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Conjugal Parkinsonism and Parkinson Disease: A Case Series with Environmental Risk Factor Analysis

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Abstract

PD occurring in married couples, "conjugal PD" represents a unique opportunity to study environmental risk factors for PD due to the shared environment. This retrospective study of non-related married individuals who both presented to the Washington University Movement Disorders Center between 1994 and 2005 investigated the clinical presentation, therapy response, and disease course in conjugal PD subjects. In addition, an occupational, residential, and environmental survey was administered to elucidate potential shared environmental risk factors.

Eighteen married subjects had a clinical picture suggestive of idiopathic Parkinson disease. Average age of motor symptom onset was 66.1 (±6.22) years in women, 63.4 (±7.87) years in men. Subjects cohabitated an average of 39.9 years prior to motor symptom onset in the first affected spouse and an average of nine years elapsed prior to symptom onset in their partner. Disease course in conjugal pairs varied substantially.

Seventeen out of eighteen subjects reported at least one environmental exposure of interest. Concordant exposures were residential, non-occupational pesticide and heavy metal exposure, each reported by 77.8% (7/9) of couples. Multiple exposures were reported by 88.9% (16/18) of subjects, most often residential agricultural chemical and heavy metal in combination. This case series of conjugal PD suggests that combined residential exposures may be important in the pathogenesis of idiopathic PD. Larger conjugal PD studies may permit stratification of concordant environmental exposures to determine dose responsiveness and relative contributions to PD risk.

Keywords

Parkinson disease; conjugal; environment

Introduction

Parkinson disease (PD) is a common neurodegenerative disease with no known cause in over 90% of cases, although environmental influences are suspected. Proposed environmental risk factors for PD include industrialization, rural living, and pesticide or heavy metal exposure. [1-5] Twin studies do not support a genetic cause, especially in older onset subjects.[6;7]

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Environmental and occupational exposures have been associated with the development of atypical parkinsonism, and may provide clues to the etiology of idiopathic PD. Environmental risk factors for PD strongly represented in the literature include: 1) industrialization,[8] 2) rural living, [9-11] 3) well water use, 4) pesticides and 5) heavy metal exposure.[3;12-14]

Little is known about the shared home environmental risks for PD in non-related persons. Although the prevalence of PD suggests that conjugal PD would be commonly seen in clinical practice, the report of conjugal PD in the literature is limited to single cases.[15;16] Presumably, conjugal PD cases may provide a window into significant home exposures involved in the pathogenesis of PD. We conducted a retrospective review of conjugal PD subjects seen in the last 11 years in a single academic movement disorders center to attempt to determine which shared environmental factors may play role in conjugal PD and a to provide framework for larger, future studies of conjugal PD.

Methods

Subject and Clinical Data selection

This study was approved by the Human Studies Committee at Washington University School of Medicine. We conducted a review of the clinical database in the Movement Disorders Center at Washington University and found 18 unrelated married subjects where both spouses developed parkinsonism. Subjects were identified by identical last names or overlapping addresses from all patients seen between 1994 and 2005. For the purpose of this study, each subject's clinical chart was examined for the following information: clinical history (for symptom onset, clinical features and medication response), disease course, and past medical history. Family history was reviewed for genetic factors that could potentially alter the risk of PD or modify the clinical presentation of parkinsonism.

Environmental Questionnaire and Data Analysis

Each conjugal PD couple was interviewed in person during their regular office visit, or via telephone if their next office visit was scheduled more than 3 months from the beginning of data collection. After verification of the recorded medical history, we administered a comprehensive residential, environmental and occupational history previously used in PD epidemiology studies and modified for this study.[17] The questionnaire primarily assessed potential residential exposure to pesticides (including herbicides, insecticides, fungicides, and rodenticides) via home use and living within 1 mile of farms where such chemicals were used, and potential residential exposure to heavy metals via recreational metallurgy and home proximity to metal emitting/manufacturing facilities or metal mines. We also obtained lifetime occupational histories and complete residential histories. Environmental Protection Agency facility emission data was used to verify report of proximity to metal emitting facility.[18] U.S. Census bureau data was used to estimate residential population density. All subjects were assessed at their initial office visit and at every visit thereafter with a United Parkinson Disease Rating Scale subset III (UPDRS III) score to quantify severity of parkinsonism, demonstrate dopaminergic responsiveness, and assess disease progression. Mini Mental State Exam (MMSE) scores were used to demonstrate cognitive decline in demented subjects. Each subject was assigned a motor phenotype of tremor dominant (TD), akinetic rigid (AR) or postural instability gait disturbed (PIGD) based on published clinical criteria using UPDRS II and III scores.[19;20] All descriptive data is presented as means and standard deviations where appropriate.

