Manganic Encephalopathy Due to “Ephedrone” Abuse

Yanush Sanotsky, MD, 1,* Roman Lesyk, PharmD, PhD, 2 Lyudmyla Fedoryshyn, MD, PhD, 1 Iryna Komnatska, MD, 3 Yurii Matviienko, MD, PhD, 4 and Stanley Fahn, MD 5
1 Department of Neurology, Lviv Regional Clinical Hospital, Lviv, Ukraine 2 Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halutsky Lviv National Medical University, Lviv, Ukraine 3 Department of MRI, Central Hospital of the Lviv Regional Railway, Lviv, Ukraine 4 Department of Neurology, Danylo Halutsky Lviv National Medical University, Lviv, Ukraine 5 Department of Neurology, Columbia University Medical Center, New York, New York, USA

Abstract: We describe the clinical and neuroimaging features of 6 drug-abuse patients with self-inflicted manganese poisoning. The patients injected a home-brewed mixture called “ephedrone” (slang term) that contained manganese to produce an amphetamine-like euphoria. The desired chemical product, phenylpropanoneamine (also called methcathomine), was synthesized from a common-cold–remedy compound using permanganate as the catalyst. Manganese was a by-product in the ephedrone mixture. After months of self-injections, a clinical picture emerged, consisting of apathy, bradykinesia, gait disorder with postural instability, and spastic-hypokinetic dystasia. There was no response to levodopa. The MRI revealed symmetric hyperintense T1-weighted signals in the basal ganglia, typical of manganese accumulation. © 2007 Movement Disorder Society

Key words: manganese poisoning; manganic encephalopathy; ephedronic encephalopathy; parkinsonism; drug-addiction.

*Correspondence to: Dr. Yanush Sanotsky, Department of Neurology, Lviv Regional Clinical Hospital, Nekrasova St. 6/8, Lviv 79010, Ukraine. E-mail: janush_s@yahoo.com

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LEGENDS TO THE VIDEO

Segment 1. The video shows the patient walking at different speeds before and after receiving 200 mg levodopa.

Segment 2. The first sequence was taken after a 30-min walk without levodopa. Notice the clumsy movement of the left leg and the transient action-induced bending of the trunk forward and to the left. Depending on the walking speed, inward rotation of the left leg and supination of the left foot develop.

Segment 3. The following sequences show the patient after receiving 200 mg levodopa. Shortly after the start (second sequence), minor residual symptoms are present with a clumsy left leg and a slight bending of the trunk. After a 30-min walk (third sequence), dystonic symptoms increase again.

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Manganese is an essential element for biologic function, but excessive exposure can be toxic, particularly to the central nervous system. The most common manifestation of manganese neurotoxicity is a parkinsonian syndrome with features of dystonia. Only 20 years after James Parkinson’s essay appeared, Couper described a syndrome similar to Parkinson’s disease in 5 patients who worked in a manganese ore-crushing plant. During the past 80 years there have been a number of similar reports on manganism, some with dystonia as the predominant movement disorder. Because manganese is usually absorbed into the human body by oral and respiratory routes in the form of dust, the majority of cases of manganism have been reported in underground miners, alloy plant workers, and other individuals exposed occupationally. Other sources of manganese intoxication are now recognized, including total parenteral nutrition in hospitalized patients and exposure to manganese-containing pesticides in agricultural workers. It was also suggested that parkinsonism in patients suffering from chronic liver disease is related to the accumulation of manganese in the basal ganglia due to impaired hepatic manganese metabolism.

Patients with a new cause of manganese poisoning—drug-abuse—have been reported in the Russian and Ukrainian literature, and the disorder was called “ephedronic” encephalopathy. The clinical picture consisted of spastic-hypokinetic dysarthria, postural instability with falling, “cock-gait,” parkinsonian signs (hypokinesia, hypomimia, cogwheel rigidity), bradyphrenia, hypersomnia, and myoclonus. The T1-weighted MRI demonstrated an increased signal in the globus pallidus and substantia nigra. The patients did not respond to levodopa. The abused material is home-made and injected intravenously to obtain the desired effect of an amphetamine-like “high” of euphoria, and often sexual arousal.

The starting materials for the preparation of the injected mixture are readily available commercial cold-remedy compounds containing phenylpropanolamine. Acetic acid and KMnO₄ (potassium permanganate) are added to create an oxidation reaction (see Fig. 1), with the main product being phenylpropanoneamine, also called methcathinone. During the reaction, as a side product, Mn²⁺ ions are formed, the probable cause of the akinetic-rigid encephalopathy. The chemical mixture is not purified before it is self-injected. The colloquial slang term for the mixture is “ephedrone,” hence the original reports of the syndrome being called “ephedronic” encephalopathy. Other slang terms for the mixture are “jaff” and “mul’ka.”

