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Is it Possible for Late-Onset Schizophrenia to Masquerade as Manganese Psychosis?

Answered by Jonathan Rutchik, MD, MPH, Division of Occupational & Environmental Medicine, University of California San Francisco, San Francisco, CA, USA and Neurology, Environmental and Occupational Medicine Associates, Mill Valley, California; Marcia H. Ratner, PhD, Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine, Boston, Massachusetts, USA.

Manganese (Mn) is an essential trace element and a ubiquitous metal widely used around the world in everyday products ranging from welding rods to gasoline additives. Because Mn is used in many metal alloys including steel, the risk for occupational and environmental exposures exists in many industrial settings.

The initial clinical manifestations of manganese poisoning often include behavioral changes referred to collectively as "manganese psychosis." The clinical symptoms of manganese psychosis include mood changes, emotional lability, uncontrolled laughter, and hallucinations. Parkinsonism characterized by tremor and gait disturbances emerges with continued exposure to Mn. The diagnosis of Mn-psychosis depends in part on the documentation of exposure based on an accurate and complete occupational or environmental exposure history. The presence of biological markers of exposure in blood or urine samples can aid the clinician in making a diagnosis. Biological markers of effect, such as comorbid symptoms of parkinsonism, combined with abnormal magnetic resonance imaging (MRI) studies revealing hyperintensities in the basal ganglia, facilitate the diagnosis of Mn poisoninig.

It is not uncommon for patients and their significant others to seek alternative and toxic explanations for idiopathic neurodegenerative and psychiatric disorders. Therefore, clinicians must diligently explore all explanations for the patient's symptoms before arriving at a diagnosis. Nontoxic etiologies for the patient's symptoms must be ruled out based on the family history, neuroimaging studies, neuropsychological assessment, and results of laboratory tests. Nonoccupational causes of pallidal hyperintensities on an MRI such as hepatic failure must also be ruled out. Progression of symptoms following cessation of exposure is often an indication of an underlying primary idiopathic neurodegenerative or psychiatric process. The differential diagnosis of primary versus secondary psychosis is complex and depends in part on an accurate history of occupational exposure to neurotoxicants that may exacerbate idiopathic disease.

This case report demonstrates the inherent difficulties associated with differentiating Mn-psychosis from late-onset schizophrenia when there is a risk for occupational exposure to heavy metals and solvents. It also exemplifies how a single false-positive laboratory result can lead to misdiagnosis and, serves as reminder of the importance of always confirming the results of initial laboratory tests before making a diagnosis. The importance of proper sample timing in relation to tests and procedures that have the potential to confound the results of laboratory tests for biological markers of exposure is discussed in detail.

CASE REPORT

A 42-year-old jewelry maker with no prior psychiatric history presented to an emergency department (ED) with a 3-week history of progressively worsening psychosis. His symptoms included paranoia, delusions, and auditory hallucinations. On admission to the ED, the patient's pupils were equal, round, and reactive to light. He was alert and oriented times three with no evidence of acute distress. He was afebrile and there was no nuchal rigidity. The patient reported that he does not drink or smoke and denied any history of substance abuse. His history was positive for hyperlipidemia, but he was not currently taking any medications for this. There was no family history of schizophrenia or other psychiatric disorders. His wife reported that she had noticed subtle changes in his behavior including paranoia beginning about 2 years before his current admission to the ED for acutely worsening symptoms of psychosis.

Occupational history revealed the patient to be a self-employed jewelry maker whose work required him to set diamonds and engrave jewelry. He worked 8 hours per day 6 days per week in a small shop (159 sq ft) located in a basement. He reported that he previously wore a mask and goggles when sharpening his engraving tools, but that he had stopped wearing a mask about 2 years ago. He also reported spending more time in the past couple of years sharpening his tools due to new styles and designs he was requested to engrave into jewelry. This change in his work habits was noted to coincide chronologically with his wife's observations about of the changes in his behavior.

On clinical examination, the patient was found to be alert, oriented, and cooperative. Affect was full and appropriate. Impulse control was good while insight and judgment were fair. Because of the apparent acute onset of the patient's symptoms, his age, and his occupation as a jewelry maker, a heavy metal screen was ordered. Testing for mercury, arsenic, nickel, chromium, copper, and lead were all within normal limits, but urine Mn was elevated (23.3 μg/L; Reference range 0.0 to 2.0 μg/L). An electroencephalogram and MRI of the brain were both interpreted as normal. A preliminary diagnosis of Mn-psychosis was made based on the patient's elevated serum Mn level and the clinical presentation, which was remarkably similar to that observed in a 49-year-old welder with Mn-psychosis who presented with paranoid ideation, thoughts of reference, bizarre behaviors, and sleep disturbances.[1]

The patient subsequently stopped working and his psychotic symptoms began to improve. Upon returning to work, his symptoms worsened lending additional support to the possible role of an occupational factor in the etiology of his psychosis. Follow-up hair, blood, and urine tests

Conflicts of interst: none.

