

ORIGINAL ARTICLE

A Parkinsonian Syndrome in Methcathinone Users and the Role of Manganese

Ainārs Stepens, M.D., Ināra Logina, Ph.D., Viesturs Liguts, Ph.D., Pauls Aldiņš, M.D., Ilze Ekšteina, M.D., Ardis Platkājis, Ph.D., Inese Mārtiņšone, M.Sci., Elmārs Tērauds, M.D., Baiba Rozentāle, Ph.D., and Michael Donaghy, F.R.C.P.

ABSTRACT

BACKGROUND

A distinctive extrapyramidal syndrome has been observed in intravenous methcathinone (ephedrone) users in Eastern Europe and Russia.

METHODS

We studied 23 adults in Latvia who had extrapyramidal symptoms and who had injected methcathinone for a mean (\pm SD) of 6.7 ± 5.1 years. The methcathinone was manufactured under home conditions by potassium permanganate oxidation of ephedrine or pseudoephedrine. All patients were positive for hepatitis C virus, and 20 were also positive for the human immunodeficiency virus (HIV).

RESULTS

The patients reported that the onset of their first neurologic symptoms (gait disturbance in 20 and hypophonia in 3) occurred after a mean of 5.8 ± 4.5 years of methcathinone use. At the time of neurologic evaluation, all 23 patients had gait disturbance and difficulty walking backward; 11 patients were falling daily, and 1 of these patients used a wheelchair. Twenty-one patients had hypophonic speech in addition to gait disturbance, and one of these patients was mute. No patient reported decline in cognitive function. T_1 -weighted magnetic resonance imaging (MRI) showed symmetric hyperintensity in the globus pallidus and in the substantia nigra and innominata in all 10 active methcathinone users. Among the 13 former users (2 to 6 years had passed since the last use), lesser degrees of change in the MRI signal were noted. Whole-blood manganese levels (normal level, <209 nmol per liter) averaged 831 nmol per liter (range, 201 to 2102) in the active methcathinone users and 346 nmol per liter (range, 114 to 727) in former users. The neurologic deficits did not resolve after patients discontinued methcathinone use.

CONCLUSIONS

Our observation of a distinctive extrapyramidal syndrome, changes in the MRI signal in the basal ganglia, and elevated blood manganese levels in methcathinone users suggests that manganese in the methcathinone solution causes a persistent neurologic disorder.

From the Department of Neurology (A.S., I.L.), the Department of Anesthesiology and Intensive Care (V.L.), the Department of Classical Infectology, Tuberculosis, and AIDS (P.A., I.E., B.R.), the Department of Radiology (A.P.), the Institute of Occupational and Environmental Health (I.M.), and the Department of Psychiatry and Addiction (E.T.), Riga Stradins University, Riga, Latvia; and the Department of Clinical Neurology, University of Oxford, Oxford, United Kingdom (M.D.). Address reprint requests to Dr. Donaghy at the Department of Clinical Neurology, University of Oxford, Level 3, West Wing, John Radcliffe Hospital, Headington, Oxford OX3 9DU, United Kingdom, or at joanna.wilkinson@clneuro.ox.ac.uk.

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A PARKINSONIAN SYNDROME HAS BEEN noted in methcathinone users in Russia¹ and in the Baltic states. Methcathinone is a stimulant with euphoric effects, known in Russia as ephedrone and by the street names *cat*, *mul'ka*, and *jeff*. Cathinone, originally derived from the plant khat (*Catha edulis*), has long been used as a psychostimulant; it is known to cause psychoses but not parkinsonism.^{2,3} Methcathinone is manufactured by oxidation of the ephedrine and pseudoephedrine contained in various readily available pharmaceutical agents.^{3,4} This oxidation process is often performed under home conditions. In Russia and Eastern Europe, an intravenous preparation is produced by potassium permanganate oxidation in the presence of acetic acid; in North America, powder for inhalation or nasal insufflation is made by chromate oxidation in the presence of sulfuric acid.

