Published in final edited form as:
Mov Disord. 2010 January 30; 25(2): 228–231. doi:10.1002/mds.22915.

Parkinsonism in patients with a history of amphetamine exposure

Chadwick W. Christine, MD[1], **Elisabeth R. Garwood, BS**[2], **Lauren E. Schrock, MD**[3], **Daniel E. Austin**[4], and **Charles E. McCulloch, PhD**[5]

[1]Department of Neurology, University of California, San Francisco

[2]Pennsylvania State University College of Medicine

[3]Department of Neurology, University of Utah

[4]Colby College

[5]Department of Epidemiology and Biostatistics University of California, San Francisco

Abstract

We recently found a higher rate of prolonged amphetamine exposure in patients diagnosed with Parkinson's disease (PD) than in spouse/caregiver controls. Since distinguishing features have been described in some patients with parkinsonism due to environment exposures (e.g. manganese), we sought to compare the clinical features of PD patients with *prolonged* amphetamine exposure with unexposed PD patients. Prolonged exposure was defined as a minimum of twice a week for ≥ 3 months, or weekly use ≥ 1 year. We reviewed the clinical records of patients with PD who had participated in a telephone survey of drug and environmental exposures and compared the clinical features of patients with a history of prolonged amphetamine exposure to patients who had no such exposure. Records were available for 16 of 17 (94%) patients with prior amphetamine exposure and 127 of 137 (92%) of those unexposed. Age at diagnosis was younger in the amphetamine-exposed group (49.8 ± 8.2 years vs. 53.1 ±7.4 years; $p < 0.05$), but other features, including presenting symptoms, initial and later treatments, development of motor fluctuations, and MRI findings were similar between these groups. Because we did not detect clinical features that differentiate parkinsonism in patients with prolonged amphetamine exposure, research to determine whether amphetamine exposure is a risk factor for parkinsonism will require detailed histories of medication and recreational drug use.

Keywords

neurotoxin; selective vulnerability; neurotoxicant

Corresponding author: Chadwick W. Christine Department of Neurology, UCSF 400 Parnassus Avenue, Box 0348 San Francisco CA 94143 chad.christine@ucsf.edu phone: 415-353-9046 fax: 415-353-3573 Reprints requests should be sent to Chadwick W. Christine..

Author Roles: Chadwick Christine conceived, designed, and organized the study, gathered and analyzed data, and wrote the first draft and final draft of the manuscript.

Elisabeth Garwood gathered data, performing the statistical analysis, and reviewed and critiqued the manuscript.

Lauren Schrock helped in the initial design of the study gathered data, and reviewed critiqued a final draft of the manuscript.

Dan Austin gathered study data and reviewed and critiqued the final draft of the manuscript.

Charles E. McCulloch was involved in the study design, statistical analysis, and extensively reviewed and critiqued the manuscript.

Disclosure: The authors have no conflicts of interest.

Introduction

Strong genetic causes of Parkinson's disease (PD) likely account for 10–15% of cases.1 The balance appears to be secondary to environmental factors or a combination of weaker genetic and environmental influences.2 Although pesticide exposure is well established as a risk factor for PD,3 other environmental factors likely exist.

Amphetamine drugs have been raised as a possible risk factor for PD.4 They have been used both therapeutically and recreationally since the 1930's and their use is common. In the U. S., about 5% of adults 35 years and older have used non-prescribed amphetamines at least once.5 Moreover, they remain accepted treatments for attention-deficit hyperactivity disorder and narcolepsy.

Increasing evidence supports a plausible biologic mechanism. For example, in human methamphetamine users, there is loss of dopamine axonal proteins consistent with injury to axon terminals of dopaminergic neurons.6,7 Numerous studies in animals confirm that amphetamine causes acute injury to axon terminals of dopaminergic neurons.8,9

In a study of environmental exposures, we found a higher rate of prolonged amphetamine exposure in PD patients than spouse or caregiver controls.10 We undertook this study to determine if the parkinsonian phenotype of exposed patients differed from those who were not exposed.

Methods

We reviewed all available hospital and outpatient records from subjects diagnosed with PD who participated in our prior case-control study of environmental and chemical exposures. 10 In the original study, subjects were asked a number of questions regarding prior medication use, environmental exposures, and other health-related behaviors. The UCSF Institutional Review Board approved both the original survey and this follow-up study.

To be eligible for the initial study, subjects must have been evaluated in the UCSF Neurology Practice between January 2001 and June 2004 and have received a diagnosis of “probable idiopathic PD” between the ages of 40 and 64 according to established clinical criteria.11 Amphetamine exposure was defined as prior use of amphetamine, methamphetamine, or dextroamphetamine. Prolonged exposure was defined as a minimum of twice a week ≥ 3 months, or weekly use ≥ 1 year

Subjects were excluded from further analysis if a diagnosis of atypical parkinsonism was determined subsequent to the initial study. Records were reviewed to determine the following measurements (if appropriate): age when first PD symptom developed, type of first symptoms, age at first use and type of first PD medication, age when levodopa treatment began, age when motor fluctuations developed, age when the patient underwent treatment with deep brain stimulation (DBS), age dementia was diagnosed, age when last evaluated at UCSF, and age of death.

