2. Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2014;29:1583–1590.
3. Klein C, Westenberger A. Genetics of Parkinson's disease. Cold Spring Harb Perspect Med 2012;2:a008888.
4. Berwick DC, Heaton GR, Azeggagh S, Harvey K. LRRK2 biology from structure to dysfunction: research progresses, but the themes remain the same. Mol Neurodegener 2019;14:49.
5. Chan SL, Tan EK. Targeting LRRK2 in Parkinson's disease: an update on recent developments. Expert Opin Ther Targets 2017;21: 601–610.
6. Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol 2012;72:893–901.
7. Gigante AF, Martino T, Iliceto G, Defazio G. Smoking and age-at-onset of both motor and non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 2017;45:94–96.
8. Grover S, Lill CM, Kasten M, Klein C, Del Greco MF, König IR. Risky behaviors and Parkinson disease: a mendelian randomization study. Neurology 2019;93:e1412–e1424.
9. Paul KC, Chuang Y-H, Shih I-F, et al. The association between lifestyle factors and Parkinson's disease progression and mortality. Mov Disord 2019;34:58–66.
10. Ascherio A, Chen H, Weisskopf MG, et al. Pesticide exposure and risk for Parkinson's disease. Ann Neurol 2006;60:197–203.
11. Trinh J, Amouri R, Duda JE, et al. A comparative study of Parkinson's disease and leucine-rich repeat kinase 2 p.G2019S parkinsonism. Neurobiol Aging 2014;35:1125–1131.
12. Dick FD, De Palma G, Ahmadi A, et al. Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. Occup Environ Med 2007;64:666–672.
13. Semple SE, Dick F, Cherrie JW, et al. Exposure assessment for a population-based case-control study combining a job-exposure matrix with interview data. Scand J Work Environ Health 2004;30:241–248.
14. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988;16:1215.
15. Brown E, Blauwendraat C, Trinh J, et al. Analysis of DNM3 and VAMP4 as genetic modifiers of LRRK2 Parkinson's disease. *bioRxiv* 2019:686550.
16. Iwaki H, Blauwendraat C, Makarious MB, et al. Penetrance of Parkinson's disease in LRRK2 p.G2019S carriers is modified by a polygenic risk score. Mov Disord 2020;35:774–780.
17. Trinh J, Gustavsson EK, Vilariño-Güell C, et al. DNM3 and genetic modifiers of age of onset in LRRK2 Gly2019Ser parkinsonism: a genome-wide linkage and association study. Lancet Neurol 2016;15: 1248–1256.
18. Trinh J, Guella I, Farrer MJ. Disease penetrance of late-onset parkinsonism: a meta-analysis. JAMA Neurol 2014;71(12):1535–1539.
19. Breckenridge CB, Berry C, Chang ET, Sielken Jr RL, Mandel JS. Association between Parkinson's disease and cigarette smoking, rural living, well-water consumption, farming and pesticide use: systematic review and meta-analysis. PLoS One 2016;11:e0151841–e0151841.
20. Galanaud J-P, Elbaz A, Clavel J, et al. Cigarette smoking and Parkinson's disease: a case–control study in a population characterized by a high prevalence of pesticide exposure. Mov Disord 2005; 20:181–189.
21. Nouira H, Ben Abdelaziz A, Rouis S, et al. Smoking behavior among students of health sciences at the university of monastir (Tunisia). Tunis Med 2018;96:557–570.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Neuropathological Findings in Ephedrone Encephalopathy

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ABSTRACT: Background: A number of cases of severe parkinsonism-dystonia have been recognized and reported following the illicit use of ephedrone prepared from pseudoephedrine and potassium permanganate. The pathology associated with ephedrone neurotoxicity has not been described yet in the scientific literature.
Objectives: To report the first neuropathological study of ephedrone toxicity.
Methods: The brain of a 33-year-old Ukrainian female ex-ephedrone addict with a long history of L-dopa-unresponsive parkinsonism with dysarthria, dystonia, profound postural instability, cock-gait, and frequent falls, and on antiretroviral treatment, was examined using routine stains and immunohistochemistry.
Results: Neuropathological findings included diffuse pallidal astrogliosis without neuronal depletion. There was also widespread vascular pathology with small vessels occluded by foreign material, associated with giant cell response without any evidence of consequent focal infarction and a cerebellar abscess.
Conclusions: Clinical findings of L-dopa-unresponsive parkinsonism with dystonia, caused by illicit use of ephedrone, are fully consistent with neuropathological

