable to *SLC39A14* mutations.[38,39] This was shown to differ from the *SLC30A10* condition by the absence of polycythemia and liver involvement. In 2015, mutations in *SLC39A8* were reported to lead to Mn and Zinc (Zn) deficiency.[40,41]

## Hypermanganesemia with dystonia 1 (HMNDYT1)-*SCL30A10* deficiency OMIM#618320

The bi-allelic mutation in Mn transporter gene *SCL30A10* leads to the systemic accumulation and Mn neurotoxicity. SLC30A10 belongs to the SLC30 family of metal transporters, expressed at the cell membrane where they are responsible for efflux of Zn and Mn from the cytosol. This gene is specifically expressed in liver, gastrointestinal tract, and brain.[36] The clinical manifestations include a distinct syndrome of hypermanganesemia, polycythaemia, dystonia, chronic liver disease (ranging from asymptomatic steatosis to cirrhosis with liver insufficiency), and depletion of iron stores. Recently, Mn deposition in thyroid gland leading to reduced thyroxine production and hypothyroidism in mice model with knocked out *SCL30A10* gene has been reported, giving rise to speculation that thyroid gland might be one of the unexplored targets in the disease pathology.[42]

The neurological manifestations start appearing in early childhood with progressive difficulty in walking and in conducting fine hand movements. The child soon develops dystonia in limbs with a characteristic high-stepping gate, also described as "cock-walk gait." Involvement of white matter can cause spasticity and pyramidal tract signs. However, cognition tends to remain intact. A late-onset form presenting as L-DOPA unresponsive Parkinsonism in adults has also been reported.[36]

Investigations reveal dramatically raised blood Mn levels, usually ten times that of normal. Brain MRI shows deposition of Mn, evident in the basal ganglia, particularly the globus pallidus and striatum with pronounced hyperintensity of T1-weighted imaging with or without corresponding hypointensity on T2-weighted imaging.[36,37,43-47] The additional involvement of the white matter occurs in the cerebrum and cerebellum, midbrain, dorsal pons, and medulla with a pathognomonic sparing of the ventral pons. The histopathological examination in post-mortem sample reportedly shows severe neuronal loss and vacuolated myelinopathy in the globus pallidus.[46] The accumulation of Mn in the liver can lead to hepatotoxicity; however, the clinical presentation ranges from mild liver disease (steatosis) to severe disease (cirrhosis). The occurrence of polycythemia in majority of the patients has been attributed

to the induction of erythropoietin gene expression via stabilization of the hypoxia-inducible factor 1 alpha and a chemical "hypoxia."[47] Moreover, since Mn and Fe compete for binding at several transporters, it leads to depletion of iron stores in individuals with *SLC30A10* mutations who show an increased total iron-binding capacity and a low ferritin.[36,37] Hence, there is juxtaposition of polycythemia in the setting of iron deficiency.

Chelating treatment with CaNa2 ethylenediaminetetraacetic acid (EDTA) has been shown to effectively reduce Mn accumulation, ameliorate neurological symptoms, and prevent liver disease progression.[47] In the majority of the cases, Mn chelation leads to resolution of polycythemia and normalization of serum iron indices. However, blood Mn levels often do not normalize, but get stabilized.[45,48] EDTA-CaNa2 is given intravenously as a 5 to 8 day course every 4 weeks with close monitoring of calcium and other trace metal levels such as zinc (Zn), copper (Cu), and selenium (Se) in order to detect fluctuations in serum levels.[49] Effect of this chelator on Mn levels can be estimated by observing reduction in T1 hyperintensity on MRI brain. Although chelation therapy with EDTA-CaNa2 has shown promising results, the need of intravenous administration significantly adds to the burden of the disease. The role of orally administered chelators like 2, 3-dimercaptosuccinic acid and d-penicillamine in halting disease progression still remains to be determined.[44,50] Supplementation with iron alone has also been shown to improve clinical symptoms to some extent and reduce Mn levels.[51] However, the synergistic action of orally supplemented iron is hypothesized to occur in addition to chelation therapy. Iron can act as a competitive ligand at Mn transporters leading to reduction of Mn absorption, stabilization of Mn levels, and further clinical improvement. However, iron therapy warrants stringent monitoring of iron parameters with the aim to keep iron levels at the high end of normal without causing iron toxicity.[36,37,42,48] Treatment options used so far in inherited hypermanganesemia are outlined in Table 2.

