

## Persistent parkinsonism after high dose intravenous methamphetamine: A case report

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### Abstract

A patient developed persistent parkinsonism after intravenously injecting a high dose of methamphetamine. Magnetic resonance imaging revealed bilateral hypoxic/ischemic basal ganglia damage, which could have been caused by the vasoconstrictive effect of methamphetamine. This case adds some circumstantial evidence to the association between methamphetamine and Parkinsonism.

*Key words:* Parkinsonism, methamphetamine, substance use disorders.

### INTRODUCTION

Methamphetamine use has been hypothetically linked to Parkinsonism.<sup>1-4</sup> However, there are no reports of Parkinsonism developing after acute/chronic use of methamphetamine. Here, we describe a polysubstance user who developed persistent Parkinsonism following a high-dose intravenous injection of methamphetamine.

### CASE REPORT

This is a 46-year-old unemployed man with an almost 30-year-history of polysubstance abuse, was admitted unconscious to the emergency department (ED). He has used intravenous heroin since his late teens, which he later supplemented with midazolam and a variety of other substances. In recent years his usual daily pattern of intravenous drug use has included 0.5 grams of heroin or 0.5 grams of heroin with 15 mg of midazolam 3-4 times per day. For the last 12 years (?), he has attended a methadone clinic where he received methadone at a daily dose of 15-55 mg. About 10 years ago he also started smoking methamphetamine. Shortly afterwards, he experienced auditory hallucinations and persecutory delusions and was prescribed antipsychotic medication, although his treatment adherence has been poor. He also developed depressive symptoms 6 years ago and has received antidepressant treatment, and benzhexol 4 mg/day was later added to his prescription medications.

Over the years, the patient developed multiple complications including hepatitis C infection with Child's B cirrhosis, a lung abscess, Volkmann's contracture of the left hand, and chronic bilateral deep vein thrombosis. He was last seen 17 days before the index admission and there was no parkinsonian features detected on that visit.

Immediately prior to his admission to ED, the patient injected 1.2 grams of heroin (cost: HK\$1,000), slightly more than his usual dose together with midazolam and oral chlorpromazine (300 mg), trifluoperazine (20 mg), and citalopram (20 mg). He also received 25 mg of depot fluphenazine the day before the admission. In addition, he injected himself with a high dose of 1.3 gram methamphetamine that cost him about HK\$ 900.

On admission, the patient scored 3 on the Glasgow Coma Scale (GCS). His blood pressure was 150/90, pulse 80 bpm, respiratory rate 10/minute, and oxygen saturation 96%. The diameters of his pupils were 2 mm bilaterally (non-reactive to light). He was given opiate antagonists (two doses of naloxone 0.2 mg), with subsequent improvement in the GCS to 9. He was then admitted to the Intensive Care Unit where he received supportive treatment and regained full consciousness 7 hours after admission. Urine toxicology showed benzhexol, chlorpromazine, citalopram, codeine, methadone, methamphetamine, midazolam, trifluoperazine, and heroin. Plasma drug levels were not available.

His liver function tests, plasma electrolytes were normal; he was negative for serology test of HIV infection. Two brain CT scans conducted 1 and 11 hours after admission revealed no sign of acute infarct or any significant abnormality.

Seven hours after admission, Mr. A was observed to have newly occurring Parkinsonian features including rigidity, resting tremor, masked face, low volume speech, and bradykinesia. He also had generalized hyperreflexia but no sustained clonus. He had weakness in all limbs and the left facial muscles; the power in the left arm was 1/5 and 3-4/5 in his other limbs. Ocular examination did not show Kayser-Fleischer rings. MRI scan of the spine on the third day of admission was also unremarkable. MRI examination of the brain 29 days after admission revealed bilateral symmetrical T2W hyperintense signals in the globus pallidus and capsular regions, and at the head of the caudate extending to the periventricular white matter (Figure 1), suggesting infarction resulting from hypoxia. T1W hyperintense signals were seen in the bilateral basal ganglia (Figure 2), suggesting haemorrhage or myelin breakdown. The signal intensity showed a decrease in the DWI map and

an increase in the ADC map, rather than acute abnormal signal intensities in the basal ganglia (Figure 3).

The patient's presentation was initially thought to be due to the side effect of antipsychotic medications. However, the rigidity, masked face and resting tremor persisted after gradually stopping both the antipsychotics and the antidepressant. Despite aggressive treatment with bromocriptine, domperidone, Madopar, and amantadine, the rigidity and tremor were still present at the last follow-up, 7 months after his admission.

