Case Report

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Manganese Poisoning Induced by Total Parenteral Nutrition in the ICU: A Case Report and Review

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Abstract: Introduction: Manganese is an essential trace element for humans. It has been recognized as a potential occupational toxic but its danger as toxic in patients under parenteral nutrition is often forgotten. **Case report**: 73-year-old man, logged 210 days in Intensive Care Unit (ICU), receiving total parenteral nutrition (TPN) for a month, current disease chorea-type movements in the head and neck and left hemi body. **Diagnostic tests**: Magnetic resonance image findings suggest manganese deposit, total blood manganese concentration (34 μg. L^{-1}) (reference range: less than 13 μg. L^{-1}). **Diagnosis**: Abnormal movements can be caused by manganese poisoning due to parenteral nutrition and are associated with liver failure in the ICU**. Discussion and Conclusions**: After a prolonged stay in ICU, assessing liver failure caused by septic and protracted parenteral nutrition, manganese poisoning should be considered as a cause of chorea-type movements.

Keywords: nutrition; neurotoxicity; parenteral nutrition; trace elements; manganese

1. Introduction

Manganese is an essential trace element for human life, and its various metabolic functions require its presence as a nutrient. Involved in bone formation (activates the glycosyltransferase required for mucopolysaccharide used by cartilage); the metabolism of amino acids (it constitutes the arginase); and energy metabolism (as part of the pyruvate carboxylase and the isocitrate dehydrogenase) and as an antioxidant (the superoxide dismutase) [1,2] (1) (2)

Its deficiency in humans, associated with clinical defects, has been reported very rarely [3] (3)the clinical symptoms are weight loss and clotting problems. The first documented instance of a possible manganese deficiency involved a male participant in a study [4] examining vitamin K requirements. For seventeen weeks, his strictly controlled diet unintentionally lacked manganese. As a result, he experienced mild dermatitis, redness in his black hair and beard, slowed the growth of hair, nails, and facial hair, sporadic nausea and vomiting, and moderate weight loss. His total daily intake of manganese from both food and water was only 0.35 mg. From 2 to 3 mg of Mn containing a normal diet only it is absorbed 3 to 4% and retained less than 1% after biliary and intestinal excretion.

Typically, human diseases associated with biological abnormalities are found in excess, not deficiency. Human exposure to Mn primarily occurs in occupational settings where Mn is utilized, such as in ferroalloy production, mining, smelting, battery manufacturing, and welding industries. Epidemiological research has indicated that workers exposed to Mn through inhalation of dust may develop neurotoxicity and neurodegenerative conditions. Additionally, individuals residing near industrial Mn sources, where airborne Mn concentrations are elevated (including fumes and

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particulate matter), are at risk of excessive Mn inhalation. In fact, neurotoxic effects such as motor dysfunction and hand tremors have been observed in these populations, highlighting the significance of high Mn exposure as a public health concern.

Beyond occupational exposure, Mn-contaminated food and drinking water represent the primary sources of non-occupational Mn toxicity. Mn contamination in water can result from geological formations rich in Mn, leading to elevated levels in groundwater.

Considering the extent of industrial use, it is important to consider occupational poisoning, called manganism, whose symptoms resemble those of Parkinson's disease [5].

Another possibility of Mn poisoning is parenteral nutrition (PN). Certain diseases and medical conditions can prevent enteral nutrition and proper absorption in the gastrointestinal tract, resulting in micronutrient deficiencies and necessitating the use of parenteral nutrition. In such cases, parenteral solutions serve as a source of essential micronutrients, including vitamins and trace elements, which are crucial for key metabolic functions. Additionally, PN is utilized to correct deficiencies and compensate for ongoing micronutrient losses in patients.

National and international nutrition societies have established guidelines to assist healthcare professionals in the appropriate use of PN for both adults and children. However, the absence of consensus-based recommendations regarding the practical administration of micronutrients in parenteral nutrition poses challenges in patient management and safety monitoring.

Dystonia and movement disorders have been reported in patients receiving total parenteral nutrition (TPN) for extended periods. These cases are associated with abnormalities observed in magnetic resonance imaging (MRI), which shows increased signal intensity on T1-weighted images in the basal ganglia. Since intestinal absorption plays a crucial role in maintaining manganese (Mn) homeostasis, the parenteral administration of nutrients disrupts this important regulatory mechanism. The literature lists [6](6) several cases of manganese toxicity linked to the use of parenteral solutions containing manganese.