## Hypermanganesemia with dystonia 2 (HMNDYT2)- *SCL39A14* deficiency

### *OMIM# 608736*

Mutations in *SCL39A14* gene leading to Mn-induced neurotoxicity were first reported in the year 2016 by Tuschl *et al*.[39] SLC39A14 is a part of the solute carrier 39 family present at the cell membrane that has been shown to facilitate influx of Mn, Fe, Zn, and Cadmium into the cytosol.[52-55] However, mutations leading to loss of function of this gene predominantly disturb Mn homeostasis, having little effect on other metals.[55,56] Clinical symptoms start becoming evident early in life and included loss of developmental milestones, progressive dystonia, and bulbar dysfunction. Around the age of 10 years, most patients develop severe, generalized dystonia that seems resistant to treatment, spasticity, limb contractures, and scoliosis and loss of locomotor abilities. Some patients might also show features of parkinsonism, such as hypomimia, tremor, and bradykinesia.[39] In contrast to *SCL30A10* deficiency, these patients have an earlier onset of symptoms and absence of polycythemia and liver involvement. Although Mn levels are raised about 3–25 times the normal limit, iron indices tend to remain in a normal range. The absence of Mn accumulation in liver in affected individuals can be explained by the fact that SLC39A14 is mainly required

**Table 2: Treatment options in inherited hypermanganesemia**

| Treatment options | Mechanism of action | Dose | Additional comments |
|---|---|---|---|
| NaCa2-EDTA | Chelating agent which enhances urinary Mn excretion | 1 gm/m$^2$/day in two divided doses<br>Intravenous application for 5 days every 4 weeks | -Necessitates admission and intravenous administration<br>-Good clinical, biochemical, and imaging response in *SLC30A10*.[37]<br>-Variable response reported in *SLC39A14* mutations.[39] |
| D-Penicillamine | Chelating agent | 10 mg/kg per day titrated gradually to 20 mg/kg/ day | -Very little data. Tried by Mukhtiar *et al* in 3 patients; one patient showed a relatively good clinical response, after initial chelation with EDTA.[50] |
| 2, 3-Dimercaptosuccininic acid (DMSA) | Chelating agent | 30 mg/kg/day for 3 consecutive days then rest for 11 days (cycle of 2 weeks) | -Oral regimen<br>-Designed and used by Zaki *et al*. in 9 patients[44] |
| Para-amino salicylic acid (PAS)[61] | Two proposed mechanisms:<br>i. Chelating agent<br>ii. Antiinflammatory property due to salicylate moiety which may play a role in neurodegenerative manganism. | 4-8 g sodium salt of PAS (dissolved in 500 mL of 10% glucose) per day as IV drip infusion for 4 days and rested for 3 days as one therapeutic course. Multiple courses given. | -Usually used as an antitubercular drug in resistant TB management<br>-Unlike NaCa2-EDTA which does not cross the blood-brain barrier, PAS can cross the BBB.<br>-Practical advantage as it is an oral formulation.<br>-Gastrointestinal tolerability may be an issue. |
| Iron supplementation | Mn and Fe have a similar chemical structure, hence compete for the same binding protein (transferrin) and membrane transporter (DMT1). | 2-3 mg/kg/day | -Regular iron profile monitoring to avoid iron toxicity is advisable |

for Mn uptake into the liver for subsequent biliary excretion, and that the build-up of Mn in the brain occurs secondary due to impaired hepatic uptake of the metal. Neuroimaging reveals MRI brain appearances identical to those seen in HMNDYT1. Post-mortem examination of one affected individual had shown marked neuronal loss in the globus pallidus, while relative preservation of neurons in the caudate, putamen, thalamus, and cerebral cortex. Patchy loss of myelin associated with coarse vacuoles in the cerebral and cerebellar white matter, and axonal loss were also observed.[39]