In Latvia, the intravenous methcathinone users with parkinsonism were all positive for the human immunodeficiency virus (HIV). A variety of extrapyramidal disorders are recognized as unusual occurrences in patients with HIV infection and the acquired immunodeficiency syndrome (AIDS).^{5,6} Parkinsonian syndromes have occurred as part of HIV-associated dementia and encephalopathy,⁷⁻⁹ in association with focal opportunistic infections involving the basal ganglia,¹⁰⁻¹² or occasionally, as an isolated manifestation of HIV infection.¹³ Patients with AIDS are especially sensitive to the parkinsonian side effects of neuroleptic medications.⁶ We questioned the role of HIV as the underlying cause of the severe parkinsonian syndrome in our patients after encountering the syndrome in patients who were HIV-negative. Among those with the syndrome who were infected with HIV, less than half had progressed to AIDS, although the movement disorders associated with HIV infection are typically seen in patients with AIDS. Furthermore, the movement disorder we observed was remarkably stereotyped and unlike idiopathic Parkinson's disease,¹⁴ and it was associated with distinctive hyperintensity of the T₁-weighted magnetic resonance imaging (MRI) signal in the globus pallidus. Given these distinctive clinical and imaging characteristics, and knowing that potassium permanganate had been used in the illicit manufacture of methcathinone, we investigated whether the neurologic condition of these patients was due to the toxic effects of manganese.^{14,15}

METHODS

SELECTION OF PATIENTS

Between 2003 and 2006, we identified 23 patients (20 men and 3 women) with an unusual, stereotyped disorder of gait and speech. The first 15 had been identified at the Latvian national infectious disease center because of a distinctive movement disorder associated with known HIV positivity. After initial recognition of this neurologic syndrome, another five patients who were HIV-positive as well as three who were HIV-negative were identified with the syndrome; two of the latter patients were identified by general neurologists and the third was introduced by his friend, a fellow illicit-drug user from the original cohort. All were young adults (mean [±SD] age, 37.5±6.5 years), and the average duration of intravenous methcathinone use was 6.7±5.1 years. Active users were defined as those reporting at least one methcathinone binge within the previous year, and former users were those who reported having discontinued methcathinone use completely more than 1 year previously. Written informed consent was obtained from all patients, and the study was approved by the ethics committee of Riga Stradins University.

ASSESSMENT OF PATIENTS

A detailed neurologic examination was performed by a single neurologist. Posture, speech, and writing were graded as normal or as mildly, moderately, or severely abnormal. All patients were also rated by the Unified Parkinson's Disease Rating Scale (UPDRS),¹⁶ a broad measure of parkinsonian symptoms (range, 0 to 176, with higher scores indicating more severe disability); the Hoehn and Yahr staging system for Parkinson's disease¹⁷ (range, 1 to 5, with higher scores indicating more severe disability); and the Schwab and England Activities of Daily Living Scale¹⁸ (range, 0 to 100; normal score is 100). Seventeen patients were also evaluated by the Mini-Mental State Examination (MMSE)¹⁹ (range, 0 to 30, with higher scores indicating better mental state; scores under 20 indicate marked cognitive disturbance).

All patients underwent tests for HIV and hepatitis C antibodies, CD4 lymphocyte counts, and liver function. In addition, serum ceruloplasmin and copper levels were measured.

MRI was performed with a General Electric 1.0T Signa Horizon LX high-speed system with

head coil and a standardized magnetic resonance examination protocol; sagittal, axial, and coronal T₁-weighted images, axial T₂-weighted images, and coronal fluid-attenuated inversion recovery images were obtained at a 5-mm slice thickness and a 1.5-mm interval. The images were interpreted by a single radiologist who was aware of the clinical syndrome but was uninformed about whether the images were from active or former methcathinone users. T₁-weighted signals in the globus pallidus, substantia nigra and substantia innominata, and anterior midbrain were graded as normal or as mildly (signal intensity equivalent to that of the internal capsule), moderately, or severely (signal equivalent to that of fat) abnormal.