Results

Demographics

This study group consisted of nine women, nine men with a mean age at presentation of 64.9 years (range 49 to 78 years of age). Men reported onset of motor symptoms at an average age of 63.4 (±7.87) years, women at 66.1 (±6.22) years. Duration of cohabitation prior to symptom onset was on average 39.9 years (±9.2), with an average of nine years (range 1-13 years) elapsing until the second spouse became symptomatic. All subjects were of European descent, and described themselves as “white”. Intraclass correlation analysis revealed no significant correlation between age of onset (p=0.571) or year of onset (p=0.525) between conjugal pairs.

Genetic and Medical Risk Factors

Family history identified two non married subjects with risk factors that could alter the age of onset or presentation of PD. One subject (couple #7) had a history of familial tremor in a father/paternal grandmother. She had onset of left foot rest tremor at the age of 59, followed within 3 years by asymmetric bradykinesia, shuffling gait and freezing. She had clear response to levodopa with motor fluctuations (characterized as wearing off and peak dose chorea). Another subject (couple #9), who had a father with PD, developed cervical dystonia and upper extremity rest tremor at the age of 69 followed by asymmetric bradykinesia and rigidity.

All motor phenotypes of PD were represented in our sample, with nine subjects characterized as tremor dominant, four as akinetic rigid, and five as postural instability gait disturbed. One subject had an alcohol responsive postural and action tremor of her limbs and head for 49 years prior to developing micrographia, hypophonia, asymmetric bradykinesia and rigidity, consistent with preceding essential tremor (couple #9). She had a clear response to both levodopa and subthalamic nucleus deep brain stimulation.

Medical history revealed that one subject (couple #6) was treated with thioridazine for an Axis I disorder intermittently within 12 years of developing asymmetric rest tremor, bradykinesia, postural instability and rigidity at the age of 67. He had not received thioridazine in the year prior to the onset of motor symptoms. He had a sustained response to levodopa with reduction of UPDRS III score by 50% in the ON state, and developed motor fluctuations. None of the subjects had a history of stroke, encephalitis, or head injury.

Clinical Features

All subjects exhibited parkinsonism manifest as a combination of rest tremor, bradykinesia, rigidity, or postural instability. Thirteen subjects had a resting tremor of upper or lower extremities. Motor sign asymmetry was present in 15 of 18 subjects. No subjects had atypical eye movement abnormalities (square wave jerks, nystagmus, or gaze paresis), prominent dysautonomia, cerebellar signs, or spasticity. One patient had an atypical presentation of PD, with parkinsonism developing at age 68 characterized by early, prominent postural instability, symmetric bradykinesia and rigidity (couple#3). She had sustained moderate response to levodopa with peak dose chorea and wearing off phenomenon after four years of levodopa therapy. She expired 11 years after disease onset. There was no significant difference in mean age of onset between those subjects with early cognitive impairment, dystonia, neuroleptic exposure or a positive family history (63.5 years, SD 5.26), and those without these features (64.71 years SD 7.13), p=0.75. The clinical features of all subjects are summarized in Table 1.

Treatment Response and Disease Course

All treated subjects had both subjective and objective evidence of dopa responsivity as evidenced by a decline in ON UPDRS III score and subjective improvement of tremor,

slowness, ambulation or balance. Patients experienced an average of 32.3% improvement in the UPDRS III score from the initial office visit to optimal treatment. Sixty percent of treated subjects experienced motor fluctuations such as wearing off, dyskinesias, or dose failures at the time of this study. The average time to motor fluctuation was 3.25±1.98 years of treatment with levodopa or dopamine agonists. Progression of disease characterized by increase in UPDRS III score in the ON state occurred in all subjects, regardless of treatment status at a rate of 1.48 ±2.48 points per year.