All authors contributed equally to the manuscript.

The authors have no current specific competing interests to declare. However, Dr. Rutchik served as expert witnesses in this case. Drs. Rutchik and Ratner are occasionally asked to serve as expert witnesses and/or consultants in occupational and environmental chemical exposure injury cases.

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for Mn exposure were all within normal limits (see Table 1). A subsequent workplace environmental hazard assessment showed that ambient air Mn levels were below the action levels. Air monitoring during sharpening of his tools revealed ambient air Mn levels of 4.0 μg/m^3. Wipe samples from the patient's bench revealed Mn dust concentrations of 400 mg/kg; background levels in soil average 330 mg/kg with a range of 4 to 900 mg/kg.[2] Risk assessment estimated that his exposures via the respiratory route were well below the level regulated by CALOSHA at 200 μg/m^3. This was noted to be significantly below a level that would be expected to cause neurotoxic sequelae of Mn exposure.[3] On the basis of these findings and the observation that the patient had no symptoms of parkinsonism and normal imaging studies, a diagnosis of acute Mn psychosis was excluded.

The differential diagnosis in this case also included B12 deficiency, substance abuse, affective disorder, central nervous system infection, epilepsy, young-onset frontotemporal dementia (FTD), and late-onset schizophrenia Vitamin B12 deficiency was ruled out on the basis of laboratory work, which showed B12 was normal. The patient denied substance abuse. There was no evidence of HIV or other central nervous system infections. Epilepsy was ruled out based on the normal electroencephalogram. Bipolar disorder was ruled out based on the lack of depressive symptomology.[4–6] Neuroimaging studies showed no evidence of stroke or neoplasm. FTD was ruled out based on the lack of learning and memory deficits.[7] A diagnosis of late-onset schizophrenia was ultimately arrived at after ruling out other causes for his psychosis. The patient was managed with olanzapine.

DISCUSSION

An occupational and environmental neurological evaluation must include a differential diagnosis and consider the epidemiology of commonly known idiopathic disorders. Abnormalities found during an investigation such as positive laboratory tests, examination findings, and imaging studies much be reconsidered for false positivity and relevance. In this case, it could not be determined that this patient had a condition secondary to occupational exposure to Mn. The assessment of patients for neurotoxicological disorders is challenging and may be made more so by misleading false-positive laboratory tests and incomplete or poorly documented history of the exposure circumstances.

The differential diagnosis of schizophrenia also remains a difficult task despite decades of research. There is no disease-specific biological marker or neuroimaging findings, and so, the clinical presentation and ruling out other organic causes of psychosis remains the basis for a clinical diagnosis of schizophrenia.[8,9] That said, this case report demonstrates the importance of confirming initial laboratory results from a heavy metal screen before making a diagnosis of neurotoxicant-induced psychosis.

Atypical parkinsonism and psychosis were well described in historical papers from Moroccan, Egyptian, and Chilean authors who saw miners with high levels of acute exposure to Mn.[10,11] These patients were found to have irreversible conditions with poor prognosis. More contemporary occupational exposures to high level Mn have been associated with both atypical parkinsonism that progresses in a dose dependent manner with continued exposure[12] and idiopathic Parkinson disease (IPD) that presents with an earlier onset.[13] Some studies have reported that clinical, imaging, and pathological characteristics of these patients with IPD are indistinguishable from those with Mn-induced Parkinsonism.[14–17] At lower levels, in occupational settings, Mn exposure is also associated with clinical symptoms without neurological examination findings. Subclinical neuropsychological testing abnormalities have been found in both occupational[18] and environmental settings.[19] Psychotic symptoms have been described in welders more recently. In one active welder from the Netherlands, MRI revealed bilateral hyperintensities of the basal ganglia were noted on T1 imaging along with a serum Mn of 52 to 97 nmol (range 7 to 20).[1] Dopamine Transporter (DaT) SPECT Imaging was normal. Neurological examination was normal. The patient responded to Risperidone after 2 weeks, serum Mn lowered, and MRI intensities lessened. Neuropsychological testing revealed apathy and rigidity and a diagnosis of Mn-induced apathy was determined.

