



Hyperpermanganesemia with dystonia

Hyperpermanganesemia with dystonia is an inherited disorder in which excessive amounts of the element manganese accumulate in the body (hyperpermanganesemia). One place manganese builds up in particular is in a region of the brain responsible for the coordination of movement, causing neurological problems that make controlling movement difficult. Consequently, the condition is characterized by involuntary, sustained muscle contractions (dystonia) and other uncontrolled movements. Two types of hyperpermanganesemia with dystonia, called hyperpermanganesemia with dystonia, polycythemia, and cirrhosis (HMDPC) and hyperpermanganesemia with dystonia 2, have been identified. They are distinguished by their genetic causes and certain specific features.

In HMDPC (also known as hyperpermanganesemia with dystonia 1), manganese accumulates in the blood, brain, and liver. Signs and symptoms of the condition can begin in childhood (early-onset), typically between ages 2 and 15, or in adulthood (adult-onset). Most children with the early-onset form of HMDPC experience dystonia in the arms and legs, which often leads to a characteristic high-stepping walk described as a "cock-walk gait." Other neurological symptoms in affected children include involuntary trembling (tremor), unusually slow movement (bradykinesia), and slurred speech (dysarthria). The adult-onset form of HMDPC is characterized by a pattern of movement abnormalities known as parkinsonism, which includes bradykinesia, tremor, muscle rigidity, and an inability to hold the body upright and balanced (postural instability).

Individuals with HMDPC have an increased number of red blood cells (polycythemia) and low levels of iron stored in the body. Additional features of HMDPC can include an enlarged liver (hepatomegaly) due to manganese accumulation in the organ, scarring (fibrosis) in the liver, and irreversible liver disease (cirrhosis).

In hyperpermanganesemia with dystonia 2, manganese accumulates in the blood and brain. Signs and symptoms of this type of the disorder usually begin between ages 6 months and 3 years. Development of motor skills, such as sitting and walking, may be delayed, or if already learned, they may be lost. Dystonia can affect any part of the body and worsens over time. By late childhood, the sustained muscle contractions often result in joints that are permanently bent (contractures) and an inability to walk unassisted. Some affected individuals have an abnormal curvature of the spine (scoliosis). People with hyperpermanganesemia with dystonia 2 can have other neurological problems similar to those in HMDPC, such as tremor, bradykinesia, parkinsonism, and dysarthria. Unlike in HMDPC, individuals with hyperpermanganesemia with dystonia 2 do not develop polycythemia or liver problems.

Frequency

The prevalence of hypermanganesemia with dystonia is unknown. A small number of cases of each type have been described in the scientific literature.

Genetic Changes

The two types of hypermanganesemia with dystonia have different genetic causes. HMDPC is caused by mutations in the *SLC30A10* gene, and hypermanganesemia with dystonia 2 is caused by mutations in the *SLC39A14* gene. These genes provide instructions for making proteins that transport manganese across cell membranes. Manganese is important for many cellular functions, but large amounts are toxic, particularly to brain and liver cells. The *SLC30A10* and *SLC39A14* proteins are thought to work together to remove excess manganese from the body.

Both proteins are found in the membranes surrounding several types of cells, as well as in the membranes of structures within these cells. Studies suggest that when too much manganese builds up in the blood, the *SLC39A14* protein transports the element into liver cells. From there, the *SLC30A10* protein moves the manganese out of the liver cells into bile so that it can be removed from the body. Bile is a fluid produced in the liver that is important for digestion and the removal of waste material. The *SLC30A10* protein may also transport manganese out of brain cells to protect them from an accumulation of the element.

Mutations in the *SLC39A14* gene impair the transport of manganese into liver cells, allowing the element to build up in the blood. When levels are high in the blood, manganese accumulates in brain cells. Mutations in the *SLC30A10* gene impair the transport of manganese out of liver cells and possibly brain cells, leading to its accumulation in the blood and brain.

Manganese accumulation in the brain damages the cells, resulting in the movement problems characteristic of HMDPC and hypermanganesemia with dystonia 2. It is unclear why some of the movement problems differ between the two conditions despite both being caused by excess manganese. Damage from manganese buildup in the liver leads to liver abnormalities in people with HMDPC. Because *SLC39A14* gene mutations prevent manganese from entering liver cells, people with hypermanganesemia with dystonia 2 do not have liver damage. High levels of manganese help increase the production of red blood cells, so excess amounts of this element may underlie polycythemia in people with HMDPC. It is unknown why individuals with hypermanganesemia with dystonia 2 do not develop polycythemia.