Blood samples were collected in lithium heparin and immediately frozen at -18°C until analysis. Whole blood was broken down in a closed system with a microwave apparatus (MARS 5, CEM), with 2 ml of blood added to 4 ml of 65% (vol/vol) nitric acid (Merck) and 2 ml of 30% (vol/vol) hydrogen peroxide (Merck). The samples were mineralized at 1200 W for 15 minutes.²⁰ Manganese was measured by graphite furnace-atomic absorption spectrometry. The samples were injected into a Zeeman spectrometer (SpectrAA 220Z, Varian) (wavelength, 279.5 nm; lamp current, 5.0 mA; slit width, 0.2 nm; 10- μ l matrix modifier) and analyzed with Zeeman-effect background correction.²¹ The recognized upper limit of normal for manganese was 209 nmol per liter.²²

RESULTS

TIMING OF METHCATHINONE USE AND ONSET OF FIRST NEUROLOGIC SYMPTOMS

There was wide variation in the duration of methcathinone use before formal clinical diagnosis of the disorder (Table 1). The variation could be accounted for by different frequencies and intensities of use, presumed variations in the methcathinone solution, and delayed initial recognition of the syndrome. On the basis of the history provided by the patients, the first neurologic symptoms were estimated to have developed an average of 5.8 \pm 4.5 years after the start of methcathinone use. The initial symptom was gait disturbance in 20 patients (87%) and hypophonia in 3 (13%) (Table 1).

NEUROLOGIC EXAMINATION

All patients showed a characteristically impassive face and generally slowed movement or speech reactions. No patient had resting tremor of the hands. Voluntary facial movements and voluntary and reflex palatal movements were normal in all patients. No jaw, palmomentary, or pout reflexes were present in any patient. None had loss of upward gaze or axial rigidity. No patient reported a decline in intellectual function. Of the 17 patients who were assessed by the MMSE, 16 had normal scores and 1 had a score of 18 that was thought to reflect a low level of literacy and low intellectual background from childhood. The other six patients showed no evidence of intellectual decline during clinical evaluation or UPDRS testing. UPDRS scores ranged from 22 to 59 (average, 40 \pm 12) (Table 1). No patient had notable impairment in the UPDRS domains measuring mental activity, behavior and mood, salivation, gait freezing, tremor, sensory complaints, or rigidity. The average Hoehn and Yahr stage of Parkinson's disease was 3.4 \pm 0.8, and the average Schwab and England Activities of Daily Living score was 58 \pm 18.

Twenty patients (87%) showed a slight forward tilt of the trunk from the hips on standing but did not have a hunched shoulder posture. Twenty-one patients (91%) held their arms slightly abducted from the sides when walking, with reduction or loss of arm swinging. Nineteen patients (83%) tended to walk on the balls of the feet when walking forward, seemingly falling forward into the next stride, and sometimes with mild dystonic inversion of the ankle of the free leg during a stride. When attempting to turn, 21 patients (91%) frequently took a corrective step sideways to preserve balance. Nineteen patients (83%) sat down from a standing position by deliberately placing themselves in front of the seat and gently flexing their knees until they fell backward. The most severe gait abnormality was evident when the patients walked backward, which resulted in falling in 19 patients (83%). Four patients were able to walk backward without falling by using very short and uncertain steps. At diagnosis, 11 patients (48%) reported falling at least once daily. One of these 11 patients was unable to walk independently and used a wheelchair; he found it difficult to reverse his wheelchair by hand, despite being able to propel it forward normally.

Table 1. Characteristics of the Patients Stratified According to Duration of Use of Methcathinone for Active Users and Duration of Cessation for Former Users.*

