

## Clinical/Scientific Notes

### Rapidly Progressive Parkinsonism in a Self-Reported User of Ecstasy and Other Drugs

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**Abstract:** A 38-year-old man developed parkinsonism that progressed to Hoehn and Yahr stage 5 within 4 years of onset. Response to ropinirole deteriorated, levodopa was not tolerated, and subthalamic nucleus stimulation has provided only partial relief of symptoms. He reported heavy use of Ecstasy through most of his twenties and thirties. His neurological problems may be unrelated to his drug use, but it is also possible they represent an idiosyncratic reaction. © 2003 Movement Disorder Society

**Key words:** parkinsonism; MDMA; drug use; young onset

For almost 3 years, we have been treating a man for young-onset rapidly progressive parkinsonism, culminating with bilateral subthalamic nucleus stimulation. When renewed attention was focused on 3,4-methylenedioxymethamphetamine (MDMA, colloquially “Ecstasy”) as a possible neurotoxin, he admitted to heavy episodic use of Ecstasy in the previous 12 years.

#### Case Report

#### Clinical Course

In late 1997, at age 38 years, this man developed fatigue and dragging of his left leg followed by stiffness of the left leg and arm, which led him to quit his construction job and to start work in sales. He sought neurological opinion 16 months later. The exam was recorded to show mild rigidity and bradykinesia with a normal gait, and he was diagnosed with hemiparkinsonism. Pramipexole was started and increased to 1.5 mg/day, then discontinued because of nausea.

He first came to our attention 4 months after this. He had poverty of spontaneous movement, decreased blink rate, a soft but clear voice, bursts of rapid left arm tremor while apparently at rest, bilateral postural arm tremor, moderate rigidity and slowness of left worse than right limbs. Left arm and leg reflexes were brisk. Power, sensation and eye movements were normal. He was able to stand without using his arms after repeated rocking motions, and could walk with absent left arm swing but almost normal stride and turn. Pramipexole was started at low dose but again was not tolerated.

By August 2000, his rigidity had worsened, his tremor at rest was more prominent, and he could not achieve a standing position without using his arms. He could still walk safely but with shorter steps, and he required 10 steps to turn 360 degrees. Carbidopa–levodopa (L-dopa) was started at 25/100, and the dose was titrated to 2 tablets three times per day, achieving partial relief of his symptoms. Within 1 week at this dose, however, he developed jaundice. Liver enzymes were three to ten times the upper limits of normal, and a hepatic consult attributed this to an idiosyncratic response to L-dopa. He was also found to have had hepatitis C infection with undetectable viral RNA, which was attributed to tattoos. Selegiline 5 mg and ropinirole 5 mg three times per day were prescribed with subjective improvement in his gait, stiffness and speech. In June 2001, he was recorded to have *on* periods lasting 6 hours. Examined in an *on* state he was able to stand without using his arms, and had mild rigidity, minimal tremor, and a safe stride. Over the following months the *on* duration progressively shortened. By February 2002, the *on* duration was 3 hours and he was taking ropinirole 5 mg five times a day in addition to Selegiline; however, the quality of the *on* response also became poorer. He was shuffling, needed a walker, and had difficulty dressing and feeding. The Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore in the *off* state was 63.

An Activa system deep brain stimulator (Medtronic, Minneapolis, MN) was implanted in both subthalamic nuclei in June 2002. Marked reduction in contralateral rigidity and bradykinesia were recorded with intraoperative stimulation of each side.

The stimulators were activated 3 weeks postoperatively, with immediate improvement in mobility: he could stand without using his arms and could walk safely, although with short steps. Rigidity and alternate motion breakdown, however, were reversed only partially. Over the following 10 days, the initial benefits gradually faded. Stimulation was being adjusted on eight further occasions with temporary but quite good incremental improvement after each adjustment, which later regressed. Off medication, on optimal stimulation at 3.1 and 2.5 volts monopolar, the UPDRS motor subscore was 48 (see Video).