Inheritance Pattern

Hypermanganesemia with dystonia is inherited in an autosomal recessive pattern, which means both copies of the *SLC30A10* or *SLC39A14* gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- familial manganese-induced neurotoxicity
- HMNDYT

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Hypermanganesemia with dystonia
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C2750442/>
- Genetic Testing Registry: Hypermanganesemia with dystonia 2
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4310765/>

Other Diagnosis and Management Resources

- GeneReview: Dystonia/Parkinsonism, Hypermanganesemia, Polycythemia, and Chronic Liver Disease
<https://www.ncbi.nlm.nih.gov/books/NBK100241>
- GeneReview: SLC39A14 Deficiency
<https://www.ncbi.nlm.nih.gov/books/NBK431123>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Health Topic: Cirrhosis
<https://medlineplus.gov/cirrhosis.html>
- Health Topic: Dystonia
<https://medlineplus.gov/dystonia.html>

- Health Topic: Movement Disorders
<https://medlineplus.gov/movementdisorders.html>
- Health Topic: Neurologic Diseases
<https://medlineplus.gov/neurologicdiseases.html>

Genetic and Rare Diseases Information Center

- Hypermanganesemia with dystonia polycythemia and cirrhosis
<https://rarediseases.info.nih.gov/diseases/10706/hypermanganesemia-with-dystonia-polycythemia-and-cirrhosis>

Additional NIH Resources

- National Digestive Diseases Information Clearinghouse: Cirrhosis
<https://www.niddk.nih.gov/health-information/liver-disease/cirrhosis>
- National Institute of Neurological Disorders and Stroke: Dystonias Fact Sheet
<https://www.ninds.nih.gov/Disorders/All-Disorders/Dystonias-Information-Page>

Educational Resources

- Agency for Toxic Substances and Disease Registry: Manganese
<https://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=101&tid=23>
- Disease InfoSearch: Hypermanganesemia with dystonia polycythemia and cirrhosis
<http://www.diseaseinfosearch.org/Hypermanganesemia+with+dystonia+polycythemia+and+cirrhosis/3580>
- Dystonia Medical Research Foundation: What is Dystonia?
<https://www.dystonia-foundation.org/what-is-dystonia>
- Kennedy Krieger Institute: Movement Disorders
<https://www.kennedykrieger.org/patient-care/diagnoses-disorders/movement-disorders>
- MalaCards: hypermanganesemia with dystonia 1
http://www.malacards.org/card/hypermanganesemia_with_dystonia_1
- MalaCards: hypermanganesemia with dystonia 2
http://www.malacards.org/card/hypermanganesemia_with_dystonia_2
- Merck Manual Consumer Version: Dystonia
<https://www.merckmanuals.com/home/brain-spinal-cord-and-nerve-disorders/movement-disorders/dystonia>
- Oregon State University Linus Pauling Institute: Manganese
<http://lpi.oregonstate.edu/mic/minerals/manganese>
- Orphanet: Cirrhosis-dystonia-polycythemia-hypermanganesemia syndrome
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=309854

Patient Support and Advocacy Resources

- American Liver Foundation
<https://liverfoundation.org/>
- The Dystonia Society (UK)
<https://www.dystonia.org.uk/>
- The Global Dystonia Registry
<https://www.globaldystoniaregistry.org/>

GeneReviews

- Dystonia/Parkinsonism, Hypermanganesemia, Polycythemia, and Chronic Liver Disease
<https://www.ncbi.nlm.nih.gov/books/NBK100241>
- SLC39A14 Deficiency
<https://www.ncbi.nlm.nih.gov/books/NBK431123>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28parkinsonism/dystonia,+polycythemia,+chronic+liver+disease%29+OR+%28hepatic+cirrhosis,+dystonia,+polycythemia+and+hypermanganesemia%29+OR+%28hypermanganesemia%29+AND+%28dystonia%29+OR+%28hypermanganesemia%29%29+AND+english%5Bla%5D+AND+%22last+3600+days%22%5Bdp%5D>

OMIM

- HYPERMANGANESEMIA WITH DYSTONIA 1
<http://omim.org/entry/613280>
- HYPERMANGANESEMIA WITH DYSTONIA 2
<http://omim.org/entry/617013>

MedGen

- Hypermanganesemia with dystonia
<https://www.ncbi.nlm.nih.gov/medgen/412958>
- Hypermanganesemia with dystonia 1
<https://www.ncbi.nlm.nih.gov/medgen/426978>
- Hypermanganesemia with dystonia 2
<https://www.ncbi.nlm.nih.gov/medgen/934732>

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