Patient No.	HIV Status†	Age at Onset of Symptoms	Duration of Use	Duration of Symptoms	Duration of Cessation	Clinical Severity				Assessment Scores			Manganese‡	Hyperintensity on T ₁ -Weighted MRI§		
						Gait	Speech	Writing	UPDRS¶	Hoehn and Yahr	Schwab and England ADL**	MMSE††		Globus Pallidus	Substantia Nigra and Substantia Innominata	Anterior Midbrain
Active users																
1	AIDS	44	20	3		Severe	Moderate	Severe	46	4	50	28	396	Moderate	Mild	
2	AIDS	43	17	2		Severe	Severe	Moderate	46	5	30	29	1326	Moderate	Mild	
3	Positive	31	11	4		Severe	Moderate	Moderate	33	3	70	27	2102	Severe	Severe	
4	AIDS	39	7	6		Moderate	Moderate	Normal	32	3	60	28	221	Moderate	Mild	
5	Positive	34	6	0		Moderate	Moderate	Mild	38	3	70	25	423	Moderate	Mild	
6	Positive	20	5	3		Moderate	Moderate	Mild	31	3	80	ND	1751	Mild	Normal	
7	Positive	33	4	1		Moderate	Moderate	Moderate	23	3	80	29	1074	Severe	Severe	
8	Negative	31	4	1		Severe	Moderate	Severe	51	4	40	25	201	Moderate	Mild	
9	Positive	37	3	1		Moderate	Moderate	Mild	36	3	60	ND	456	Severe	Mild	
10	AIDS	38	1	1		Mild	Mild	Mild	28	3	80	ND	356	Moderate	Moderate	
Former users																
11	Positive	43	11	3	2	Severe	Severe	Moderate	58	4	50	24	265	Mild	Mild	
12	Positive	31	12	3	2	Severe	Severe	Moderate	58	4	60	26	413	Normal	Normal	
13	AIDS	30	5	2	2	Moderate	Moderate	Mild	51	3	60	18	620	Normal	Normal	
14	AIDS	36	3	3	2	Severe	Severe	Moderate	59	4	30	28	310	Severe	Moderate	
15	AIDS	38	5	2	2	Severe	Severe	Moderate	37	4	40	25	300	Normal	Normal	
16	Negative	29	1	3	3	Severe	Severe	Severe	52	5	30	ND	308	Normal	Normal	
17	Positive	40	10	4	3	Moderate	Moderate	Severe	47	4	30	24	114	Normal	Normal	
18	AIDS	35	3	3	3	Severe	Severe	Moderate	45	3	60	30	356	Normal	Normal	
19	Positive	27	9	3	3	Mild	Mild	Mild	28	3	60	27	272	Normal	Normal	
20	Negative	28	1	3	3	Moderate	Moderate	Moderate	39	4	50	28	290	Normal	Normal	
21	Positive	29	1	4	4	Severe	Severe	Severe	37	3	80	ND	727	Normal	Normal	
22	AIDS	40	6	5	5	Mild	Normal	Normal	22	2	80	ND	211	Normal	Normal	
23	Positive	40	9	6	6	Mild	Normal	Normal	23	2	80	26	317	Normal	Mild	

* ADL denotes activities of daily living; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; MMSE, Mini-Mental State Examination; ND, not done; and UPDRS, Unified Parkinson's Disease Rating Scale.
 † Patients are classified according to stage of HIV infection, categorized either as AIDS (including grades A3, B3, C1, C2, and C3 according to the Centers for Disease Control and Prevention [CDC] classification²³) or as HIV-positive without AIDS (including grades A1, A2, B1, and B2 according to the CDC classification).
 ‡ Normal values for manganese are less than 209 nmol per liter.
 § T₁-weighted signals were graded as normal or as mildly (signal intensity equivalent to that of internal capsule), moderately, or severely (signal equivalent to that of fat) abnormal.
 ¶ Scores on the UPDRS¹⁶ range from 0 to 176, with higher scores indicating more severe disability.
 || Scores on the Hoehn and Yahr staging system for Parkinson's disease¹⁷ range from 1 to 5, with higher scores indicating more severe disability.
 ** Scores on the Schwab and England ADL Scale¹⁸ range from 0 to 100; the normal score is 100.
 †† Scores on the MMSE¹⁹ range from 0 to 30, with higher scores indicating better mental state and scores under 20 indicating marked cognitive disturbance.

No patient demonstrated weakness or lead-pipe rigidity, and plantar responses were normal in all patients. Ankle-tendon jerks were lost in six patients (26%), all of whom had a history of chronic excessive alcohol consumption. Rapidly alternating finger-thumb opposition was slightly bradykinetic and was markedly reduced in amplitude in 15 patients (65%). Seventeen patients (74%) performed rapidly alternating pronation and supination of the forearm with a characteristic abduction-adduction winging movement at the shoulders. Complex arm movements tended to be decomposed into a sequence of individual component movements.

