

## CASE REPORT

# Manganese-induced parkinsonism responsive to intranasal insulin: A case report

Mehri Salari<sup>1</sup>  | Masoud Etemadifar<sup>2</sup> | Leila Dargahi<sup>3</sup> | Neda Valian<sup>3</sup> | Malihe Rezaee<sup>1</sup>

<sup>1</sup>Functional Neurosurgery Research Center, Shohada Tajrish Comprehensive Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Neurosurgery, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

<sup>3</sup>Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## Correspondence

Mehri Salari, Functional Neurosurgery Research Center, Shohada Tajrish Comprehensive Neurosurgical Center of Excellence, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.  
Email: mehri.salari@gmail.com

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## Abstract

Here, we introduced a patient with Mn-induced parkinsonism who was responsive to intranasal insulin, and his parkinsonism and dystonia responded to this treatment.

## KEYWORDS

insulin, intranasal, manganese, parkinsonism

## 1 | INTRODUCTION

Manganese (Mn) is an essential heavy metal, which is widely distributed in the environment. Overexposure to this element causes neurotoxicity, mainly characterized by specific damage to the basal ganglia. This syndrome, termed manganism, presents with extrapyramidal manifestations,<sup>1</sup> parkinsonism is the typical manifestation of Mn overexposure, which may be difficult to distinguish from idiopathic Parkinson's disease,<sup>2</sup> health conditions, total parenteral nutrition, and genetic mutations causing Mn dyshomeostasis. In this review, we critically analyze Mn and discuss its sources of exposure, pathophysiology, and clinical manifestations. We have highlighted the global public health impact of Mn and emphasize that

movement disorder specialists should record a detailed social and occupational history to ensure that a toxic etiology is not misdiagnosed as a neurodegenerative disease. In the absence of a definite therapeutic option, early diagnosis and timely institution of preventive measures are the key to managing its toxic effects.

Occupational exposure, such as mining, welding, and battery manufacturing, is of significant concern in Mn intoxication. Usually, 6 months to 2 years of occupational exposure to Mn can lead to manganism, which may persist for up to 14 years after the last exposure.<sup>3</sup>

While chelation therapy has been suggested by some studies, therapeutic measures have generally not been very successful in achieving clinical remission.<sup>4</sup> Herein, we describe a manganese mine worker affected by Mn-induced

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parkinsonism, who responded remarkably to intranasal insulin.

## 2 | CASE PRESENTATION

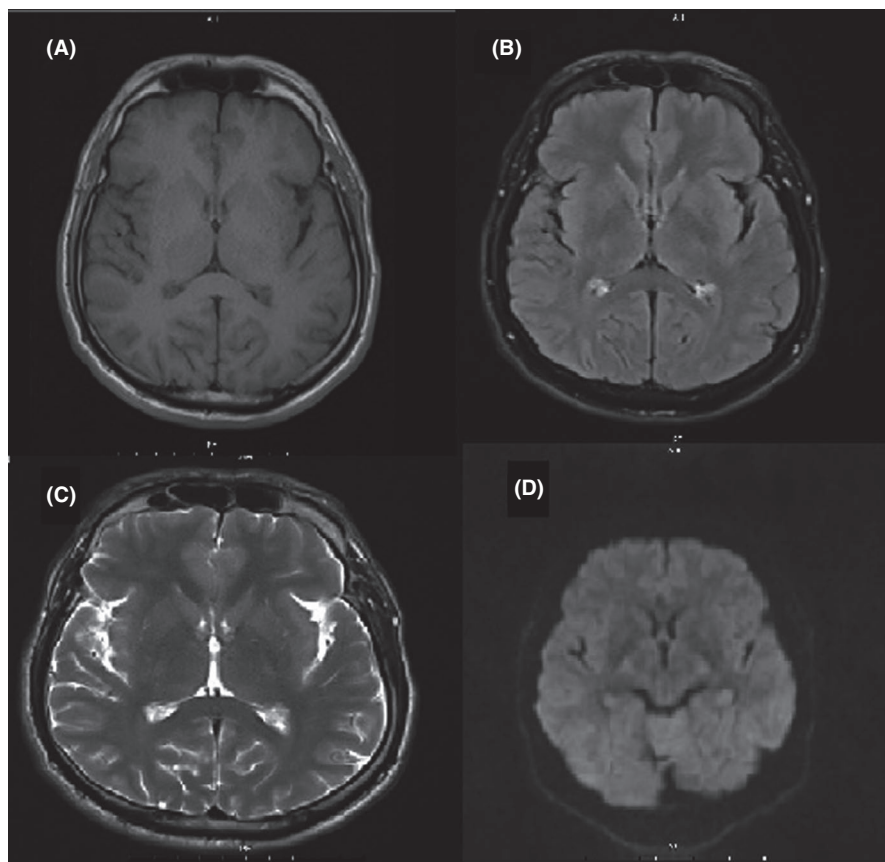
A 33-year-old right-handed man was born to nonconsanguineous parents, who worked at a manganese mine for 35 days at the age of 16. After 7 days of working, he suffered from aggression, which was not like him, and after around 20 days, three workers including him developed imbalance and suffered multiple episodes of falling and they left the mine. After several months, the mine was closed. Because of bradykinesia, levodopa and trihexyphenidyl were started for him by diagnosis of Parkinson's disease. The symptoms seem to be exacerbated in the cold and have not responded to the long-term use of levodopa and trihexyphenidyl. The symptoms were progressed and then became static. Past medical history was unremarkable. No family history of parkinsonism and other movement disorders had been reported.