CASE REPORTS

In the Department of Neurology of Lviv Regional Clinical Hospital (Lviv, Ukraine) we evaluated 6 patients who presented with a hypokinetic syndrome after having injected themselves over a period of time ranging from 2 months to 2 years with the above-mentioned chemically prepared ephedronic mixture. All patients underwent general clinical investigations, including complete blood count, ESR, electrolytes, renal and hepatic function tests, VDRL test, ECG and abdominal sonography. All of these tests were normal, and no signs of extraneural disorder were detected.

Patient 1

In 2003 this 38-year-old man began to prepare and use ephedrone with a frequency of 1 to 2 times/day because he had a social-situational depression. In 2004 he began having speech and gait disturbances, frequent falling, increased appetite and apathy. After symptoms of slowness developed, he ceased using the drug without signs of withdrawal. He sought medical attention and was seen by us. Examination revealed hypothymia, with lack of initiative, but also inappropriate lack of worry about his ailment. Memory and intellect were preserved, but he did not ask spontaneous questions and showed no interested in his laboratory results or treatment. He did read during his stay in the hospital. We observed low verbal activity, diminished attention, and simplified reasoning. He described impotence. There was facial seborrhea.

Neurological examination revealed hypomimia, speech characterized as a spastic-hypokinetic dysarthria, hypophonia, preserved swallowing, moderate hypokinesia, and symmetric rigidity of the arms, legs and trunk. There was no arm swing, but his steps were normal when he walked with support. He was unable to walk independently because of marked postural instability with retro-
pulsion and falling. There was slight dystonic rotation of the feet during walking.

He was treated with amantadine, intravenous infusions of calcium EDTA, and intravenous injections of Cerebrolysin. (Cerebrolysin is produced by enzymatic breakdown of purified brain proteins and consists of low-molecular-weight peptides and amino acids.) After 3 months, there was an increase in his emotional affect and his motor activity, and he was able to walk with a cane. A trial of levodopa was without effect and was stopped (see Results).

**Patient 2**

This 23-year-old man had been injecting ephedrone daily for half a year in 2000. We observed and treated him over the next 3 years. Examination revealed marked psychomotor depression with periodic explosions. He required verbal stimulation to become active. He talked little and had diminished attention, simplified reasoning, and bradyphrenia. Autonomic features included impotence and seborrhea.

Neurological examination revealed facial hypomimia, soft voice with monotonous fading speech, spastic-hypokinetic dysarthria, dysphagia, dystonic smile, hypokinesia, rigidity, and marked gait disturbances—cock-gait, twisting feet, no arm swing, postural instability with frequent falling, retropulsion, and lateral falling. He was unable to walk independently without falling.

After treatment with calcium EDTA, amantadine, and Cerebrolysin, the general status of the patient improved. There was increased psychomotor activity, and he began to make contact with the external environment and to talk more readily. He was able to walk independently without support. However, retropulsion, postural instability, and dystonia of the feet were unchanged.

**Patient 3**

This 29-year-old woman had been using 2 to 3 g of ephedrine every other day for 2 months in 2003. She stopped the injections after the appearance of slowness of movement. A withdrawal reaction did not occur. She experienced total loss of the interest in her job, family, and external environment. Examination revealed the patient to be highly emotional during conversation and with impaired memory. She failed to understand the serious nature of her problem.

Neurological examination revealed moderate hypomimia, spastic-hypokinetic dysarthria, dysphagia, hyperorality, slowed movements, cogwheel rigidity, and micrographia. On walking, there was moderate postural instability with retropulsion and left-sided falling.

She was treated with calcium EDTA, amantadine, and Cerebrolysin without improvement.

**Patient 4**

In 2003 to 2004 this 28-year-old man used ephedrine 1 to 2 times/month. He stopped it when he developed slowness of movement, and there were no symptoms of dependence or withdrawal effect.

Examination revealed normal emotional reactions to verbal contact and responses to questions, but there was low spontaneous verbal activity, inadequate self-assessment, and euphoria. The patient complained of speech disturbances (“sticking”), with inability to say the letters “k” and “r.” Autonomic features included impotence and seborrhea.

Neurological examination revealed dysarthria, slow speech, preserved swallowing, and dystonic smile. Walking was mostly intact, but sometimes he retropulsed. There was postural instability.

He was treated with calcium EDTA, amantadine, and Cerebrolysin, without improvement.

**Patient 5**

This 28-year-old man began injecting ephedrine once daily for half a year in 2003. In February 2004 he suddenly developed hyperthermia and sought medical attention. Examination revealed no initiation of spontaneous speech. He showed no interest to his state and responded only briefly to questions. He did not connect with people around him, and remained uninterested in his treatment.