Of 21 patients (91%) who had speech disturbance, 20 had low volume. Eight (35%) had difficulty communicating with speech; one was mute (but was able to communicate by pointing to letters of the alphabet), and seven were difficult to understand. The speech disorder in these 21 patients was not the typical "hot potato" speech of persons with a pseudobulbar dysarthria or a cerebellar disorder involving scanning dysarthria. Of all 23 patients, 19 (83%) were able to enunciate individual consonants but were slow in switching between a sequence of consonants (e.g., "p" to "b" to "m" or "l" to "g" to "k"), although they eventually sounded each individual consonant accurately. Four patients (17%) had mild difficulty swallowing.

Twenty patients (87%) had difficulty with handwriting. Fourteen of these patients (70%) had moderate to severe micrographia, with progressively deteriorating micrographia within each word, and six (30%) had uniform micrographia.

HIV AND HEPATITIS C VIRUS

Of 20 HIV-positive patients (Table 1), 9 had AIDS according to the Centers for Disease Control and Prevention classification,²³ and 7 were asymptomatic with normal CD4 counts. All patients were positive for hepatitis C virus. Hepatic alanine aminotransferase levels were mildly elevated in 13 patients (less than three times the upper limit of normal) and moderately elevated in 1 (less than six times the upper limit of normal). Serum alkaline phosphatase was measured in 22 patients and was mildly elevated in 2 (less than one time the upper limit of normal), serum albumin (measured in 22 patients) was borderline low in 2 (more than 70% of the lower limit of normal), and prothrombin levels (measured in 16 patients) and

hepatic ultrasonography results (obtained in 11 patients) were normal. No patient had jaundice or was clinically judged to have portal hypertension. Two patients underwent hepatic biopsy, which showed chronic active hepatitis but no cirrhotic changes.

MANGANESE AND COPPER LEVELS

Whole-blood manganese levels were elevated above the normal range in 9 of the 10 patients who reported active methcathinone use (mean, 831 nmol per liter; range, 201 to 2102) (Table 1). The levels in the 13 patients who reported cessation of methcathinone use were lower than those in the active users (mean, 346 nmol per liter; range, 114 to 727), and 1 of these patients had a normal manganese level. Ceruloplasmin levels were normal in all patients, and copper levels were mildly elevated in six (range, 24.5 to 31.5 μ mol per liter [156 to 391 μ g per deciliter]; upper limit of normal, 24.4 μ mol per liter [155 μ g per deciliter]).

MRI

All but two patients had increased bilateral and symmetric T₁-signal intensity in the globus pallidus (Fig. 1 and Table 1). All 10 active methcathinone users had hyperintensity of the globus pallidus, and 9 of the 10 also had hyperintensity of the substantia nigra and innominata and of the anterior midbrain. Of the 13 who reported discontinuation of methcathinone, 11 had hyperintensity of the globus pallidus, which was generally less severe than that in active users, with residual changes in the substantia nigra in 2 and the anterior midbrain in 3. No signal abnormalities were noted on T₂-weighted images. No other abnormalities were seen on MRI.

CHANGES AFTER STOPPING USE OF METHCATHINONE

Thirteen patients reported cessation of methcathinone use for 2 to 6 years. Some of these patients had stopped using methcathinone because they were in custody or a long-term health care facility or had motor impairments that made them unable to inject. None noted substantial improvements in gait or speech after cessation. Their average blood manganese levels were markedly lower and their MRI changes were less frequent and intense than those of active users (Table 1). We were able to examine MRI scans from four former users that were obtained while the patients