## DISCUSSION

Our patient was diagnosed with substance-induced hypoxic/ischemic brain damage manifesting with a typical Parkinson syndrome. Onset of the symptoms was acute after an intravenous dose of methamphetamine three times higher than his standard daily dose. Methamphetamine was found to have a selective vasoconstriction effect in the striatum<sup>17</sup>, leading to striatal hypoxia. The brain damage of our patient was restricted to

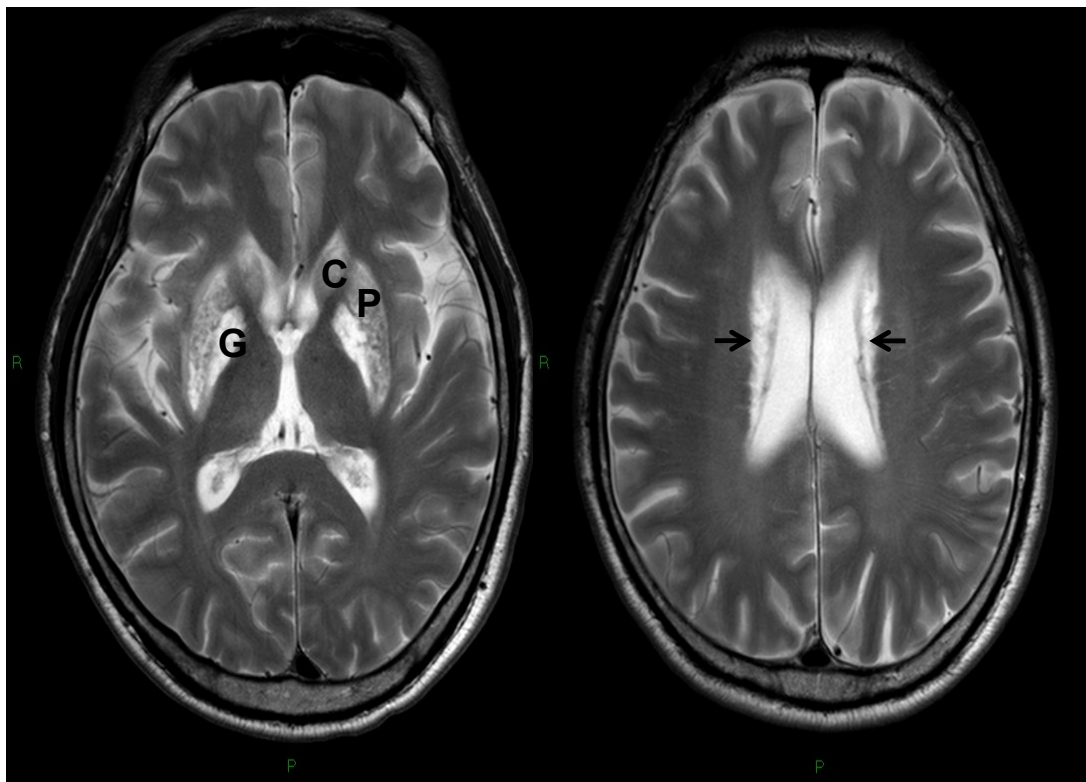


Figure 1. T2-weighted axial image showing bilateral symmetrical T2 hyperintensity over caudate nuclei (C), putamen (P) and globus pallidi (G) and periventricular white matter (arrows). The above changes are considered to be most likely related to infarction resulting from poor oxygenation.

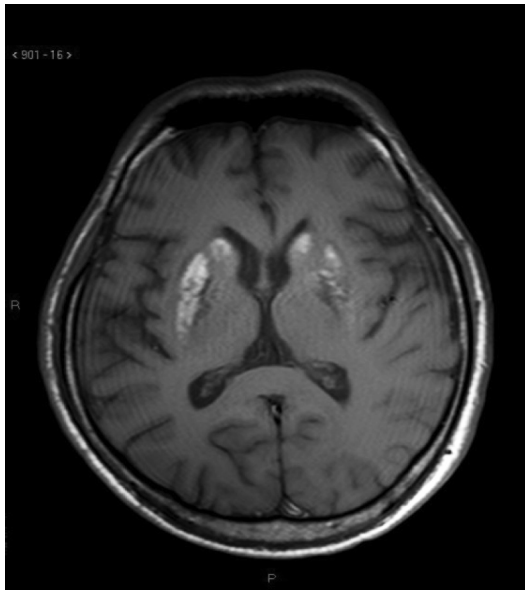


Figure 2. T1-weighted axial image showing hyperintense signals over bilateral caudate nuclei and putamen.

the bilateral stratum. Hence, it was assumed that methamphetamine was mainly responsible for the brain damage, although he also took heroine, midazolam, antipsychotics, and an antidepressant. Other likely causes of the newly emerging Parkinsonism include Wilson's disease, extra-pontine myelinolysis, HIV infection and neuroleptic-induced side effects. Wilson's disease was excluded as he had normal liver functions and no Kayser-Fleischer rings were observed.