When the patient was referred to our Movement Disorders Clinic, on examination, he had masked face, generalized bradykinesia that was more severe on the legs, generalized rigidity that was more prominent on the

legs, rest tremor on hands, postural instability, and tip toe walking (Cock-walk gait), and his score for MDS-UPDRS part III was 33 (Video S1). Deep tendon reflexes were generally +3, and on cognitive assessment, his validated Persian SCOPA (the scales for outcomes in Parkinson's disease) score was 33/43. Other systemic and neurological investigation were unremarkable including ophthalmologic, ocular movement, motor, cerebellar, and sensory examination. The patient suffered from insomnia, anosmia, depression, anxiety, and impaired activities of daily living.

The laboratory tests, including serum and urine ceruloplasmin, serum copper, and serum Mn, were within normal range. Brain magnetic resonance imaging (MRI) was normal when he referred to our clinic, and the previous brain imagines were not available. (Figure 1).

The patient was diagnosed with manganese toxicity, and as his request, he included in a study, which approved by Iran National Committee for Ethics in Biomedical Researches (IR.SBMU.PHNS.REC.1398.094). After signing patient consent, he was administered intranasal regular insulin, 20 IU twice a day, for one month, his motor symptoms improved dramatically, and his MDS-UPDRS reduced to 25, and cognitive reassessments showed SCOPA score of 35/43. After 3-month follow-up, he is still doing well (Video S2).



**FIGURE 1** Sagittal (A) T1, (B) FLAIR, (C) T2, and (D) DWI did not show any abnormal signal changes in basal ganglia

### 3 | DISCUSSION

Excessive occupational manganese exposure may be associated with neurodegenerative processes, including progressive parkinsonism syndrome, dystonic gait disorder (“cock gait”), dystonia, psychosis, cognitive dysfunction, and emotional lability. Manganese-induced parkinsonism is often characterized by intention tremor with absent or little resting tremor; gait and balance dysfunction, especially with difficulty in backward walking; rigidity; speech impairment; bradykinesia; and poor response to levodopa.<sup>1</sup>

Although Mn can target different regions of the central nervous system (CNS), it has shown a tendency to accumulate in the basal ganglia, particularly in the striatum, globus pallidus (GP), and the substantia nigra (SN). The main neurotransmitter system affected by Mn toxicity is the dopaminergic system, but cholinergic and gamma-aminobutyric acid (GABA)ergic systems can also be damaged. However, the specific mechanism of Mn neurotoxicity has not yet been fully identified.,<sup>34</sup>

Some studies have demonstrated that chelation therapy with ethylene diamine tetraacetic acid (EDTA) and its calcium disodium salt can be useful for the treatment of severe cases of Mn-induced parkinsonism, but there are some reports that this treatment is not effective in some patients. Moreover, odium para-amino salicylic acid (PAS), an antibacterial drug, has been shown to be effective in the treatment of severe chronic Mn intoxication, but its effects are usually seen after several months of treatment.<sup>4</sup>

A prospective, placebo-controlled, double-blinded study has shown that the administration of intranasal insulin is safe and may improve cognitive and motor impairment in Parkinson disease.<sup>5</sup> In addition, a case report observed significant improvement of symptoms in a patient with myoclonic dystonia (DYT11), who had been treated with insulin due to diabetes mellitus type1.<sup>6</sup>

Here, for the first time, we report a case of Mn-induced parkinsonism, which responded dramatically to intranasal insulin. The current preliminary findings require further investigations to determine whether intranasal insulin might really be considered as an effective and safe therapeutic alternative in Mn-induced parkinsonism.

#### ACKNOWLEDGMENT

None.

#### CONFLICTS OF INTEREST

There is no conflict of interest.

#### AUTHOR CONTRIBUTION

MS involved in conception, organisation, and execution of the research project; analysis or interpretation of data; and review and critique of the manuscript preparation. ME involved in conception of the research project; and analysis or interpretation of data. LD involved in organisation and execution of the research project; and review and critique of the manuscript preparation. NV involved in organisation and execution of the research project; and review and critique of the manuscript preparation. MR involved in organisation of the research project; and writing the first draft of the manuscript.

#### ETHICAL APPROVAL

This study has been reviewed by Iran National Committee for Ethics in Biomedical Researches (IR.SBMU.PHNS.REC.1398.094). We confirm that all authors have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

#### CONSENT

Patient's consent form was signed by the patient, and it is available on request. Written valid and informed consent was obtained from the patient for video recording, and both print and online publication of his videos.

#### DATA AVAILABILITY STATEMENT

Data are available on request.

#### ORCID

Mehri Salari  <https://orcid.org/0000-0001-7102-821X>

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### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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