Hypermanganesemia and the presence of clinical symptoms depend on the dose of Mn in the TPN, the duration of use, and the presence of liver disease. As the excretion of Mn from the body occurs mainly in bile (90%) and its homeostasis is achieved mainly by regulation of biliary excretion, patients with liver dysfunction, particularly cholestasis, receiving PN containing Mn generally develop signs and symptoms of intoxication more rapidly than the long-term PN patient without liver disease. Since its transport mechanism involves the transferrin receptor and divalent metal transporter type I (DMT-I) and its elimination is via the liver, co-morbidities such as iron deficiency and cholestasis are risk factors for the neurotoxicity of Mn [7](7).

Mn concentration measurement in clinical laboratories is not very regular. Our laboratory has Graphite Furnace Atomic Absorption Spectrophotometry (GFAAS) PinAAcle 900-Z® Perkin-Elmer, with Zeeman correction, and has validated methods for the determination of Mn in blood [8](8). The whole blood samples were collected in trace metal-free tubes to prevent contamination. Samples were diluted with a matrix modifier (2% palladium nitrate) to break down proteins and improve atomization at 2600ºC. GFAAS system consists of a graphite furnace, which provides high-temperature atomization, and a hollow cathode lamp specific to manganese. During atomization, manganese atoms absorb light from the Mn-specific lamp at 279.5 nm, and the absorbance is measured. The absorbance is directly proportional to the Mn concentrations in the sample. Certified reference materials were measured to ensure accuracy.

Usually, the only trace elements serum concentrations measured in long-term total parenteral nutrition are iron, copper, and zinc. But others like selenium, chromium, or manganese are infrequent. Mn must be measured by GFAAS with Zeeman correction or inductively coupled plasma mass spectrometry (ICP MS) when intoxication is suspected.

2. Case Report

A 73-year-old man was referred to neurology consultation from the long-stay residence for evaluation of abnormal movements.

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2.1. Personal Background:

No known drug allergies. Type 2 Diabetes Mellitus, treated with oral antidiabetic medications, with a last recorded glycated hemoglobin (HbA1c) of 4.6% (27 mmol/mol). Usual treatment: omeprazole 20 mg 1-0-0, repaglinide 1 mg 0-1-0.

The summary of the clinical examination describes: No history of hypertension. No toxic habits. Evaluated by pneumology due to dyspnea. Thoracic CT scans showed parenchymal changes suggestive of interstitial neuropathy and non-idiopathic pulmonary fibrosis, along with emphysema and bronchiectasis. Given the patient's clinical condition, no further complementary studies or specific treatments were pursued. Surgical History: Hemorrhoid surgery. Cholecystectomy. Cataract surgery in the left eye. Baseline Functional Status: Lives in a family home. Ambulates with a cane. Mild to moderate cognitive impairment.

Patient with gastric adenocarcinoma presenting as a large nodular mass in the gastric body, staged as T3NXM0 treated with chemotherapy (three cycles of epirubicin cisplatin/fluorouracil (ECF) scheme) and subtotal gastrectomy, Bill Roth Il surgery. Five days after surgery the patient presented hypotension (70/30 mm Hg), tachycardia (heart rate 120 bpm), and tachypnea, radiographic findings suggestive of acute pulmonary edema. He was reoperated after being found to have supramesocolic peritonitis due to dehiscence of anastomosis in the gastric side of the previous jejunostomy. The patient presented candidemia in ICU associated with catheter infection, bacteremia by *S aureus MS*, recurrent pneumonia, septic shock with multiple organ failure, remained logged 210 days in ICU receiving TPN for two months. The patient delayed in resuming consciousness after the withdrawal of sedation, later he needed neuroleptics and benzodiazepines. Discharge from the ICU to the internal medicine ward had severe generalized atrophy and paresis. Two months after he was moved to a long-stay residence for rehabilitation of severe critical illness polyneuropathy.

We used the Pierson, Bradford Hill, and Newcastle-Ottawa tool to determine the degree of bias and the quality of evidence of the case description and found that it duly meets the selection, verification, causality, and reporting criteria [9].(9)

2.2. Current Disease:

Doctors at the residence reported chorea-type movements in the head and neck and left hemi body that increase and unrelieved with anticholinergics or benzodiazepines. The family reported that they had observed these movements since their stay in the ICU, at that time only mildly. The movements made walking practically impossible. The patient appears conscious, attentive, and oriented, his speech is normal.