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changes in the pallidum, lack of change in the SN, and preserved tyrosine hydroxylase activity. The findings in the basal ganglia are compatible with manganese toxicity. The vascular pathology is likely a joint effect of infection and the ephedrone toxicity on the vessels. © 2020 International Parkinson and Movement Disorder Society

Key Words: dystonia; ephedrone encephalopathy; manganism; methcathinone; parkinsonism

Ephedrone-induced neurotoxicity has been recognized in several hundred young adults from the countries of the former USSR and Eastern Europe, who used kitchen chemistry to try to produce a psychostimulant called methcathinone. Levodopa-unresponsive hypokinesia, rigidity, dystonia with a cock-gait, dysarthria, and postural instability with falls backward are common clinical findings, and there are characteristic high-signal changes on MRI T_1 imaging.[1-6] Methcathinone is an amphetamine-like substance known as ephedrone, "jeff," or "talker" in post-Soviet countries. It is produced by the oxidation of potassium permanganate in the presence of acetic acid and pseudoephedrine, contained in over-the-counter pharmaceutical preparations.[7,8] Intravenous injection of ephedrone results in high manganese (Mn) concentrations in the brain and other tissues of a drug user.

The clinical picture of ephedrone encephalopathy closely resembles previous reports on chronic Mn poisoning in miners as do the MRI findings.[9,10] The neurological syndrome is irreversible and may continue to worsen, even after cessation of ephedrone injection. The major neuropathological findings described in Mn toxicity are loss of nerve cells in the pallidum, especially marked in the medial segment, prominent decrease of myelinated fibers, and moderate astrocytic proliferation. The SN remains intact.[11,12] Although these reports help elucidate a pathomorphology of Mn neurotoxicity, they lack quantification of cell types. No autopsied cases of human Mn-induced movement disorders have been examined ultrastructurally so far.

Coroners' reports of suspected ephedrone abuse were reported by Sherstyuk and Pigolkin in 1996, but did not include cases with clinical features of parkinsonism-dystonia. Cerebral angiopathy with a high load of ischemia and hemorrhages was noted.[13] In 2014, Stepens and colleagues reported on the brain biopsy of a patient with ephedrone toxicity and human immunodeficiency virus (HIV) infection, which revealed decompacted myelin sheaths, oligodendroglial osmophilic bodies, and mitochondrial abnormalities in axons and glial cells.[14] The biopsy specimen did not inspect gray matter of the globus pallidus (GP) and did not evaluate other brain structures with immunohistochemistry. We present the first neuropathological study of the brain of a patient with parkinsonism with dystonia, caused by illicit use of ephedrone.

Our objectives were to describe the pathomorphological substrate of parkinsonism-dystonia, induced by ephedrone abuse, to look for the impact of ephedrone on brain damage and evaluate by immunohistochemistry the basal ganglia toxicity caused by previous chronic Mn poisoning.

Clinical History

A 33-year-old female first presented in 2006 with a 4-year history of falls backward. She reported a stepwise deterioration within 2 months preceding her initial assessment in 2006. She had been injecting intravenous ephedrone daily for 8 months before her symptom onset. On initial neurological assessment in 2006, she had an akinetic-rigid syndrome, severe dysarthria, dystonia in the arms and feet, risus sardonicus, perseverations, profound postural instability, impaired walk, and frequent falls. She was treated with ethylenediaminetetraacetic acid, L-dopa, and amantadine without success. She had repeated inpatient neurorehabilitation. Her neurological symptoms continued to deteriorate despite drug cessation and she was wheelchaired since 2009. She experienced some transient improvement several years ago, when she began walking again for a few months. When assessed 6 months before death, she was wheelchaired, her speech was illegible, she had dystonia in the arms, and was unable to write. There was a mild cognitive deficit, but no dementia (see Video 1).