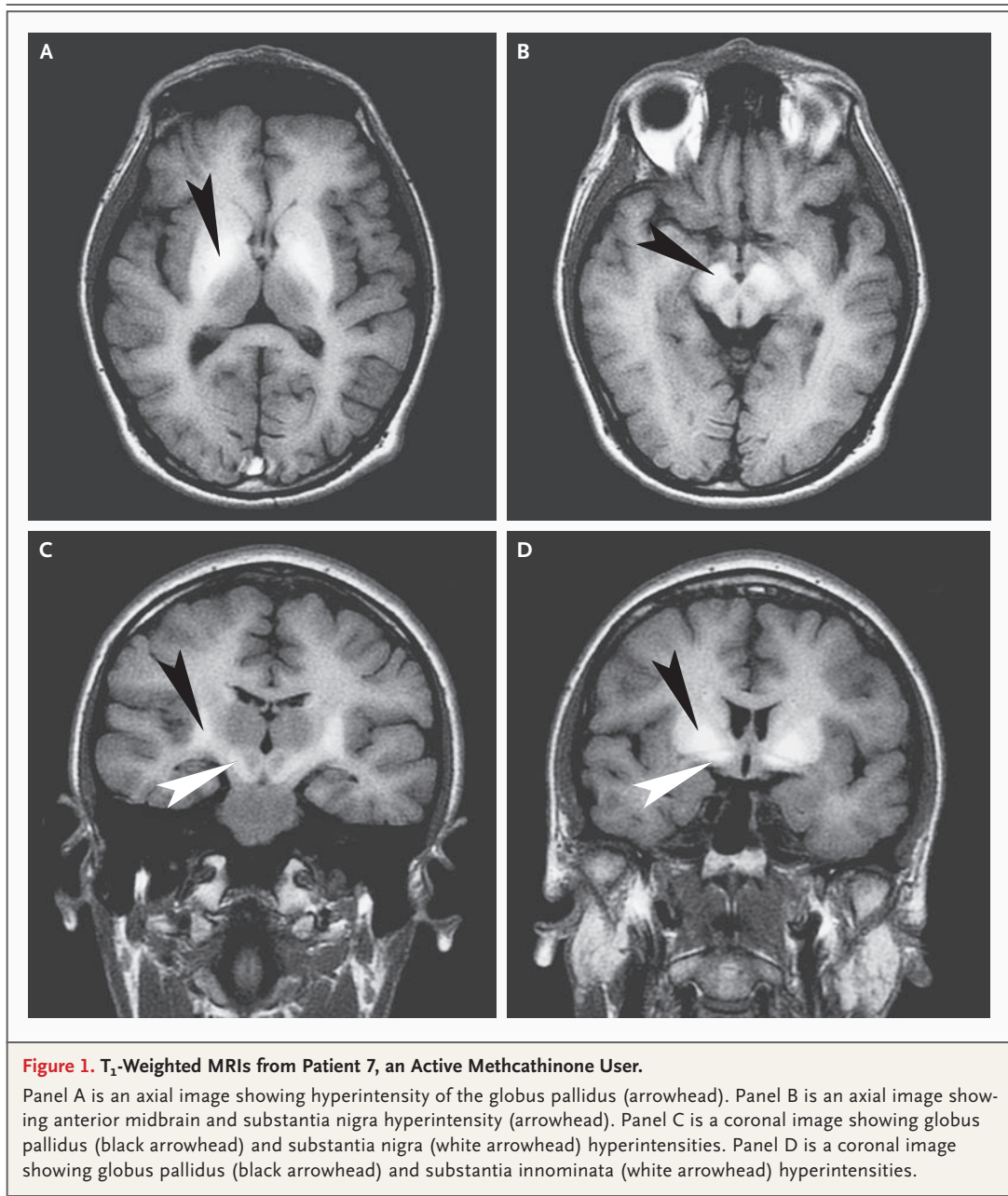


Figure 1. T₁-Weighted MRIs from Patient 7, an Active Methcathinone User.

Panel A is an axial image showing hyperintensity of the globus pallidus (arrowhead). Panel B is an axial image showing anterior midbrain and substantia nigra hyperintensity (arrowhead). Panel C is a coronal image showing globus pallidus (black arrowhead) and substantia nigra (white arrowhead) hyperintensities. Panel D is a coronal image showing globus pallidus (black arrowhead) and substantia innominata (white arrowhead) hyperintensities.

were still actively using methcathinone; in all four patients, the original globus pallidus hyperintensities faded or disappeared with time (Fig. 2).

THERAPY

Administration of levodopa in three patients produced no observable or symptomatic change in the movement disorder. In one patient with onset of symptoms 2 months previously, chelation therapy with three administrations of parenteral cal-

cium diethylenetriamine pentaacetic acid over a period of 6 days produced a 28% reduction in the blood manganese level without any change in the movement disorder.