There were no electrolyte abnormalities and extra-pontine myelinolysis was also excluded. He was HIV negative. However, our patient was treated with neuroleptic medications including chlorpromazine, trifluoperazine and fluphenazine, which may have been the cause of parkinsonism as it can persist for a long time after exposure. However, neuroleptic-induced parkinsonism typically develops gradually and not as acutely as it happened in our patient.

The relationship between methamphetamine and Parkinsonism is controversial. In two retrospective, population-based cohort studies, lifetime methamphetamine abuse/dependence increased the risk of Parkinson's disease.<sup>1,4,5</sup> Dopamine depletion and reduction of dopaminergic terminal markers following acute<sup>6,7</sup> and chronic methamphetamine use have been described in rodents, non-human primates, and human studies.<sup>2,8,9</sup> High doses of methamphetamine cause dopaminergic neuron death in the substantia nigra in mice,<sup>10,11</sup> which is similar to that observed in Parkinson's disease.<sup>3,11</sup> However, methamphetamine mainly damages the dopamine system in the caudate, putamen, and nucleus accumbens.<sup>6,8,12</sup> In methamphetamine users, some of the dopaminergic terminal markers affected in Parkinson's disease remain in the normal range, such as the vesicular monoamine transporter (VMAT2).<sup>8,12</sup> No cell body loss was found in the substantia nigra in methamphetamine users at autopsy.<sup>8</sup> Further, motor impairments observed in chronic methamphetamine abuse are fine

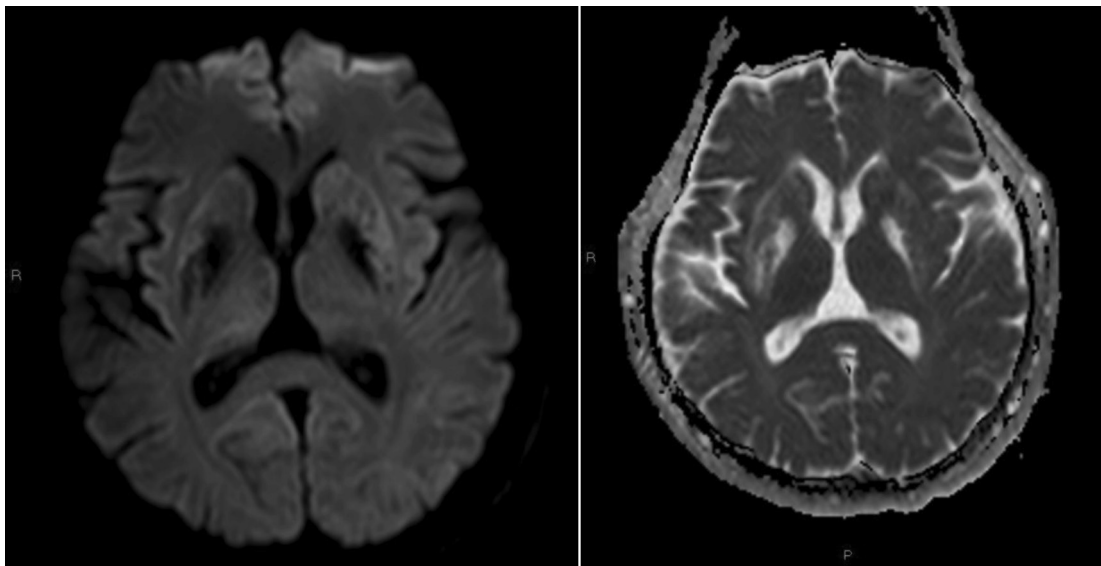


Figure 3. Diffusion weighted image (DWI, left) and ADC map (right) show no evidence restricted diffusion in the basal ganglia but T2-shine through effect (hyperintensity) on ADC.