#### Diagnostic Data

The patient had no family history of parkinsonism, although a maternal uncle had some gait and cognitive impairment attributed to repeated closed head injuries. Our patient's 24-

A videotape accompanies this article.

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hour urine copper and heavy metals were normal, as were serum ceruloplasmin and human immunodeficiency virus (HIV) assays. Neuropsychometric testing revealed average abilities for problem solving, auditory attention, mental flexibility, construction, and verbal fluency. He had moderate depression as indicated by score of 20 on the Beck depression index. His brain and cervical magnetic resonance imaging (MRI) with gadolinium were normal. After a urine drug screen in January 2002 revealed cocaine metabolites, he confessed to episodic cocaine use. At that time he denied, as he had previously, prior use of this or other illicit drugs. After the recent suggestion that MDMA could affect primate dopaminergic neurons, he admitted he had used Ecstasy. His period of heaviest use was in 1985 during Navy leave, at which time he took two to four tablets every day for a month. He did not recall the dose but reported the tablets were obtained over the counter in bars in California. He subsequently took repeated doses a few times a year for approximately 10 years. He had used alcohol heavily, at least intermittently, since late teenage years, had taken lysergic acid diethylamide (LSD) occasionally in his early 20s, had snorted cocaine through his 20s and early 30s, and had smoked cocaine episodically in his 30s. He maintained that he had never injected narcotics.

### Discussion

For most cases of non-familial PD, a specific cause is not found, although environmental agents are probably responsible for some. Based on case series, certain herbicides and pesticides,<sup>1</sup> carbon monoxide poisoning,<sup>2</sup> manganese,<sup>3</sup> and cyanide<sup>4</sup> are believed to induce young-onset atypical parkinsonism in certain situations. Epidemiological surveys confirm as risk factors well water consumption, occupational exposure to copper and manganese,<sup>5</sup> and use of pesticides.<sup>6</sup> Animal research supports rotenone as a plausible toxin,<sup>7</sup> and suggests that exposure to certain organic chemicals can have delayed and combinatorial effects on substantia nigra.<sup>8</sup> Since MPTP a generation ago,<sup>9</sup> no predictably toxic source of human parkinsonism has been identified. This may be because toxin-induced parkinsonism is rare. Alternatively, we speculate that environmental causes of parkinsonism under our noses avoid suspicion because they affect only a susceptible subset of exposed people, perhaps after a latent period. Such subtle toxins, if they exist, are less likely to come under investigation as compared with more acute and predictably potent agents such as MPTP. Only by setting a lower threshold for investigation would greater numbers of such toxins be identified. Of course, there are practical limitations as to how many candidate toxins can be subjects of exposure surveys, and the lower the threshold for suspicion, the greater will be indiscriminate and erroneous associations.

Ecstasy use has become increasingly widespread over the past 20 years. By the most recent estimates, 8.2% of students use ecstasy during 12th grade, and 1.4 million Americans currently aged 18 to 25 years have used it on one or more occasions.<sup>10</sup> Acutely, this amphetamine derivative releases acetylcholine<sup>11</sup> serotonin, and dopamine,<sup>12</sup> producing temporarily elevated or euphoric feelings. Parkinsonism in a rat model can be briefly reversed by this acute effect of MDMA.<sup>13</sup> With repeated use in rodents, however, reduced levels of dopamine<sup>14,6</sup> and serotonin<sup>15,16</sup> are observed. Primates exposed to MDMA also develop reduced levels of serotonin and its metabolites.<sup>17-19</sup> Tissue samples show striatal axon degeneration in rodent substantia nigra.<sup>20</sup> Primate histologic studies have

typically found damage to serotonergic neurons, sometime preserving dopaminergic axons<sup>21,22</sup> but in at least one study there was persistent and widespread loss of dopamine axonal markers.<sup>23</sup> Although only 2 animals in this last study had mobility impairment, the others had increased susceptibility to  $\alpha$ -methyl-para-tyrosine-induced motor dysfunction.