DISCUSSION

The distinctive extrapyramidal movement disorder observed in 23 Latvian intravenous methcathinone users was typical of manganese poisoning.

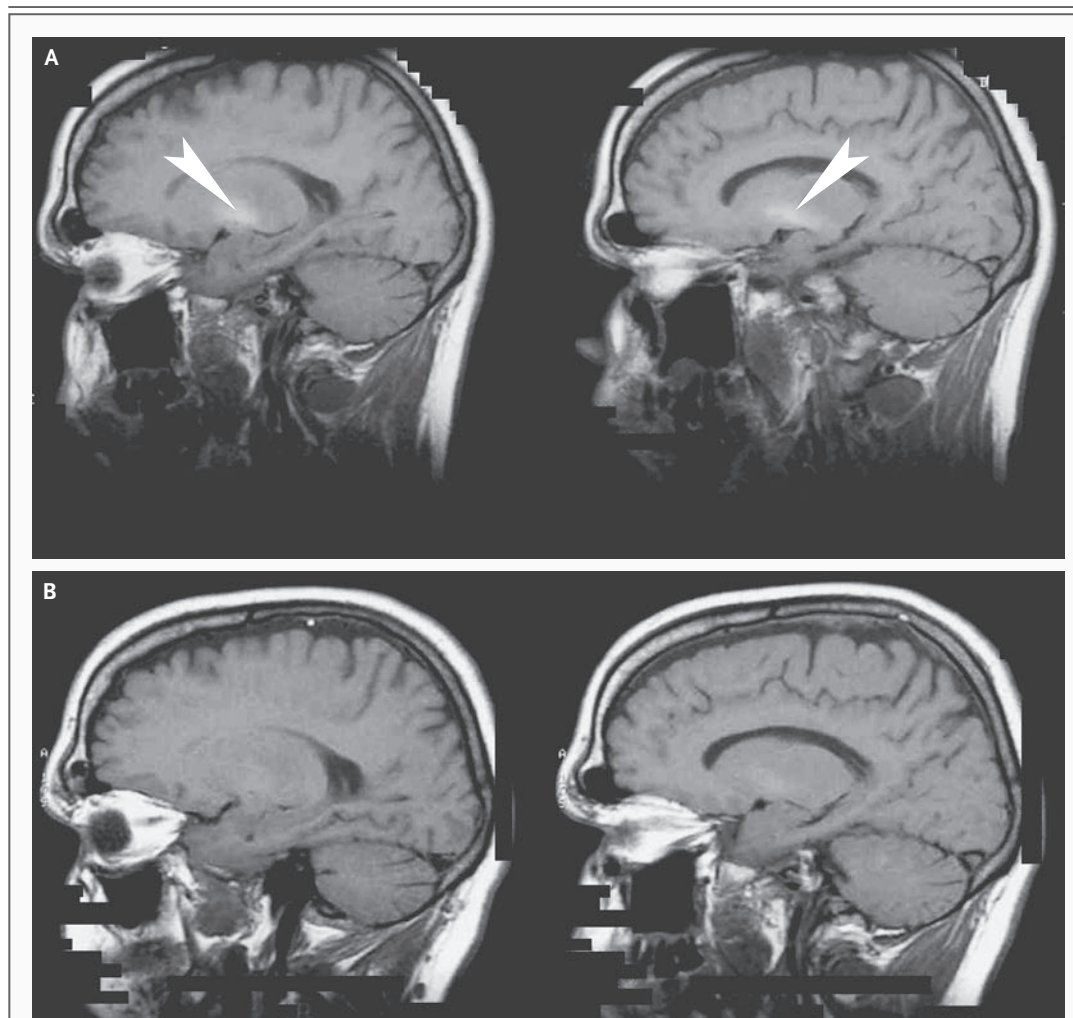


Figure 2. Sequential T₁-Weighted Parasagittal MRIs from Patient 21.