motordexterity, which is different from the typical, gross motor deficit seen in Parkinson's disease.<sup>8,13</sup> This discrepancy may be explained by the fact that dopamine transporter reductions equally affect the caudate and putamen in chronic methamphetamine abuse, whereas such damage is more predominant in the putamen in Parkinson's disease.<sup>8,13</sup>

There have been only few reports of methamphetamine-induced brain abnormalities<sup>14</sup> such as ischemic stroke<sup>15</sup> and white matter hyperintensity.<sup>16</sup> In our case, the brain damage was restricted to the bilateral stratum and, to a lesser extent, part of the perivascular region. Methamphetamine was recently found to have a selective vasoconstriction effect in the stratum<sup>17</sup>, leading to striatal hypoxia. This emerging neurotoxic mechanism of methamphetamine is in line with the assumed hypoxic/ischemic striatal damage<sup>17</sup> in this case report. The most convincing evidence for the link between was the close temporal relationship between methamphetamine overdose and Parkinsonism is also suggestive of a causal relationship. In conclusion, vasoconstriction may selectively affect the stratum following a single, high-dose intravenous injection of methamphetamine, which, in turn may subsequently induce persistent Parkinsonism. The case reported here raises the possibility of a causal relationship between acute methamphetamine administration and Parkinsonism.

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## DISCLOSURE

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## REFERENCES

- Callaghan RC, Cunningham JK, Sykes J, Kish SJ. Increased risk of Parkinson's disease in individuals hospitalized with conditions related to the use of methamphetamine or other amphetamine-type drugs. *Drug Alcohol Depend* 2012; 120(1-3):35-40.
- Christine CW, Garwood ER, Schrock LE, Austin DE, McCulloch CE. Parkinsonism in patients with a history of amphetamine exposure. *Mov Disord* 2010; 25(2):228-31.
- Granado N, Ares-Santos S, Moratalla R. Methamphetamine and Parkinson's disease. *Parkinson Dis* 2013; 2013:308052.
- Thrash B, Thiruchelvan K, Ahuja M, Suppiramaniam V, Dhanasekaran M. Methamphetamine-induced neurotoxicity: the road to Parkinson's disease. *Pharmacol Rep* 2009; 61(6):966-77.
- Callaghan RC, Cunningham JK, Sajeew G, Kish SJ. Incidence of Parkinson's disease among hospital patients with methamphetamine-use disorders. *Mov Disord* 2010; 25(14):2333-9.
- Richards JB, Baggott MJ, Sabol KE, Seiden LS. A high-dose methamphetamine regimen results in long-lasting deficits on performance of a reaction-time task. *Brain Res* 1993; 627(2):254-60.
- Ricaurte GA, Mehan AO, Yuan J, et al. Amphetamine treatment similar to that used in the treatment of adult attention-deficit/hyperactivity disorder damages dopaminergic nerve endings in the striatum of adult nonhuman primates. *J Pharmacol Exp Ther* 2005; 315(1):91-8.
- Moszczynska A, Fitzmaurice P, Ang L, et al. Why is parkinsonism not a feature of human methamphetamine users? *Brain* 2004; 127(2):363-70.
- Guilarte TR. Is methamphetamine abuse a risk factor in Parkinsonism? *Neurotoxicology* 2001; 22(6):725-31.
- Schmued LC, Bowyer JF. Methamphetamine exposure can produce neuronal degeneration in mouse hippocampal remnants. *Brain Res* 1997; 759(1):135-40.
- Yamamoto BK, Moszczynska A, Gudelsky GA. Amphetamine toxicities: classical and emerging mechanisms. *Ann NY Acad Sci* 2010; 1187:101-21.
- Wilson JM, Kalasinsky KS, AI, Bergeron C, et al. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. *Nat Med* 1996; 2(6):699-703.
- Volkow ND, Chang L, Wang GJ, et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry* 2001; 158(3):377-82.
- Jan RK, Kydd RR, Russell BR. Functional and structural brain changes associated with methamphetamine abuse. *Brain Sci* 2012; 2(4):434-82.
- Rothrock JF, Rubenstein R, Lyden PD. Ischemic stroke associated with methamphetamine inhalation. *Neurology* 1988; 38(4):589-92.
- Bae SC, Lyoo IK, Sung YH, et al. Increased white matter hyperintensities in male methamphetamine abusers. *Drug and Alcohol Depend* 2006; 81(1):83-8.
- Kousik SM, Graves SM, Napier TC, Zhao C, Carvey PM. Methamphetamine-induced vascular changes lead to striatal hypoxia and dopamine reduction. *Neuroreport* 2011; 22(17):923-8.