Treatment with EDTA-CaNa2 according to the protocol used in HMNDYT1 has been observed to be less effective with only marginal improvement in neurological symptoms.[39,57] This could be explained by the differences in disease severity. It seems likely in this condition, since the onset is very early and progression is rapid, the treatment becomes potentially ineffective as neurodegeneration has already reached an irreversible stage. In addition, the genotype might play a role in treatment response.[39] The two oral chelators, 2, 3-dimercaptosuccinic acid and d-penicillamine, also failed to show a clinical response in this disorder in one patient.[57] It has been reported that dietary Mn restriction in the form of 2 to 3 "Mn free days" per week might have a synergistic effect along with chelation therapy in improving the neurologic symptoms.[57] This entails the use of an Mn depleted formula in conjunction with a multivitamin free of Mn on the "Mn free" days. However, designing an Mn-free or low Mn diet is challenging due to the ubiquitous occurrence of the metal in food items.

### Congenital disorder of glycosylation 2N (CDG2N)-SLC39A8 deficiency (OMIM#616721)

Mutations in *SLC39A8*, an Mn uptake transporter, were first reported to cause an inherited disorder of Mn and Zn deficiency in the year 2015.[40,58] Patients with a bi-allelic mutation leading to loss of function show an abnormal glycosylation pattern consistent with a type II congenital disorder of glycosylation. This could be attributed to the impaired function of Mn-dependent enzymes such as the β-1,4-galactosyltransferase required for the galactosylation of glycoproteins.[40,58,59] Dysfunction of the mitochondrial MnSOD, another Mn dependent enzyme, can lead to Leigh-like mitochondrial disease characterized by elevated CSF lactate and abnormal respiratory chain enzymology.[59] Systemic Mn deficiency causes developmental delay, intellectual disability, failure to thrive, short stature, dwarfism, cranial asymmetry, seizures, hypotonia, dystonia, strabismus, and deafness. Characteristically, blood Mn levels are low. MRI brain imaging is nonspecific, showing cerebellar and/or cerebral atrophy in majority of the patients and hyperintensity of the basal ganglia on T2-weighted MR imaging in some patients.[59]

Oral Mn supplementation appears to be an effective treatment strategy. It has shown to cause improvement in the locomotor function and hearing along with normalization of Mn-dependent enzyme functions.[60] Initial galactose priming to normalize glycosylation pattern has not shown to be as effective as the resolution of Mn deficiency by supplementation. However, regular monitoring of blood Mn levels and brain MRI changes are imperative to avoid Mn toxicity in these patients.[60]

## Conclusions

In this review, we have summarized the key features of inherited Mn defects. The discovery and knowledge about the inherited disorders of Mn metabolism has improved our understanding about the intricate Mn homeostasis in the human body. Since these inherited Mn transporter defects form an important differential diagnosis in children with unexplained developmental delay or a movement disorder, determination of blood Mn level can serve as a simple and cost-effective screening test in the routine neurological work-up of such patients with supportive ancillary features. Diagnostic clues of Mn toxicity include the constellation of dystonia, Parkinsonism, polycythaemia, and liver disease, and abnormal brain MRI findings in the form of T1 hyperintensities in the basal ganglia in the case of hypermanganesemia. Early diagnosis is crucial to identify the disorder, initiate appropriate treatment, and avoid irreversible disease progression.

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### Conflicts of interest

There are no conflicts of interest.

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