Neurological examination revealed hypomimia, dystonic smile, hardly understandable, fading, and tremulous speech, elements of dysphagia, marked postural instability, disturbed gait, and falling backwards.

He was treated with calcium EDTA, amantadine, and Cerebrolysin, without improvement.

**Patient 6**

This 45-year-old man had been injecting ephedrine for 5 months in 2003 during imprisonment. Suddenly he developed joint aches, gait disturbances, speech disturbance, depression, and suicidal ideation.

Examination revealed him to be emotionally active and responsive to questions, but with low spontaneous verbal activity. His memory and intellect was preserved.

Neurological examination revealed spastic-hypokinetic dysarthria, postural instability, emotional lability, and bradyphrenia.
He was treated with calcium EDTA, amantadine, and Cerebrolysin. His speech slightly improved (during reading aloud, but not in spontaneous conversation), and there was improved postural stability, although there was still relatively frequent falling.

RESULTS

Analysis of our 6 cases demonstrated no relation between clinical symptoms and duration of drug usage. Frequency of injections was 1 time/week (2 patients), 3 times/week (2 patients), and 7 times/week (2 patients). In all cases the source of phenylpropanolamine to produce ephedrine was Coldact® (Ranbaxy Laboratories, India). A single injection of the ephedrine mixture was 10 ml. Occurrence of symptoms and their severity did not depend on the age of the patients, but all were young to middle-age adults. All of them had practically identical signs. Distribution of these signs at the time of admission is shown in Table 1.

The MRIs of the brain showed a striking bilaterally symmetric increased signal in selected regions on T1-weighted scans. These regions are the lentiform nucleus, substantia nigra, and the dentate nucleus in the cerebellum, as seen in Patient 4 (Fig. 2a–d). Similar increased signals have been reported in other cases of manganese intoxication.12,18 Patient 4 underwent MRI within 1 month after the last injection of ephedrine. In contrast, Patient 2, who had an almost identical clinical picture, underwent MRI 2.5 years after the last injection of ephedrine (Fig. 3a–d). The marked difference in the scans, with the latter patient showing much less increased T1 signal, suggests that there could be elimination of Mn2+ from the brain while residual neurologic impairment remains.

The semiquantitative intensities of the signal amplification on the T1-weighted scans in the different brain regions in all 6 patients are shown in Table 2. The most consistent regions with the greatest signal intensity are the globus pallidus and substantia nigra.

Treatment was empirical, but EDTA is a standard treatment for heavy metal poisonings. Mild to moderate improvement was observed in 4 patients, while no improvement was seen in the other two. Whether the improvement seen was due to any of the agents or just cessation of the self-administered ephedrine mixture cannot be stated. The semiquantitative degree of clinical

TABLE 1. Distribution of the symptoms among the 6 investigated patients at the time of admission to hospital

<table>
<thead>
<tr>
<th>Neurologic sign</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysarthria</td>
<td>6</td>
</tr>
<tr>
<td>Gait disturbances</td>
<td>4</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>5</td>
</tr>
<tr>
<td>Postural instability</td>
<td>6</td>
</tr>
<tr>
<td>Autonomic signs</td>
<td></td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>1</td>
</tr>
<tr>
<td>Impotence</td>
<td>5</td>
</tr>
<tr>
<td>Seborrhea</td>
<td>6</td>
</tr>
<tr>
<td>Cognitive dysfunctions</td>
<td>6</td>
</tr>
<tr>
<td>Emotional lability, apathy, lack of spontaneity</td>
<td>6</td>
</tr>
</tbody>
</table>

FIG. 2. T1-weighted MRIs in Patient 4. Increased signals are seen in the substantia nigra (2a,d), dentate nucleus (2a), and lentiform nucleus (2b–d).

FIG. 3. T1-weighted MRIs in Patient 2. The increased signals seen in substantia nigra (3c), dentate nucleus (3a), and lentiform nucleus (3a–d) are much less than those seen in Patient 4 (Fig. 2a–d).
improvement with regard to particular signs and symptoms is presented in Table 3. Hypokinesia improved in 3 patients, gait in 3, speech in 2, while none had an improvement in postural instability.

Because drug addicts who injected themselves with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) developed parkinsonism which responded to low doses of levodopa, we evaluated the effect of levodopa in our patients. All 6 patients were given carbidopa/levodopa (37.5/100 mg) 3 times daily for 10 days; there was no effect. Although this low dose was given as a test during hospitalization, we initiated chronic levodopa therapy after the patients were discharged from the hospital. The patients continue to receive carbidopa/levodopa (37.5/150 mg) 3 times per day.