Cranial Nerves (CN): Normal fundus oculi (FO), Extraocular Movements (EOM) normal; Oculomotor Reflex (OR): Normal motor and consensual response. No facial asymmetries were observed. The lower cranial nerves are normal. Motor examination shows a strength of 4+/5 in both upper and lower limbs, with absent deep tendon reflexes (DTR). Pain and touch sensitivity were preserved. No dysmetria or adiadochokinesia was observed.

2.3. Additional Tests:

T I-weighted MRI revealed symmetrical high-intensity lesions in the globus pallidus.

There were no ischemic or demyelinating lesions.

Syphilis, Borrelia, Brucella, and HIV and HBV serology were negative.

Onconeural antibodies (anti-Hu-, anti-Yo-, anti-Ri-, anti-CMV2) were negatives.

Serum glucose, creatinine, calcium, and phosphorus concentrations were normal.

Serum total bilirubin was 2.5 $mg \cdot L^{-1}$. Serum GGT (γ – Glutamyl Transpeptidase) was 71 $U \cdot L^{-1}$. Serum ALP (Alkaline phosphatase) was 130 $U \cdot L^{-1}$. Serum TSH (Thyroid Stimulating Hormone) was normal,1.33 $\mu U \cdot mL^{-1}$.

During admission, treatment with haloperidol and clonazepam was started with good tolerance and significant improvement in his movements, allowing him to walk with a walker.

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Mn determination in whole blood by GFAAS proved a total of 34 μg·L^{-1}, higher than the normal upper limit (13 μg· L^{-1}).

2.4. Clinical Trial

Dropped the paraneoplastic origin of the movement, basal ganglia metastasis was ruled out, and no metabolic disorders were found. No ischemic or demyelinating lesions were observed. The only significant finding was observed on magnetic resonance imaging (MRI), which revealed T1 hyperintensity in the basal ganglia, a finding suggestive of metal deposition. The Mn (II) ion has five unpaired electrons in the 3d orbit, causing the shortening of T1-relaxation time and an increase in signal intensity on T1-weighted MRI. Signs of supra and infratentorial atrophy are observed with enlargement of sulci, cisterns, and the ventricular system correlating with age.

Upon reviewing the patient's medical history, it was noted that during the ICU stay, the patient developed liver failure with a cholestatic pattern, secondary to multiorgan failure associated with septic shock, parenteral nutrition, and pharmacological treatment. Further analysis revealed that the patient was receiving parenteral nutrition during the period in which liver failure occurred.

An evaluation of the parenteral nutrition formula showed the Mn content (300 μg Mn·day^{-1} nominal for two months). Updates in parenteral nutrition (PN) guidelines reflect growing concerns about hypermanganesemia in home parenteral nutrition (HPN) patients. In 2012, A.S.P.E.N. revised its recommended manganese dose from 60–100 μg/day to a lower dose of 55 μg·day^{-1}, a recommendation increasingly supported by experts [10,11](10) (11). An often-overlooked source of manganese exposure is contamination from PN components, as solutions such as calcium gluconate, magnesium sulfate, potassium chloride, amino acids, and glucose may contribute up to 38 μg of manganese per 2 L of PN solution.

In light of these recommendations, the patient's manganese intake of 300 μg·day^{-1} appears to be significantly elevated and potentially toxic. This excessive exposure likely contributed to manganese accumulation, as evidenced by MRI findings and the subsequent development of chorea. The presence of liver dysfunction, which may have impaired manganese clearance, further supports the likelihood of manganese toxicity as the underlying cause of the patient's neurological symptoms. This diagnosis was confirmed by the quantification of manganese levels using graphite furnace atomic absorption spectrophotometry.

After 12 months whole blood Mn concentration decreased to 8.1 μg·L^{-1}. One year later, treatment with haloperidol could not be stopped due to worsening of his involuntary movements. On neurological examination, there was no rigidity or bradykinesia. Choreiform movements did not prevent the maintenance of the sitting posture, nor is there any impact on walking. He didn't tiptoe and did not present tremor.

3. Discussion

Parenteral exposure to Mn with impaired excretory gallbladder has been the cause of the poisoning, suspected by the radiological images.

Parkinsonian-type symptoms make suspect this poisoning whose incidence is often underestimated [12](12).