According to the Agency for Toxic Substances and Disease Registry, although subclinical neurological effects have been observed in workers chronically exposed to Mn at air levels as low as 70 μg/m^3, overt symptoms of Mn neurotoxicity typically emerge when air levels of Mn exceed 2 mg/m^3.[3] It is possible that the patient's occupational exposure history may have included prior exposure to Mn at higher ambient air levels. However, in this case, the patient had no symptoms or signs of parkinsonism associated with his psychiatric symptoms, and an analysis of the exposure circumstances suggested that his occupational exposure to Mn was insufficient to establish a clear causal relationship between this and his psychiatric symptoms. His brain MRI was normal and his clinical features did not resolve with cessation of exposure. Also, there were other explanations for his elevated urine Mn levels such as false positive due to use of a gadolinium contrast agent on MRI.

It is possible, that the gadolinium used as a contrast agent contributed to the false positive in the initial urine sample. High concentrations of gadolinium have been reported to interfere with tests for heavy metals. The half-life of gadolinium is about 90 minutes, and therefore, the majority is expected to be eliminated within 9 hours after administration.[20] Nevertheless, most laboratories advise waiting at least 96 hours after administration of gadolinium before taking a blood or urine sample for heavy metal screening.

Although older than the average, it was more likely that the patient's symptoms are due to idiopathic schizophrenia. Late-onset schizophrenia, which is characterized by onset of symptoms after age 44 years, is difficult to diagnose due to the atypical age at onset and complex differential diagnosis, which includes dementia and other age-related neurological disorders. Persons with late-onset schizophrenia show fewer negative symptoms such as flat affect, and less pronounced cognitive impairments.[21]

Persistent changes in nervous system function induced by prior events such as a chemical exposure or genetic factors can remain clinically silent until these are "unmasked" by a second experimental or natural processes such as a subsequent chemical exposure later in life or aging.[22] Exposure to chemicals that share common mechanisms with those implicated in neurological disorders can lead to interactions that may hasten disease progression and unmask latent disease.[23–25] These complex

TABLE 1. Biological Markers of Manganese Exposure

Biomarker	Patient's Values			Reference Values
	Lab 1	Lab 2	Lab 3	
Urine Mn	23.3 μg/L	0.4 μg/L	1.7 μg/L	0.0–2.0 μg/L
Hair Mn	N/A	0.13 μg/g	0.16 μg/g	<3 μg/g
Serum Mn	N/A	0.9 μg/L	1.4 μg/L	0.0–2.0 μg/L
Whole Blood	N/A	7.7 μg/L	10.0 μg/L	4.2–16.5 μg/L

interactions are exacerbated by genetic polymorphisms that influence the metabolism of chemicals.[25,26] Although we were not able to identify a specific acute exposure event in this case, it is possible that this patient's chronic exposure to low levels of chemicals used in jewelry making may have played a role in unmasking his late-onset schizophrenia. It is important to note that the first episode of psychosis in schizophrenia has been associated with exposure to a wide array of chemicals, including cannabis, dopamine agonists, and organic solvents.[27–29]

Although neurotoxic consequences from exposures to metals and solvents can be a diagnosis of exclusion based on biological markers of effect (eg, tremor) when supported by peer reviewed literature, a high index of suspicion for a diagnosis of Mn-induced psychosis is supported by (1) an elevated blood or serum Mn that is consistent with high-level occupational exposure and industrial hygiene data; (2) brain MRI showing pallidal hyperintensities consistent with Mn-induced neurotoxicity; (3) neurological examination revealing extrapyramidal dysfunction; and, (4) clinical improvement with cessation of exposure. Unless this unique constellation of biological markers of exposure and effect are seen, an alternative diagnosis should always be sought.