MRI reports from unexposed patients were selected to match age and gender with the available MRI reports from exposed patients. Reports were reviewed for description of atrophy, basal ganglia abnormalities, and presence of foci of T2 hyperintensity. In addition, all available scans of those with prolonged exposure were reviewed for evidence of atypical findings.

The analysis includes observations from all subjects, even from those for whom incomplete data was available. Proportions were compared using Fisher's exact test. Differences in

means between the two groups were compared using Student's t-test. Time from diagnosis to event times were analyzed using the log rank survival test, and was censored on death for non-fatal outcomes. Hazard ratios were determined using Cox proportional hazards regression. All data analyses were performed with Stata 10.

Results

Four subjects in the non-exposed group were excluded from analysis because atypical features became apparent and the diagnosis was changed to atypical parkinsonism. Records were available for 16 of 17 (94%) with prolonged amphetamine exposure and 127 of 137 (92%) who had no exposure. Amphetamine was used for a prescribed purpose by 7 subjects, while 9 used it recreationally.

Age at diagnosis, gender, age at onset, and presenting symptoms were similar in subjects with and without amphetamine exposure (Table 1). Because of the small number of exposed subjects and the similarities between the prescribed and non-prescribed groups, we did an analysis comparing all subjects with prolonged amphetamine exposure to unexposed subjects. In this analysis, the age at diagnosis of PD was younger in the amphetamine exposed group than the non-exposed group (49.8 ± 8.2 years vs. 53.1 ±7.4 years; $p < 0.05$). Proportions of patients receiving initial treatments and of those reaching disease hallmarks (wearing off, dyskinesias, dementia, and use of DBS) were similar between the two groups. Moreover, survival analysis curves were prepared for a number of endpoints, including: time to first treatment, time to levodopa, time to wearing off, time to development of dyskinesia, time to dementia, and time to deep brain stimulation. None of the survival analyses demonstrated a significant difference between groups. All subjects responded well to standard PD treatments including DBS.

Brain MRI reports were available for 11 exposed and unexposed patients; the mean age at the time of scan was 54.5 in the exposed group and 53.7 in the unexposed group. Rates of reported foci of T2 prolongation were similar (54% in the exposed vs 46% in the unexposed) and each cohort had 1 patient with diffuse atrophy (9%). Review of the images in 10 exposed subjects by one author (CWC) revealed no consistent abnormalities in the basal ganglia or substantia nigra.

Discussion

In this study, we were unable to identify distinguishing features in subjects with prolonged exposure to amphetamine. Although we found a slightly earlier age at diagnosis in the amphetamine exposed group, no clinical or obvious MRI findings distinguished these two groups. Moreover, the response to treatments and rate of development of disease complications (motor fluctuations and dementia) were similar. However, because of the relatively small sample size and retrospective design, differences between these groups cannot be excluded entirely.

Even though we did not have high power for all outcomes tested, the narrow Cox confidence intervals (data not shown) for a number of measures (e.g. initiation of pharmacological treatment, initiation of levodopa) provides assurance that these cohorts are relatively similar for these outcomes. These findings contrast with parkinsonism described in manganese toxicity—as described in some welders12, some with liver failure13, and some methacathione users14— in which a number of clinical features differ from PD.

An autopsy study of young methamphetamine users found that dopamine levels were reduced more in the caudate than the putamen, a pattern opposite that seen in PD.15 The authors use this finding to explain why parkinsonism is not a feature of young human

methamphetamine users (mean age at autopsy, 31 years). However, since dopaminergic neurons are lost with aging,16 their finding of a 50% reduction of putaminal dopamine does not contradict our hypothesis that by damaging dopaminergic neurons, remote amphetamine exposure is risk factor for the later development of PD.

Our inability to identify unique clinical features in the amphetamine-exposed individuals does not preclude amphetamine as a risk factor for PD. However, the lack of a distinct clinical phenotype or biological marker may prevent clinicians who do not obtain a detailed history of amphetamine exposure from appreciating this potential association. Further research to determine whether amphetamine exposure is a risk factor for PD will require detailed histories of prescribed and recreational amphetamine exposure.

Acknowledgments

This study was supported using finds from the UCSF Department of Neurology.

Financial disclosures: the authors report no conflicts of interest. CWC was supported by UCSF Department of Neurology funds and support from Genzyme through a grant to the University of California. ERG was supported by Doris Duke Charitable Foundation Fellowship. LES has been supported by the San Francisco VA PADREC. DEA's work was self-supported. CEM is supported by numerous NIH grants.