**DISCUSSION**

Although reports on the neuropathology of chronic manganese poisoning are rare, Canavan and colleagues observed shrinkage, neuronal degeneration, and gliosis of the basal ganglia in 1 postmortem case. Yamada and colleagues showed that the predominant degeneration involved the medial globus pallidus in another case. In experimental primates, manganese poisoning caused degeneration of the basal ganglia, particularly in the globus pallidus and substantia nigra reticulata.

Because manganese is paramagnetic, signal changes compatible with lack of involvement of dopaminergic nigrostriatal neurons and dopamine deficiency. This would explain lack of response to levodopa, and supports the concept that postdopaminergic lesions, such as the pallidum, are responsible for the parkinsonian syndrome seen in manganic encephalopathy.

Besides manganese, increased signal on T1-weighted MRI-scans can be caused by accumulation of fat, mela-

### Table 2. Semiquantitative analysis of the intensity of signal amplification on T1-weighted MRI scans in different brain regions

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Globus palidus</th>
<th>Putamen</th>
<th>Substantia nigra</th>
<th>Dentate nucleus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>+++++</td>
<td>-</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>+++++</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>+++++</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
</tr>
</tbody>
</table>

### Table 3. Semiquantitative degree of clinical improvement with regard to particular signs and symptoms

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysarthria</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gait disturbances</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
</tr>
<tr>
<td>Postural instability</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Autonomic features</td>
<td>+/−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Depression</td>
<td>++</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>
medications remain equally unproven. The primary therapy remains removing the patient from manganese exposure and preventing further exposure.

The 21 cases of so-called ephedronic encephalopathy reported by Levin et al.13,14 and our own 6 cases add another cause of manganese encephalopathy. That the encephalopathy from self-injections of the ephedrine mixture is due to the manganese in the mixture is supported by the typical clinical picture of manganism and the typical symmetric MRI appearance of increased T1-weighted signals in the lentiform and other nuclei. In both Levin’s14 and our series of cases, some improvement in symptoms occurred in some patients, whether spontaneously or because of chelation therapy is uncertain. Some differences were seen between our cases and those of Levin’s,13,14 in that he reported myoclonus and hypersomnia, while we did not see these in our patients. Because MPTP toxicity and ephedronic encephalopathy were observed among drug-addicts, it is interesting to compare the two disorders, both of which cause a parkinsonian syndrome.19 Because the euphoria-producing substances of abuse are different, the early behavioral alterations appear to differ in the two conditions. The pathologic changes also are different, with MPTP damaging dopaminergic neurons and manganese, the postdopaminergic neurons. A tabulation of the clinical differences between these two types of drug-addict-induced parkinsonism is presented in Table 4. Therapeutic response to dopaminergic agents characterizes MPTP intoxication, whereas these do not have any obvious benefit in ephedronic encephalopathy.

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REFERENCES


GAD Antibody Positive Paraneoplastic Stiff Person Syndrome in a Patient with Renal Cell Carcinoma

John C. McHugh, MRCPI,* Brian Murray, MD,† Radhakrishnan Renganathan, MRCPI,‡ Sean Connolly, FRCPI,§ and Tim Lynch, FRCP†

1Department of Neurology, Mater Misericordiae University Hospital, Dublin, Ireland; 2Department of Clinical Neurophysiology, St Vincent’s University Hospital, Elm Park, Dublin, Ireland

Abstract: Stiff person syndrome (SPS) is an unusual cause of muscle rigidity and spasms. It is believed to have an autoimmune pathogenesis and is associated with autoantibodies to glutamic acid decarboxylase (GAD). Paraneoplastic SPS (PSPS) has been described mainly in relation to breast cancer and is associated with antibodies to amphiphysin. Few reports of PSPS document the finding of GAD autoantibodies. We present the first reported case of anti-GAD positive PSPS in a 53-year-old male with occult renal carcinoma. Clinical benefit was marked following nephrectomy and intravenous immunoglobulin treatment. Renal carcinoma should be considered in patients with SPS.

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Key words: stiff person syndrome; GAD; paraneoplastic; IVIG.

Stiff person syndrome (SPS) is an uncommon CNS disorder comprising stiffness and spasms of axial muscles with continuous motor unit activation (CMUA), and abnormal exteroceptive reflexes on EMG. Stiff limb syndrome (SLS) is a variant of SPS where symptoms are disproportionate to a limb. It is believed that both disorders share an autoimmune mechanism and there is a strong association with autoantibodies to glutamic acid decarboxylase (GAD). A small proportion of cases are considered to be paraneoplastic. The autoantibody to amphiphysin was considered an important marker for such cases, particularly in association with breast cancer. More recently, however, a number of other antibodies, including GAD, have been described in association with paraneoplastic SPS (PSPS)/SLS and a variety of...