MRI brain at first presentation in 2006 showed the presence of symmetrical hyperintensivity in the nuclei of the brainstem (Fig. 1A,B). On MRI made 5 years later, these changes completely resolved (Fig. 1C).

Past Medical History: Hepatitis C

Acquired immunodeficiency syndrome (AIDS) was diagnosed in 2011; she was treated with antiretroviral therapy in the period leading to her death.

Terminal Illness

She was admitted to the general medicine department with deterioration of general weakness, shortness of breath, and feeling unwell. There was no acute neurological deterioration. She died unexpectedly on the ward after a sudden deterioration with symptoms of

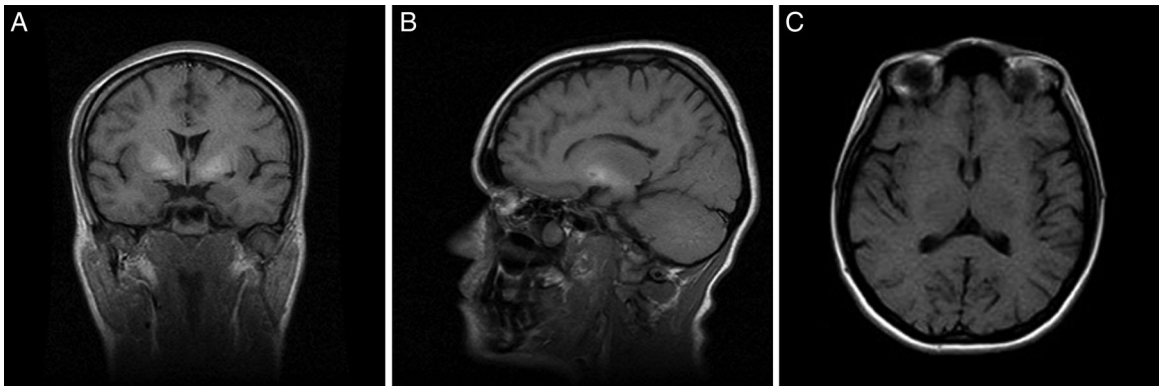

FIG. 1. MR brain image in ephedrone-induced parkinsonism. (**A,B**) Nonenhanced coronal (**A**) and saggital (**B**) T_1-weighted MR images from 2006 showing bilateral markedly hyperintense signal in the GP, most severe in its medial part and, to a lesser degree, in the SNr, subthalamic nuclei, putamen, and caudate nucleus. (**C**) Normal repeat MR brain image in methcathinone-induced parkinsonism after 5 years without exposure.

cardiovascular collapse, progressive arterial hypotension, and asystole with unsuccessful resuscitation.

Postmortem diagnosis was: AIDS, stage 4; atrophy of lymphoid tissues, spleen, and gut; generalized histoplasmosis with damage of the lungs, myocardium, liver, kidney, and spleen; and purulent pneumonia.

Pathological Methods

Following postmortem retrieval, the brain was fixed in 10% buffered formalin, selected tissue blocks were processed into paraffin wax, and 8-μ thick sections were cut and stained using routine stains and immunohistochemistry protocols at the Queen Square Brain Bank (London, UK).

Postmortem examination with analysis of the brain tissues was performed in accordance with the Ukraine government legislation procedure. Written informed consent for the participation in research and video recording was received from the patient on recruitment into the longitudinal study.

Results

At autopsy, the brain weighed 1,200 g. Apart from moderate enlargement of the ventricular system, brain macroscopic examination was normal.