References

1. Gasser T. Update on the genetics of Parkinson's disease. Mov Disord. 2007; 22(Suppl 17):S343–350. [PubMed: 18175395]
2. Chade AR, Kasten M, Tanner CM. Nongenetic causes of Parkinson's disease. J Neural Transm Suppl. 2006:147–151. [PubMed: 17017522]
3. Elbaz A, Moisan F. Update in the epidemiology of Parkinson's disease. Curr Opin Neurol. 2008; 21:454–460. [PubMed: 18607207]
4. Guilarte TR. Is methamphetamine abuse a risk factor in parkinsonism? Neurotoxicology. 2001; 22:725–731. [PubMed: 11829406]
5. Substance Abuse and Mental Health Services Administration OoAS. National household survey on drug abuse: main findings 1998. U.S. Dept. of Health and Human Services; Rockville, MD: 2002. p. 32
6. McCann UD, Wong DF, Yokoi F, Villemagne V, Dannals RF, Ricaurte GA. Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C]WIN-35,428. J Neurosci. 1998; 18:8417–8422. [PubMed: 9763484]
7. Wilson JM, Kalasinsky KS, Levey AI, et al. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. Nat Med. 1996; 2:699–703. [PubMed: 8640565]
8. Davidson C, Gow AJ, Lee TH, Ellinwood EH. Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment. Brain Res Brain Res Rev. 2001; 36:1–22. [PubMed: 11516769]
9. Ricaurte GA, Mechan 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; 315:91–98. [PubMed: 16014752]
10. Garwood ER, Bekele W, McCulloch CE, Christine CW. Amphetamine exposure is elevated in Parkinson's disease. Neurotoxicology. 2006; 27:1003–1006. [PubMed: 16620991]
11. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol. 1999; 56:33–39. [PubMed: 9923759]
12. Josephs KA, Ahlskog JE, Klos KJ, et al. Neurologic manifestations in welders with pallidal MRI T1 hyperintensity. Neurology. 2005; 64:2033–2039. [PubMed: 15888601]

13. Klos KJ, Ahlskog JE, Josephs KA, Fealey RD, Cowl CT, Kumar N. Neurologic spectrum of chronic liver failure and basal ganglia T1 hyperintensity on magnetic resonance imaging: probable manganese neurotoxicity. Arch Neurol. 2005; 62:1385–1390. [PubMed: 16157745]

14. Stepens A, Logina I, Liguts V, et al. A Parkinsonian syndrome in methcathinone users and the role of manganese. N Engl J Med. 2008; 358:1009–1017. [PubMed: 18322282]

15. Moszczynska A, Fitzmaurice P, Ang L, et al. Why is parkinsonism not a feature of human methamphetamine users? Brain. 2004; 127:363–370. [PubMed: 14645148]

16. Kish SJ, Shannak K, Rajput A, Deck JH, Hornykiewicz O. Aging produces a specific pattern of striatal dopamine loss: implications for the etiology of idiopathic Parkinson's disease. J Neurochem. 1992; 58:642–648. [PubMed: 1729408]

Mov Disord. Author manuscript; available in PMC 2011 January 30.

Table 1

Demographic characteristics, initial symptom(s) at diagnosis, and treatment of subjects according to prolonged amphetamine exposure.

	Not exposed (n=137)	Prescribed amphetamine (n=7)	Prescribed amphetamine vs not exposed	Non-prescribed use (n=9)	Non-prescribed use vs not exposed
	N (%)	N (%)	p	N (%)	p
Male	85/137 (62%)	2/7 (29%)	0.11	5/9 (56%)	0.73
Age at initial symptom	51.3 ± 7.5	49.6 ± 5.9	0.27[1]	47.2±9.5	0.06[1]
Age at diagnosis	53.1 ± 7.4	50±5.8	0.14[1]	49.7±10	0.09[1]
Asymmetrical symptoms	127/131 (97%)	7/7 (100%)	1.00	7/8 (88%)	0.26
Tremor	87/131 (66%)	5/7 (71%)	1.00	5/9 (56%)	0.49
Bradykinesia	49/131 (37%)	3/7 (43%)	1.00	4/9 (44%)	0.73
Rigidity	18/131 (14%)	1/7 (14%)	1.00	0/9 (0%)	0.60
Gait Abnormality	7/131 (5%)	0/7 (0%)	1.00	1/9 (11%)	0.42
Initial treatment					
Amantadine	9/130 (7%)	0/7 (0%)	1.00	1/9 (11%)	0.50
Monamine oxidase inhibitor	27/131 (21%)	2/7 (29%)	0.64	1/9 (11%)	0.69
Dopamine agonist	30/131 (23%)	1/7 (14%)	1.00	1/9 (11%)	0.68
Anticholinergic	14/131 (11%)	1/7 (14%)	0.56	2/9 (22%)	0.27
Later treatments					
Levodopa	116/133 (87%)	6/7 (86%)	1.00	7/9 (78%)	0.35
Deep Brain Stimulation	52/131 (40%)	3/7 (43%)	1.00	3/9 (33%)	1.00
Disease Progression					
Wearing off	73/132 (55%)	4/7 (57%)	1.00	7/9 (78%)	0.30
Dyskinesia	59/131 (45%)	4/7 (57%)	0.70	4/9 (44%)	1.00
Dementia	15/130 (12%)	1/7 (14%)	0.59	0/8 (0%)	0.60

P-values from Fisher's exact test unless otherwise noted

[1] Student's t-test.