To the extent that human neurochemistry is affected by MDMA, there is more evidence for serotonin as compared with dopamine deficiency in users. Spinal fluid levels of 5-hydroxy-indoleacetic acid, a serotonin metabolite, are low in Ecstasy users whereas homovanillic, a dopamine metabolite, is not deficient.<sup>24,25</sup> I<sup>123</sup>-labeled 2 $\beta$ -carbomethoxy-3  $\beta$ -(4-iodophenyl) tropane ( $\beta$ -CIT) labeling of serotonin transporter in neocortex is low,<sup>26,27</sup> but delayed uptake to the striatum, a surrogate for dopamine transporters on nigrostriatal terminals, is not deficient<sup>28</sup> unless amphetamines are also used.<sup>29</sup> The only detailed brain autopsy published of a chronic Ecstasy user (also a user of heroin and cocaine) showed striatal levels of serotonin were decreased over 50%, with a similar reduction of dopamine occurring only in the nucleus accumbens.<sup>30</sup>

The question of long-term clinical consequences of MDMA use has not yet been settled. Single doses were followed, in some naive volunteers, by periods of altered mentation and adventitious movement.<sup>31</sup> Repeat users tend to have subjective and objective impairment in cognitive performance, including inaccuracy of verbal memory and slowed serial calculations.<sup>32-34</sup> We found a single case report of parkinsonism in a young man who admitted to prior Ecstasy use: a 29-year-old man developed rapidly progressive parkinsonism within a year of taking 10 or so doses.<sup>35</sup>

Limited inferences should be drawn from our case, and from the previous case report. In both cases the association may be coincidental, and the attribution to MDMA may reflect our limited knowledge of alternative causes of parkinsonism. Rapidly progressive parkinsonism clearly can occur among young people who have not used illicit drugs. Our patient reported using cocaine, amphetamine, and alcohol in addition to Ecstasy, and of course Ecstasy pills can be and often are contaminated.<sup>36</sup> We cannot even verify forensically that he did actually ingest MDMA. Although our patient describes periodic use over a decade or more, our patient's most concentrated use was a 4-week period about 12 years before onset of the parkinsonism; he did not experience parkinsonism acutely around this time. The delay in development of symptoms could be interpreted either as evidence against MDMA as a cause, or evidence for a process set in motion by MDMA resulting in clinical signs only with further aging or additional toxic exposure. No recent epidemic of young-onset parkinsonism has been noted, and this would argue against a widespread susceptibility to Ecstasy, which has been in escalating use throughout America and Europe in the recent decades. It is unclear that systems for collecting public health data are sufficient to pick up a meaningful uptick in incidence. Ultimately, an association may only be established or refuted convincingly by sound epidemiological studies of Ecstasy use in young-onset non-familial parkinsonism patients compared with age-matched controls. Such studies, if undertaken prompted by further anecdotal observations, would have to factor in veracity regarding drug use among both cases and controls. Our patient was at first reluctant to relate his history of drug use, fearing disapproval or perhaps fearing alteration of his medical care. It was only after

publicity about a possible link between MDMA and parkinsonism was aired that he talked about it.

We were disappointed at how quickly our patient's partial response to a dopamine agonist deteriorated, and we have some concern about how modest the response was to subthalamic stimulation. He had felt L-dopa was providing the best benefits of any of the attempted treatments, but even this seemed to be partial, and we could not determine safely the full extent or persistence of his response. In this case report of parkinsonism in an Ecstasy user, there was little benefit from agonists or from L-dopa. If MDMA is actually a cause for parkinsonism in certain circumstances, prevention rather than intervention will be important.

### Legend to the Video

A 38-year-old man with parkinsonism, off ropinirole for 12 hours.