Microscopic Examination

Neocortical regions showed good preservation of the cortical architecture, and there was good preservation of myelin in the subcortical white matter. Examination of the hippocampal formation showed preservation of neuronal populations with no evidence of acute hypoxic change. The caudate, putamen, GP, and thalamus were well preserved. In the midbrain, the SN was well populated with pigmented neurons. Tyrosine hydroxylase (TH) activity was well preserved in the SN, caudate, and putamen and also in axons within the GP. The pons and medulla appeared unremarkable. Examination of the cerebellum showed very mild Purkinje cell depletion. An abscess cavity was present in the cerebellar hemispheric white matter and dentate nucleus, infiltrated by a mixture of Gram-positive and -negative organisms. The upper cervical cord was present and contained a single microglial nodule in the anterior horn.

Throughout the brain, there was scattered pathology affecting small blood vessels in the form of basophilic, occasionally birefringent, material within vessels associated with CD68 immunoreactive giant cells and macrophages. Glial fibrillary acidic protein (GFAP) immunohistochemistry revealed moderate diffuse astrogliosis in the subcortical white matter, hippocampus, caudate, putamen, GP, thalamus, midbrain, pons, and cerebellum. Astrocytosis was accentuated around the abnormal vessels. Staining for P24 to detect HIV infection was negative. There was no amyloid beta (Aβ-), tau-, alpha-synuclein, or TAR-DNA binding protein 43 kDa (TDP43) pathology (Fig. 2).

Discussion

The coexistence of ephedrone poisoning and HIV infection presents a challenge in interpretation of the pathological findings in this case. Whereas the pathological findings of chronic Mn toxicity and HIV have been described previously, it is not known whether ephedrone may induce additional damage as a result of methcathinone. Autopsy-confirmed neuropathology of Mn-induced parkinsonism is limited to a few descriptive reports, performed before modern