Cognitive Impairment

Cognitive impairment unrelated to medication developed mostly later in the disease course. Four subjects experienced progressive memory difficulty, reduced ability to problem solve and decreased executive function with documented decline in MMSE to less than 26. These symptoms began on average 11.25 years after motor symptom onset, at a mean age of 71.5 ±5.09. Two subjects had cognitive decline less than 5 years after motor symptom onset. The first subject (couple #1) had word finding difficulties begin at four years after the onset of parkinsoniam, but complained of short term memory loss beginning 1 year prior to noticing motor symptoms of slowness, stiffness and altered gait. She had a rapid cognitive decline, modest asymmetry, and a modest response to levodopa with no motor fluctuations at the time of this study. A diagnosis of Parkinson disease with dementia (PDD) versus diffuse lewy body disease (DLB) was considered. The other subject (couple #5) developed rapid cognitive decline after abdominal catastrophe and prolonged illness two years after PD motor symptoms began at age 67, which may represent unmasked senile dementia.

Environmental and Exposure Assessment

All subjects completed the environmental questionnaire and interview. Residence in sparsely (<5,000 people), moderately (10,000- 50,000 people) and heavily (>100,000 people) populated areas was equally distributed in this group. Ninety four percent (n=17) of subjects reported at least one exposure of interest. Most often, residential pesticide use was reported in conjunction with heavy metal exposure (Table 2). Three subjects three or more exposures during their marriage.

The most commonly reported concordant exposures were residential pesticide use (reported by 77.8% of couples for an average of 34 years/person). Living within 5 miles of a metal manufacturing/emitting factory was verified by facility data in the Environmental Protection Agency's Toxic Release Inventory for 77.8% of couples for an average of 21.9 years/person. Other notable exposures reported included living within 5 miles of a heavy metal mine (1 couple for 14 years), and living within 1 mile of a farm where pesticides were used (1 couple for 49 years).

Discordant exposures included farming, welding, auto assembly, and commercial painting with leaded paint. Overall, occupational exposures to pesticides or heavy metals were reported by 3/18 (16.7%) subjects. Two subjects had more than one occupational exposure during marriage. Occupational exposures were reported by none of the subjects with atypical features.

Discussion

Although many PD risk factors have been suggested in epidemiology studies, [1;4;11;21-25] there is very little direct evidence implicating the environment as the primary etiology in the pathophysiology of PD. This manuscript describes clinical features and exposures to previously described PD risk factor exposures in 18 cohabitating unrelated spouses with parkinsonism. For the most part, the clinical presentation and disease course of these patients represents the full spectrum of idiopathic PD. One subject may have had MSA with parkinsonism;

nevertheless, there was still diagnostic uncertainty in this subject given the paucity of additional atypical features, the continued response to levodopa and evolution of motor fluctuations. Several patients developed dementia, most often >5 years after motor symptom onset. Another potential benefit to studying conjugal PD subjects is the ability to investigate the shared home environmental exposures in much greater detail. If home environmental exposures are important in the pathophysiology of PD, conjugal PD subjects may have substantially greater exposures than other sporadic PD subjects. Presumably, concordant exposures would be the most informative potential neurotoxins. Our preliminary environmental analysis revealed a number of interesting findings. The predominant concordant exposures seemed to be residential pesticide use and proximity to metal manufacturing/heavy metal emitting facilities. The finding that most subjects had more than one concurrent toxin exposure may explain the historical difficulties in clearly attributing PD risk to pesticides or heavy metals alone. Interestingly, there was a substantial difference in the date of onset of PD between conjugal PD subjects but the age of onset was quite similar. This seems to argue against a shared environment risk factor although our sample size was small. In a large sib-pair cohort, investigators found that the age at onset correlation was greater than the date of onset in 203 sibling pairs with PD.[26] These investigators concluded that their study supported a genetic component to PD. Presumably the same type of analysis in a large conjugal PD cohort could provide evidence for a shared home exposure if date of onset between conjugal pairs correlated more strongly than age at onset. Assuming a prevalence of PD of 1.1% and a population of almost 60 million over the age of 55 in the US,[27] the prevalence of conjugal PD should be 0.01% (the square of the population prevalence). Using those assumptions, we would expect approximately 7,300 cases of conjugal PD. Identification of some of these cases may provide increased sample power for assessment of shared home environmental exposures and the etiopathogenesis of PD.