No clear standard has been recommended for the daily dose of parenteral Mn, with the published literature indicating a broad, 200-fold range in the recommended daily Mn dose for adults on TPN ranging from a low dose of 0.18 - 0.91 μmol (0.01-0.05 mg) to a high dose of 40 μmol (2.2 mg).

Despite the usual doses of Mn contained in the TPN, it could be toxic concentration by altering homoeostatic and we cannot rule out contamination by the metal in the preparation of parenteral nutrition. A report (13) [13] found that Mn concentrations in TPN solutions ranged from 5.6 to 8.9 μg·L^{-1} in the absence of any supplementation. Probably, a problem is the contamination of raw products used to produce these solutions, including the polyvinyl chloride (PVC) bags and tubing.

Mn intoxication associated with TPN solutions providing ≥0.1 mg Mn day^{-1} is well established [14,15](14) (15). These patients developed elevated serum Mn levels (16) [16], and they exhibit

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symmetrical high-intensity MRI lesions in the globus pallidus consistent with the preferential accumulation of Mn at this site, in association with characteristic psychiatric symptoms and clinical signs of Mn-induced parkinsonism-like syndrome.

In the patient's course, there has been an improvement in their movements by getting to walk with a walker. Mn concentrations remained slightly elevated in the first year despite the time elapsed since the TPN. However, one year later blood Mn concentration dropped to 8.1 μgL^{-1}. Removal of the patient from exposure, Mn from PN in this case, seems to be the current best therapeutic intervention for Mn intoxication, because in most cases the symptoms regressed, levels of high-intensity MRI returned to normal, and blood Mn concentrations decreased.

4. Conclusions

Mn supplementation should be used with caution in patients receiving long-term PN, and attention should be paid to the Mn content when serum total bilirubin is elevated [17](17). Current guidelines for PN recommend biomonitoring in patients receiving manganese supplementation for more than 30 days [18] (18). The globus pallidus is especially vulnerable to manganese toxicity due to its high concentration of dopamine receptors, which readily bind Mn. In contrast, Parkinson's disease (PD) primarily involves the degeneration of dopaminergic neurons in the substantia nigra pars compacta. Mn accumulation can be detected before symptoms appear, either as hypermanganesemia (elevated Mn levels in the blood) or as increased signal intensity in the basal ganglia on T1-weighted magnetic resonance imaging (MRI). As the condition progresses, patients may develop Parkinsonian-like symptoms, including tremors, hypertonia, bradykinesia, and gait disturbances. However, there is an ongoing debate in the literature regarding the most effective method for assessing manganese levels in the human body and no definitive biomarker for manganese exposure or neurotoxicity has been established. The utility of serum Mn has been questioned as a marker for whole-body Mn as it was reported that intra-cerebral Mn levels were elevated in the presence of normal serum values (19) [19]. While whole-blood manganese levels are commonly used as an exposure marker, they provide limited insight into manganese-induced neurotoxicity. But, in any case, the quantification of Mn in whole blood may become a valuable option given its attainable cost and availability.

Given these limitations, periodic brain MRI scans may be necessary to monitor manganese accumulation in PN patients. However, MRI is not routinely employed for diagnostic purposes due to its high cost and limited availability. Additionally, the correlation between basal ganglia hyperintensities and the onset of subclinical manganese neurotoxicity remains unclear and requires further investigation. Further research is needed to clarify the relationship between manganese (Mn) levels in tissues, MRI signal intensities, and Mn concentrations in the blood. Currently, it is still uncertain whether hyperintensities in the basal ganglia indicate abnormal but non-toxic Mn levels, and the exact threshold at which Mn becomes neurotoxic has yet to be established.

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Data Availability Statement: This article, being a case report and review, does not contain any primary data for sharing. The data discussed are derived from previously published studies and the patient's medical records.

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Abbreviations

The following abbreviations are used in this manuscript:

ICU	Intensive Care Unit
TPN	Total Parenteral Nutrition
DMT-1	Divalent Metal Transporter type-1
GFAAS	Graphite Furnace Atomic Absorption Spectrometry
ICP MS	Inductively Coupled Plasma Mass Spectrometry
MRI	Magnetic Resonance Images
GGT	γ- Glutamyl Transpeptidase
ALP	Alkaline Phosphatase
PN	Parenteral Nutrition
PVC	Polyvinyl Chloride
PD	Parkinson's disease

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