REFERENCES

1. Verhoeven WM, Egger JI, Kuijpers HJ. Manganese and acute paranoid psychosis: a case report. *J Med Case Rep*. 2011;5:146.
2. Barceloux DG. Manganese. *J Tox Clin Tox*. 1999;37:293–307.
3. ATSDR. Toxicological Profile for Manganese. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry; September 2012.
4. Yassa R, Nair V, Nastase C, Camille Y, Belzile L. Prevalence of bipolar disorder in a psychogeriatric population. *J Affect Disord*. 1988;14:197–201.
5. McGlashan TH. Adolescent versus adult onset mania. *Am J Psychiatry*. 1988;145:221–223.
6. Verhoeven WM, Egger JI, Gunning WB, Bevers M, de Pont BJ. Recurrent schizophrenia-like psychosis as first manifestation of epilepsy: a diagnostic challenge in neuropsychiatry. *Neuropsychiatr Dis Treat*. 2010;6:227–231.
7. Ng AS, Sias AC, Pressman PS, et al. Young-onset frontotemporal dementia in a homozygous tau R406W mutation carrier. *Ann Clin Transl Neurol*. 2015;2:1124–1128.
8. Bonilha L, Molnar C, Horner MD, et al. Neurocognitive deficits and prefrontal cortical atrophy in patients with schizophrenia. *Schizophr Res*. 2008;101:142–151.
9. Bonilha L, Elm JJ, Edwards JC, et al. How common isbrainatrophy in patients with medial temporal lobe epilepsy? *Epilepsia*. 2010;51:1774–1779.
10. Rodier J. Manganese poisoning in Moroccan miners. *Br J Ind Med*. 1955;12:21–35.
11. Abdel-Naby S, Hassanein M. Neuropsychiatric manifestations of chronic manganese poisoning. *J Neurol Neurosurg Psychiatry*. 1965;28:282–288.
12. Racette BA, Searles Nielsen S, Criswell SR, et al. Dose-dependent progression of parkinsonism in manganese-exposed welders. *Neurology*. 2017;88:344–351.
13. Racette BA, McGee-Minnich L, Moerlein SM, Mink JW, Videen TO, Perlmutter JS. Welding-related parkinsonism: clinical features, treatment, and pathophysiology. *Neurology*. 2001;56:8–13.
14. Cersosimo MG, Koller WC. The diagnosis of manganese-induced parkinsonism. *Neurotoxicology*. 2006;27:340–346.
15. Rutchik JS, Zheng W, Jiang Y, Mo X. How does an occupational neurologist assess welders and steelworkers for a manganese-induced movement disorder? An international team's experiences in Guanxi, China, part I. *J Occup Environ Med*. 2012;54:1432–1434.
16. Rutchik JS, Zheng W, Jiang Y, Mo X. How does an occupational neurologist assess welders and steelworkers for a manganese-induced movement disorder? An international team's experiences in Guanxi, China Part II. *J Occup Environ Med*. 2012;54:1562–1564.
17. Andruska KM, Racette AB. Neuromythology of manganism. *Curr Epidemiol Rep*. 2015;2:143–148.
18. Bowler RM, Roels HA, Nakagawa S, et al. Dose-effect relationships between manganese exposure and neurological, neuropsychological and pulmonary function in confined space bridge welders. *Occup Environ Med*. 2007;64:167–177.
19. Zoni S, Lucchini RG. Manganese exposure: cognitive, motor and behavioral effects on children: a review of recent findings. *Curr Opin Pediatr*. 2013;25:255–260.
20. McLachlan SJ, Eaton S, De Simone DN. Pharmacokinetic behavior of gadoteridol injection. *Invest Radiol*. 1992;27:S12–S15.
21. Howard R, Rabins PV, Seeman MV, Jeste DV. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group. *Am J Psychiatry*. 2000;157:172–178.
22. Kraft AD, Aschner M, Cory-Slechta DA, Bilbo SD, Caudle WM, Makris SL. Unmasking silent neurotoxicity following developmental exposure to environmental toxicant. *Neurotoxicol Teratol*. 2016;55:38–44.
23. Ratner MH, Feldman RG. Parkinson's disease. Pfeiffer RF, Ebadi M, editors. Chapter 6. Environmental Toxins and Parkinson's Disease. Boca Raton, FL: CRC Press; 2004:51–62.
24. Ratner MH, Farb DH, Ozer JS, Feldman RG, Durso R. Younger age at onset of sporadic Parkinson's disease among subjects occupationally exposed to metals and pesticides. *Interdiscip Toxicol*. 2014;7:123–133.
25. Ratner MH. A critical review of the interrelationships between genetics, neurotoxicant exposure, and age at onset of neurodegenerative diseases. *Curr Topics Toxicol*. 2016;12:1–10.
26. Feldman RG, Ratner MH. The pathogenesis of neurodegenerative disease: neurotoxic mechanisms of action and genetics. *Curr Opin Neurol*. 1999;12:725–731.
27. Batki SL, Harris DS. Quantitative drug levels in stimulant psychosis: relationship to symptom severity, catecholamines and hyperkinesias. *Am J Addict*. 2004;13:461–470.
28. Stein Y, Finkelstein Y, Levy-Nativ O, Bonne O, Aschner M, Richter ED. Exposure and susceptibility: schizophrenia in a young man following prolonged high exposures to organic solvents. *Neurotoxicology*. 2010;31:603–607.
29. Mallet J, Ramoz N, Le Strat Y, Gorwood P, Dubertret C. Heavy cannabis use prior psychosis in schizophrenia: clinical, cognitive and neurological evidences for a new endophenotype? *Eur Arch Psychiatry Clin Neurosci*. 2017 [Epub ahead of print].