**Segment 1.** Bilateral STN stimulation off.

**Segment 2.** Bilateral STN stimulation on.

### Note Added in Proof

This case report was prompted by a paper that has now been retracted.<sup>23</sup> Significant dopaminergic neuronal damage by MDMA has not been demonstrated in primates at this time. Another case of young-onset parkinsonism in a reported Ecstasy user has also been published (Kuniyoshi SM, Jankovic, J. *N Engl J Med* 2003;349:96).

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### Severe Cervical Dystonia in Pathologically Proven Parkinson's Disease and Dementia

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**Abstract:** We describe and present a videotape of a patient with parkinsonism and dementia who developed severe cervical dystonia, despite treatment with levodopa and botulinum toxin. The clinical diagnosis of Parkinson's disease and dementia (PDD) was confirmed at autopsy. © 2003 Movement Disorder Society

**Key words:** cervical dystonia; parkinson's disease; dementia

Parkinson's disease and dementia (PDD), and dementia with Lewy Bodies (DLB) are disorders that are pathologically char-

acterized by widespread Lewy body neuronal inclusions.<sup>1</sup> Cervical dystonia may occur in patients with Parkinson's disease (PD), although its presence often suggests the possibility of multiple system atrophy (MSA).<sup>2–4</sup> The incidence of cervical dystonia in PDD is unknown, but to our knowledge, only 2 such patients have been reported previously.<sup>5</sup> We describe and demonstrate a patient with parkinsonism and dementia who developed severe anterolaterocollis, in whom the clinical diagnosis of PDD was confirmed at autopsy.

#### Case History

A 62-year-old man presented to our movement disorders center 7 years after symptoms of slowness and stiffness in the left hand led to a diagnosis of PD. Treatment with levodopa 2 years before presentation improved his gait, but he experienced marked drowsiness that was only mildly improved by treatment with selegiline. His wife noted that he would occasionally become confused and disoriented. His past medical history was unremarkable, and there was no family history of parkinsonism or dementia.

On initial evaluation, he was alert and fully oriented, but had difficulty with short-term memory tasks. His speech was hypophonic and his handwriting micrographic. Moderate parkinsonism was present, worse on the left, with a slight postural tremor of the left arm and an action tremor of both hands. He walked with stooped posture and mild right truncal tilt, but recovered unaided on the pull test.

Over the next several years, he developed increasing confusion and disorientation, marked diurnal fluctuations in alertness and orientation, and nocturnal visual hallucinations. His parkinsonism worsened with increasing stiffness, bradykinesia, and gait difficulty, and he became incontinent of urine. Each dose of carbidopa-levodopa induced sleep for approximately 2 hours, and he was unable to delay the first dose because of severe immobility in the *off* state. Over time, his head assumed a posture of anterocollis and severe right tilt. His head tilt became so profound that he spent much of the day with his right ear pressed against his right shoulder. The right trapezius, splenius, and levator scapulae became progressively hypertrophied and hardened, and he lost the ability to move his head. He became apathetic, immobile, and increasingly dependent on others for all activities of daily living. Disorientation, hallucinations, and paranoid delusions were more frequent, and although he maintained some benefit from levodopa, its sedative effect limited his ability to take it. Without it, he was virtually akinetic; judiciously spaced doses allowed him some mobility.

Follow-up examinations revealed a wheelchair-bound man with a fixed head posture and occasional myoclonic jerks of the limbs. Injection of botulinum toxin type A (150 units total directed to the right posterior neck) was ineffective. Ten years after presenting to our center and 17 years after his symptoms began, he died after an aspiration pneumonia.

Macroscopic examination of the brain revealed a cortical gray mantle of normal thickness and distribution, and moderate to severe depigmentation of the substantia nigra and locus ceruleus. The basal ganglia were unremarkable. Microscopic examination of the midbrain showed severe loss of pigmented neurons within the substantia nigra, associated with moderate astrogliosis. Scattered Lewy bodies and occasional pale bodies were present in the residual neurons. Lewy bodies were also identified in the deep layers of the cortex, including the transentorhinal cortex (>5, score of 2), the temporal cortex (>5, score

A videotape accompanies this article.

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