Although the sample size in our study is small, we believe that the spouse pair design provides an opportunity to investigate shared home environmental influences on PD etiology. This is potentially important since we spend the majority of our lifetimes at or near home and most studies have focused on occupational exposures. Larger studies of conjugal PD with spatial-temporal environmental analysis may be a powerful method of studying specific PD environmental risk factors. Future studies which focus on combined exposures may be able to further support the hypothesis that chronic, low-level combined community exposures (pesticide-pesticide, pesticide-metal, or metal-metal) are important in the pathogenesis of idiopathic PD.

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Table 1

Clinical features of parkinsonism in 18 married subjects. TD= Tremor dominant, AK= Akinetic- Rigid, PIGD= Postural Instability Gait Disturbed, PDD=Parkinson Disease with Dementia, DLBD= Diffuse Lewy Body Disease

Couple	Sex	Age at Symptom Onset	Initial UPDRS III score	Rest Tremor	Rigidity	Bradykinesia	Asymmetry	Gait involvement	Postural instability	Motor Phenotype	Additional Features
1	M	68	13	Y	Y	Y	Y	N	N	TD	----
	F	59	15.5	N	Y	Y	Y	N	N	AK	Early Cognitive Decline
2	M	67	16	Y	Y	Y	Y	Y	Y	TD	----
	F	65	21	N	Y	Y	Y	Y	N	AK	----
3	M	73	19.5	Y	Y	Y	Y	Y	N	AK	----
	F	68	41	N	Y	Y	N	Y	Y	PIGD	----
4	M	61	26	N	Y	Y	Y	Y	N	AK	----
	F	49	32.5	N	Y	Y	Y	Y	Y	PIGD	----
5	M	67	54.5	Y	Y	Y	Y	Y	Y	TD	Early Cognitive Decline
	F	65	15.5	Y	Y	Y	Y	N	N	TD	----
6	M	67	37	Y	Y	Y	Y	Y	Y	PIGD	Neuroleptic Exposure
	F	68	19.5	Y	Y	Y	Y	N	Y	TD	----
7	M	78	15	Y	Y	Y	Y	Y	N	TD	----
	F	59	20	Y	Y	Y	Y	Y	Y	TD	Positive Family History
8	M	51	18.5	Y	Y	Y	Y	N	N	PIGD	----
	F	65	10.5	N	Y	Y	Y	Y	Y	PIGD	----
9	M	60	12.5	Y	Y	Y	Y	N	N	TD	----

Couple	Sex	Age at Symptom Onset	Initial UPDRS III score	Rest Tremor	Rigidity	Bradykinesia	Asymmetry	Gait involvement	Postural instability	Motor Phenotype	Additional Features
	F	69	44.5	Y	Y	Y	Y	N	N	TD	Positive Family History Essential Tremor Cervical Dystonia

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Table 2

Environmental exposure questionnaire responses for 9 couples with conjugal PD.

Couple	Sex	Concordant Exposures			Discordant Exposures	
		Residential Pesticide Use	Community Pesticide exposure	Community Heavy Metal Exposure	Occupational Pesticide exposure	Occupational Metal exposure
1	M	Y	N	Y	N	Y
	F	Y	N	Y	N	N
2	M	Y	N	Y	N	N
	F	Y	N	Y	N	N
3	M	N	N	Y	Y	N
	F	N	N	Y	N	N
4	M	N	N	N	Y	Y
	F	N	N	N	N	N
5	M	Y	N	Y	N	N
	F	Y	N	Y	N	N
6	M	Y	N	Y	N	N
	F	Y	N	Y	N	N
7	M	Y	N	Y	N	N
	F	Y	N	Y	N	N
8	M	Y	Y	N	Y	Y
	F	Y	Y	N	N	N
9	M	Y	N	Y	N	N
	F	Y	N	Y	N	N

Couple	Sex	Concordant Exposures			Discordant Exposures	
		Residential Pesticide Use	Community Pesticide exposure	Community Heavy Metal Exposure	Occupational Pesticide exposure	Occupational Metal exposure
Total		7 Yes	2 Yes	7 Yes	3 Yes	3 Yes
		2 No	7 No	2 No	16 No	16 No