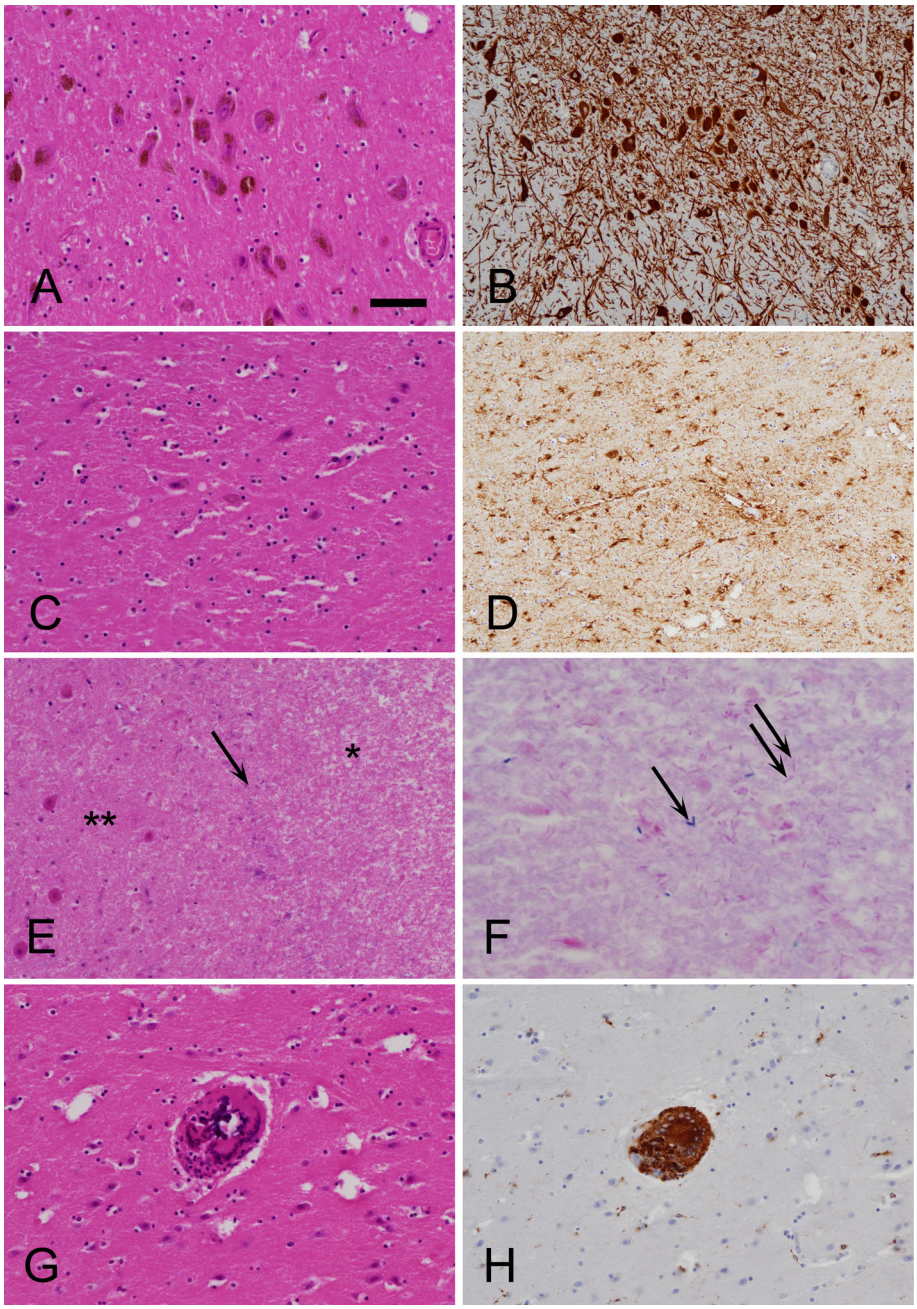

FIG. 2. Histological features of the case with methcathinone encephalopathy. Pigmented neurons (**A**) immunoreactive for TH (**B**) were well preserved in the SN. No neuronal loss was apparent in the GP (**C**), although there was moderate diffuse astrocytosis (**D**). In the cerebellum (**E**), an abscess (*) was present in the white matter adjacent to the dentate nucleus (**) with a garland on organisms at the periphery (arrow). The organisms (**F**) comprised both Gram-positive (arrow) and Gram-negative (double arrow) rods. Throughout the brain, scattered small vessels were partially occluded and associated with a foreign body giant cell response (**G**, caudate nucleus). CD68 immunohistochemistry highlights giant cells and macrophages associated with an inflamed vessel (**H**). (**A,C,E,G**) Hematoxylin and eosin; (B) TH immunohistochemistry; (**D**) GFAP immunohistochemistry; (F) Gram stain; (H) CD68 immunohistochemistry. Bar in (**A**) represents 120 μm in (**B**) and (**D**); 60 μm in (**A**), (**C**), (**E**), (**G**), and (**H**), and 20 μm in (**F**). [Color figure can be viewed at wileyonlinelibrary.com]

immunohistochemical techniques. Perl and Olanow published a comprehensive review of Mn-exposed workers with clinical features of parkinsonism, postural instability, and steppage gait, who were autopsied at death, mostly in the first half of the 20th century, and revealed substantial basal ganglia damage with marked gliosis and focal caudate and GP scarring.[15]

The evidence of the specific neuropathological pattern of Mn toxicity was reproduced in animal experiments,

in particular in primates. Olanow and colleagues subjected 3 adult rhesus monkeys to weekly intravenous Mn chloride ($MnCl_2$) injections; as a result, 2 animals developed severe Parkinson's syndrome, which did not respond to L-dopa treatment.[16] An MRI scan revealed bilateral high-signal anomalies in the striatum and globe in a T_1-weighted scan, indicating an Mn deposition. Neuropathological changes consisted of marked gliosis and astrocytosis in GPi, and there was no damage to SNc neurons.