The images in Panel A are from the patient as an active methcathinone user, and those in Panel B are from the patient 14 months after cessation of use. Globus pallidus hyperintensity (arrowheads) faded after cessation of methcathinone use, a change that persisted at 28 months (not shown).

Unlike patients with typical Parkinson's disease, but like welders and workers in the metal industry who have toxic effects of manganese, these patients did not have tremors during rest, had particular difficulty with backward motion, had a symmetric motor disorder, fell frequently, walked on the balls of the feet with a typical "cock walk," had profoundly soft speech, and did not respond to treatment with levodopa.^{14,15,24-28} This extrapyramidal disorder in methcathinone users was strikingly stereotyped, unlike the often milder and more varied disorder noted in welders and metal workers.^{14,29,30}

Most of the patients had elevated blood manganese levels, and the levels were particularly high in many of the active methcathinone users. MRI T₁-weighted image hyperintensity in the basal ganglia, principally the globus pallidus, is distinctive in cases of manganese toxicity,^{14,15,29,31} and was present in all active users. Such changes were less intense or absent in patients who had ceased to use methcathinone, a finding in keeping with observations that this signal change tends to fade after the patient is removed from occupational exposure.²⁹ Similar signal changes in the globus pallidus have been noted in patients with

chronic hepatic disease that is associated with increased manganese concentrations in the basal ganglia,^{32,33} changes that can be associated with an extrapyramidal movement disorder.³⁴ Such MRI changes resolve after successful liver transplantation, in keeping with improvement in the extrapyramidal disorder.^{35,36} Even though their MRI findings improved or resolved with cessation of methcathinone use, our patients' neurologic condition remained unimproved, a result implying that permanent neuronal damage remained despite resorption of manganese from the basal ganglia.

The source of the manganese underlying the neurotoxic effects in these patients was presumably the potassium permanganate used in the process of oxidizing ephedrine or pseudoephedrine to form methcathinone. Such syntheses often take place in the uncontrolled conditions of home laboratories, and the base drug may vary, with the result that the residual supernatant contains inorganic manganese, which is then injected intravenously. This methcathinone is not isolated in a purified form, and the injected solution is known to contain potassium permanganate and acetic acid. This parenteral route of manganese administration, in the form of the strong oxidizing agent permanganate, differs from the previously described inhalational route of exposure to manganese dust or fumes, mainly as manganese oxides.^{28,37} Toxic effects have been reported in a patient after administration of intravenous manganese during total parenteral nutrition, with an extrapyramidal syndrome and similar MRI abnormalities.³⁸ It is not known to what extent the strong oxidizing capability of permanganate contributed to the neuronal damage underlying the stereotyped clinical syndrome in these methcathinone users. It is possible that the amphetamine-like effects of methcathinone, particularly its stimulation of dopaminergic terminals,³⁹ may

have enhanced the toxic effect of manganese on the basal ganglia.

No cogent alternative diagnosis to manganese toxicity is evident to explain this movement disorder. The disorder does not have the clinical signs of idiopathic Parkinson's disease or the axial rigidity or gaze palsy of progressive supranuclear palsy (the Steele-Richardson-Olszewski syndrome). The disorder also lacks the clinical signs, the abnormalities in copper and ceruloplasmin levels, and the MRI abnormalities of Wilson's disease. Parkinsonian movement disorders occasionally occur in patients with HIV infection, usually those with HIV-associated dementia or opportunistic infections of the central nervous system,^{6,8,10} and are only rarely an isolated manifestation of HIV infection.¹³ These methcathinone users did not have the clinical features or MRI findings of such patients; further, three were HIV-negative and more than half did not have AIDS, which is normally associated with such disorders. Infection with hepatitis C virus, which was present in all our patients, is not associated with extrapyramidal disorder. Liver failure, which increases susceptibility to manganese poisoning, a circumstance that underlies the development of symptomatic toxicity in an occupational inhalational setting⁴⁰ and that is permissive of manganese toxicity in cirrhosis,^{33,34} was not present in our patients.

We describe a neurologic disorder in illicit-drug users that probably resulted from contaminants resulting from poorly controlled processes of synthesizing the drug. Our findings highlight the unanticipated and serious health consequences that can arise from chemical modification of easily available pharmaceutical agents.

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