Manganese-Induced Parkinsonism Associated With Methcathinone (Ephedrone) Abuse

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Background: Manganese intoxication may lead to a levodopa-resistant, akinetic-rigid syndrome. A new form of presumed manganese poisoning has been reported in drug-addicted persons from Russia, Ukraine, and Estonia who have intravenously injected self-prepared methcathinone hydrochloride (Ephedrone).

Patient: A 36-year-old man from Azerbaijan with hepatitis C and only modest hepatic synthetic dysfunction developed rapid-onset, levodopa-resistant parkinsonism with profound hypophonia.

Conclusion: Ephedronic encephalopathy outside the region of the former Soviet Union may become a more widespread public health problem as a result of global travel and the easy availability of the recipe for synthesis of methcathinone on the Internet.

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nounced masked facies and extreme hypophonia resulting in his speech being largely unintelligible. Cognitive assessment was limited by communication difficulties; the components of the Montreal Cognitive Assessment (MoCA) that could be tested revealed no overt deficits. He had some slowing and mild restriction in the range of vertical saccadic eye movements, horizontal saccades were somewhat slowed, and vertical optokinetic nystagmus was impaired. There was moderate bilateral limb bradykinesia. Tone in the limbs was normal, but there was mild axial rigidity. He walked with short strides with a slightly wide base, and his arms were held abducted from the sides. Turning was difficult and postural reflexes were impaired, with falling on the pull test. Neurologic examination findings revealed no other abnormalities. Findings at general examination were unremarkable. The patient had one spider nevus on his chest and injection stigmata, particularly on the left arm, although when asked about these at the initial examination, his wife immediately indicated that they were the consequence of a previous operation.

Pramipexole dihydrochloride at doses of up to 0.75 mg/d had no effect on the parkinsonism but eliminated the jerky movements of his legs at night. This drug therapy was discontinued because of excessive daytime sleepiness and its stimulating a craving for sweets. Trials of selegiline hydrochloride and levodopa-carbidopa at doses up to 600/150 mg/d were ineffective.

Magnetic resonance images of the brain showed striking symmetric increased signal in the globus pallidus, substantia nigra, dentate nucleus, and pontine tegmentum on T1-weighted images (Figure) with little correlation on T2-weighted images (not shown), which demonstrated only modest hyperintensity in the region of the posterior limb of the internal capsule. There was no evidence of edema. Laboratory tests showed normal concentrations of blood albumin, alkaline phosphatase, γ-glutamyl transferase, total bilirubin, ceruloplasmin, serum copper, and 24-hour urine copper. Prothrombin time was 51.8 seconds (reference range, 33-43 seconds); aspartate aminotransferase level, 67 U/L (reference range, 10-40 U/L); and alanine aminotransferase level, 114 U/L (reference range, 2-60 U/L). Blood manganese concentration was 49 µg/L (897 nmol/L) (reference range, 4-16 µg/L [78-289 nmol/L]), and urine manganese concentration, 2804.3 nmol/24 h. A second blood manganese concentration 5 months after the first determination was 102 µg/L (1860 nmol/L) while the patient was still self-injecting methcathinone but before he admitted this to us. Tests for hepatitis A and B yielded negative results. Hepatitis C RNA was 405 000 IU/L, and a percutaneous liver biopsy specimen showed chronic active hepatitis with fibrosis. 6-[18F]-Fluorodopa positron emission tomography performed as previously described showed a mild reduction in fluorodopa uptake (Ki) limited to the posterior putamen (Table).

Although during the course of investigations we informed the patient that we believed his symptoms were caused by elevated manganese levels, he did not inform us of his drug abuse. He continued the injections of methcathinone until his wife revealed this several months later. Referral to a rehabilitation clinic was declined. After the initial discovery of elevated manganese levels, the patient underwent treatment by a naturopathic physician that included 10 sessions during 4 months using intravenous calcium disodium–EDTA at a dose of 3 g per treatment. This had no appreciable effect on his symptoms.

**COMMENT**

The designer drug methcathinone is also known as Cat, Jeff, Mulka, and Ephedrone. It was used as an antide-
pressant in the former Soviet Union and is very addictive. Methcathinone can be produced from pseudoephedrine (Sudafed) with potassium permanganate added to produce an oxidant reaction. Cases of ephedronic encephalopathy have been reported from Russia, Ukraine, and Estonia. To our knowledge, this is the first case occurring outside this region. Global travel and easy access to the Internet, where the recipe for the synthesis of methcathinone is readily available, make it possible that this disorder will become a more widespread public health problem.

Patients manifest clinical features typical of other causes of manganeseism, most notably a levodopa-resistant form of parkinsonism, particularly with myoclonus, speech dysfunction, postural instability and gait disorder (including the "cock walk"), hypersomnolence, and bradyphrenia. Our patient also demonstrated oculomotor dysfunction, in particular, vertical gaze slowing and limitation that have been noted in other disorders in which the globus pallidus is predominantly affected. Magnetic resonance images typically demonstrate the hyperintensities seen on T1-weighted images in our patient. To date, the prognosis of the syndrome is uncertain. Some patients have had mild to modest improvement during long-term follow-up, either spontaneously or after chemotherapy with EDTA. In contrast, as well described in patients with prolonged exposure to high levels of manganese in the workplace (eg, manganese ore miners and alloy plant workers), some have experienced clear progression of neurologic symptoms with time despite cessation of the exposure.

The role of hepatic dysfunction in causing this patient’s neurologic disorder is unclear. Cirrhosis is well known to be associated with increased signal intensity in the basal ganglia on T1-weighted images, presumably related to elevated blood manganese levels, and this is a proposed mechanism for the pathogenesis of acquired heptolenticular degeneration. Recently, Schaumburg et al described a highly exposed worker who developed symptoms and signs of early manganeseism only after the onset of moderate hepatic dysfunction caused by hepatitis C infection. This case illustrates that even asymptomatic hepatic disease can be a risk factor in persons with substantial exposure to manganese. However, the route and quantity of exposure differ considerably between our patient and this case; our patient had relatively intact hepatic synthetic function, and hepatic dysfunction does not seem to have been a predisposing factor in other patients with ephedronic encephalopathy. Our patient abused intravenous methcathinone apparently prepared in the same manner in the early 1990s without neurologic consequences, presumably before development of his current level of hepatitis C-related hepatic dysfunction. The number of persons who have repeatedly abused methcathinone far exceeds the number with this neurologic syndrome. The underlying factors that contribute to the eventual development of this disorder, including variability in the preparation of the drug and the amount of manganese remaining in the solution, the presence of other contaminants, the potential direct toxic effect of methcathinone, or the presence of predisposing systemic illnesses such as hepatic dysfunction, remain to be evaluated.

6-[18F]-Fluorodopa positron emission tomography revealed only a minor reduction in presynaptic uptake limited to the posterior putamen, which suggests that the nigrostriatal dopaminergic system was relatively spared by the pathogenic process. This finding is comparable to results reported in most patients with a toxic reaction to industrial manganese and in monkeys receiving toxic doses of manganese intravenously, but it contrasts with the profound symmetric reduction in caudate and putamen reported in one patient with cirrhosis and parkinsonism partially responsive to levodopa. If this latter experience is confirmed in larger numbers of patients, it suggests that the pathogenesis of parkinsonism complicating cirrhosis may be more complex than simply manganese overload.

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REFERENCES


Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, enrollment will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of Archives of Dermatology (2005;141:76-77). Also see the Instructions to Authors on our Web site: www.archneurol.com.