In terms of clinical and neuropathological correlation, the pathological findings in our case are fully consistent with the clinical findings of L-dopa-unresponsive Parkinsonism. The findings in the basal ganglia are compatible with those observed in chronic Mn poisoning. The bulk of the evidence from the recent experimental studies suggests that Mn functionally alters neurotransmission through the dopaminergic system without altering the morphology of dopaminergic neurons, which is a fundamental difference from idiopathic Parkinson's disease (PD).[17-19]

Our pathological findings showed that the progressive course of the ephedrone-induced disease is not related to neurodegeneration, as indicated by the absence of any specific Aβ-, tau-, alpha-synuclein, or TDP43 abnormalities in all investigated brain areas, as well as absence of atrophy of cortical neurons. Despite the marked astrocytosis, there was no appreciable neuronal loss in the GP. Glial cells are an important target for Mn in the brain, both for metal sequestration and for activating inflammatory signaling pathways that damage neurons through the overproduction of numerous reactive oxygen and nitrogen forms and inflammatory cytokines.[20] We believe that this chronic active inflammatory process is the likely cause of persistent neurological dysfunction in our patient.

Our histopathological examination also raises the possibility that ephedrone-induced neurotoxicity may be only partially caused by Mn poisoning. The vasculitic changes might be attributable to the toxic effect of methcathinone or HIV pathology, but it is important to note that the patient was on retroviral therapy. Vasculitis has not been reported in Mn occupational neurotoxicity. In AIDS patients, concentric thickening of the small vessel wall, dilatation of the perivascular space, pigment deposition, vascular wall mineralization, and perivascular inflammatory cellular infiltrates were observed in 50% of former addicts.[21] Similar vascular changes can be observed in HIV-1-negative drug users.[22]

We also found foreign material in vessels causing a giant cell reaction, but no ischemic damage. The vascular changes were widely disseminated and probably represent solid contaminant of injected material with some local response. Previous autopsies in drug abusers showed an indirect vascular damage (hypersensitivity to contaminants or microemboli with the foreign materials), microglial activation, numerous glial nodules in basal ganglia, consisted of macrophages, lymphocytes and glial cells, and impairment of oligodendrocyte differentiation.[23,24] A noninflammatory vasculopathy in drug addicts is considered, by some researchers, to be the morphological substrate of a disturbed blood–brain barrier.[25]

To conclude, the neuropathological study of a case of parkinsonism with dystonia, caused by illicit ephedrone abuse, revealed diffuse astrocytosis of the GP with no clear depletion of neuronal populations. The SN was normal, and TH immunoreactivity was well preserved. There was an absence of biomarkers of neurodegeneration on immunohistochemical staining, and myelin staining in the subcortical white matter was normal. There was also a widespread vasculopathy with small vessels occluded by foreign material and a giant cell response, and an abscess was noted in the cerebellum. Pallidal gliosis was consistent with the neuropathological picture previously described with Mn toxicity. Vascular and perivascular changes in our case can be interpreted as a result of the joint effect of infection and methcathinone on the vessels. At present, ephedrone-induced encephalopathy should be considered a special case of Mn neurotoxicity. Upon receipt of new data, this concept may be revised.

Legend to the Video

Video 1. A 33-year-old female with a dystonic facial expression, bradykinesia, cock-walk, and no recovery on the pull test.

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References

1. Sanotsky Y, Lesyk R, Fedoryshyn L, Komnatska I, Matviyenko Y, Fahn S. Manganic encephalopathy due to "ephedrone" abuse. Mov Disord 2007;22:1337–1343.
2. Selikhova M, Fedoryshyn L, Matviyenko Y, et al. Parkinsonism and dystonia caused by the illicit use of ephedrine—a longitudinal study. Mov Disord 2008;23:2224–2231.
3. Levin OS. "Ephedron" encephalopathy. [Article in Russian]. Zh Nevrol Psikhiatr Im S.S. Korsakova 2005;105:12–20
4. de Bie RM, Gladstone RM, Strafella AP, Ko JH, Lang AE. Manganese-induced Parkinsonism associated with methcathinone (Ephedrone) abuse. Arch Neurol 2007;64:886–889.

5. Colosimo C, Guidi M. Parkinsonism due to ephedrone neurotoxicity: a case report. Eur J Neurol 2009;16:e114–e115.
6. Varlibas F, Delipoyraz I, Yuksel G, Filiz G, Tireli H, Gecim NO. Neurotoxicity following chronic intravenous use of "Russian cocktail". Clin Toxicol (Phila) 2009;47:157–160.
7. Emerson TS, Cisek JE. Methcathinone: a Russian designer amphetamine infiltrates the rural midwest. Ann Emerg Med 1993;22:1897–1903.
8. Zingel KY, Dovensky W, Crossman A, Allen A. Ephedrone: 2-methylamino-1-1-phenylpropane-1-one (jeff). J Forensic Sci 1991;36:915–920.
9. Couper J. On the effects of black oxide of manganese when inhaled into the lungs. Br Ann Med Pharmacol 1837;1:41–42.
10. Rodier J. Manganese poisoning in Moroccan miners. Br J Ind Med 1955;12:21–35.
11. Yamada M, Ohno S, Okayasu I, et al. Chronic manganese poisoning: a neuropathological study with determination of manganese distribution in the brain. Acta Neuropathol 1986;70:273–278.
12. Canavan M, Cobb S, Drinker C. Chronic manganese poisoning: report of a case with autopsy. Arch Neurol Psychiatr 1934;52:501–512.
13. Sherstyuk BV, Pigolkin Y. Hystopathology of the Ephedrone abuse toxicity. [Article in Russian]. Forensic-Med Expert 1996;4:26–28.
14. Stepens A, Groma V, Skuja S, et al. The outcome of the movement disorder in methcathinone abusers: clinical, MRI and manganesemia changes, and neuropathology. Eur J Neurol 2014;21:199–205.
15. Perl DP, Olanow CW. The neuropathology of manganese-induced Parkinsonism. J Neuropathol Exp Neurol 2007;66:675–682.
16. Olanow CW, Good PF, Shinotoh H, et al. Manganese intoxication in the rhesus monkey: a clinical, imaging, pathologic, and biochemical study. Neurology 1996;46:492–498.
17. Gonzalez-Cuyar LF, Nelson G, Criswell SR, et al. Quantitative neuropathology associated with chronic manganese exposure in South African mine workers. Neurotoxicology 2014;45:260–266.
18. Racette BA, Gonzales, Nelson et al. Striatal pathology associated with chronic manganese exposure. Occup Environ Med 2013;70 (Suppl. 1):A78–A79.
19. Peres TV, Schettinger MR, Chen P, Carvalho F, Avila DS, Bowman AB, Aschner M. Manganese-induced neurotoxicity: a review of its behavioral consequences and neuroprotective strategies. BMC Pharmacol Toxicol 2016;17:57.
20. Tjalkens RB, Popichak KA, Kirkley KA. Inflammatory activation of microglia and astrocytes in manganese neurotoxicity. Adv Neurobiol 2017;18:159–181.
21. Connor MD, Lammie GA, Bell JE, Warlow CP, Simmonds P, Brettle RD. Cerebral infarction in adult AIDS patients: observations from the Edinburgh HIV Autopsy Cohort. Stroke 2000;31:2117–2126.
22. Büttner A, Weis S. Neuropathological alterations in drug abusers: the involvement of neurons, glial, and vascular systems. Forensic Sci Med Pathol 2006;6:115–126.
23. Sekine Y, Ouchi Y, Sugihara G, et al. Methamphetamine causes microglial activation in the brains of human abusers. J Neurosci 2008;28:5756–5761.
24. Pigolkin YI. Morphological diagnosis of recreational drug poisoning in forensic medicine. [Russian]. Moscow: Medicine; 2004.
25. Lacagnina MJ, Rivera PD, Bilbo SD. Glial and neuroimmune mechanisms as critical modulators of drug use and abuse. Neuropsychopharmacology 2017;42:156–177.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Subclinical Cardiac Microdamage, Motor Severity, and Cognition in Parkinson's Disease

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ABSTRACT: Background: We assessed if cardiac blood markers are associated with motor and cognitive function in patients with Parkinson's disease (PD).

Methods: High-sensitivity troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were evaluated in 285 PD patients. Furthermore, N-terminal

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