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A Population-Based Study of Parkinsonism in an Amish Community

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Key Words
Parkinson's disease · Parkinsonism · Environment

Abstract
Background: Parkinson's disease (PD) is a neurodegenerative disorder with unknown cause. Genetic mutations account for a minority of cases but the role of environmental factors is unclear. ***Methods:*** We performed a population-based screening for PD in subjects in an Amish community over age 60. PD was diagnosed using standard clinical criteria and the Unified Parkinson Disease Rating Scale motor subsection 3 (UPDRS3). Community prevalence was calculated. We constructed a community pedigree and calculated kinship coefficients, a measure of relatedness between 2 subjects, for every pair of subjects in diagnostic categories: clinically definite PD, UPDRS3 score >9, Mini-Mental State Exam (MMSE) score <25, and normal. ***Results:*** Of 262 eligible subjects, 213 agreed to participate, 15 had PD, 43 had MMSE <25, 73 had UPDRS3 >9. The prevalence of PD was 5,703/100,000 with increasing prevalence in every decade of age. Excluding first-degree relatives, normal subjects were more related to each other (0.0102, SD = 0.0266) than subjects with clinically definite PD (0.0054, SD = 0.0100; p = 0.00003), subjects with UPDRS >9 (0.0076, SD = 0.0155; p = 0.00001), and subjects with MMSE <25 (0.0090, SD = 0.0180; p = 0.00003). ***Conclusions:*** PD and parkinsonian signs are common in this population and the prevalence increases with age. The finding that subjects with PD were not more related than normal subjects suggests that environmental factors may contribute to the parkinsonian phenotype in this community.

Introduction

The cause of Parkinson's disease (PD) remains unknown except for rare monogenetic mutations in genes coding for α-synuclein [1], parkin [2], DJ-1 [3], PINK-1 [4], and LRKK2 [5]. However, it is not entirely clear what roles these genes play in sporadic PD. Studies of genetic contributions to sporadic PD have provided mixed results. In a population-based Veterans Administration twin study, concordance rates in monozygotic twins were higher than those in dizygotic twins in younger onset PD, whereas the concordance rate between monozygotic and dizygotic twins was similar in older onset PD, suggesting an environmental etiology for the more common form of PD [6]. However, using an extensive population-based ge-

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nealogy to determine the genetic contribution to sporadic PD in Iceland, subjects with PD were more related than non-PD controls, suggesting a genetic etiology to sporadic PD [7]. Both of these studies employed unique and powerful methods, yet still came to opposite conclusions. Assessment of an independent sample may clarify this issue.

The Amish religion formed in 17th century in Switzerland and beginning in the 18th and 19th centuries adherents immigrated to the United States to flee religious persecution. The Amish live in communities culturally isolated from society; they shun modern conveniences and marry within their religion. However, they are socially integrated and work and do business within mainstream society. The Amish keep meticulous family records, maintain strict endogamy, and forbid consumption of alcohol or use of tobacco. Their communities are exclusively rural and occupations chosen are relatively limited to manual labor vocations. All Amish complete eighth grade and do not pursue further education, minimizing educational biases in population studies. These features make the Amish an ideal population for study of genetic and environmental causes of disease.

We previously published a report of a large multi-incidence family with PD [8]. Although genetic analyses of this pedigree are ongoing, we have extended our initial study to perform a population-based study of a single Amish community with an apparent high prevalence of parkinsonism. The specific aim of this study was to determine the genetic and environmental influences on PD in this population-based sample with potential future application to genetic-linkage and environmental epidemiology studies.

Materials and Methods

This study was approved by the Washington University School of Medicine Human Studies Committee.

Subjects

We recruited all subjects over age 60 in an Old-Order Amish community, geographically isolated from other Amish communities. Subjects were identified by a community-based study coordinator using a current version of a community directory. As of prevalence date May 1, 2001, there were 4,369 Amish in this community and 262 were aged 60 or greater. Initially, advertisements were placed in a regional Amish newspaper inviting subjects to participate in a PD screening. Subjects who did not respond were visited by our community-based study coordinator. Previously described PD genes or loci were excluded in this pedigree by either direct sequencing of the gene (α-synuclein [1], parkin [2], DJ-1 [3], PINK-1 [4]) or linkage analysis of markers flanking the known loci (PARK 3 [9], PARK 8 [5], PARK 9 [10], PARK 10 [11]) and the known genes. We also sequenced UCHL-1 [12] and found no mutations.

We obtained a complete medical and PD-specific history with a validated and weighted questionnaire [13] and performed a neurologic examination that included the Unified Parkinson Disease Rating Scale motor subsection 3 (UPDRS3) and Mini-Mental State Exam (MMSE, in English) [14] on each subject. We classified individuals as clinically definite PD if they exhibited three of the following: rest tremor, rigidity, bradykinesia or postural instability, or two of these features with one of the first three displaying asymmetry. Supportive criteria and exclusionary criteria were taken from the United Kingdom Parkinson Disease Society Brain Bank criteria with the exception of 'more than one affected relative' [15, 16]. We also used a case definition of 'parkinsonism' as UPDRS3 >9 since we had previously shown that this threshold of parkinsonism was highly predictive of a clinician's diagnosis of parkinsonism [17]. To determine the relationship between selected parkinsonian signs and age or cognitive function, we subdivided the UPDRS3 score into axial signs, bradykinesia, and rigidity. Axial signs included a sum of voice, facial expression, arising from a chair, gait, and postural instability scores. Bradykinesia included the sum of limb bradykinesia scores. Rigidity included the sum of limb and neck rigidity scores. For the purpose of this study, 'normal' subjects were defined as those with a UPDRS3 <3 and MMSE >25.

Kinship Calculations

A community-based pedigree was constructed with the program Cyrillic 2.1 (Cherwell Scientific) using Amish family books and the Anabaptist Genetic Database [18, 19]. The kinship coefficient is a measure of genetic relatedness between 2 subjects and is defined as the probability that an allele will be shared identically by descent from a common ancestor. For example, the kinship coefficient for siblings in the absence of consanguinity is 0.25 since each parent may contribute one of two alleles for a given gene. We calculated the pairwise kinship coefficients between all subjects in the following diagnostic categories: normal, definite PD, parkinsonism, and MMSE <25. We calculated a mean kinship coefficient within these diagnostic categories and compared the results between normal subjects and the other diagnostic categories. Given the substantially smaller number of subjects within the other diagnostic categories, we also performed calculations excluding comparisons between first-degree relatives in both groups to minimize weighting of the kinship coefficients based upon large family size [7].

Data Analysis

All statistics were performed using SPSS v12.0, Chicago, Ill., USA. All means for the sample are expressed as mean ± standard deviation. Mean kinship coefficients were compared using a two-tailed t test. Correlation between clinical variables (UPDRS3, bradykinesia, axial signs, rigidity, and MMSE) and age was assessed with a two-tailed Pearson correlation coefficient. To test the independent and dependent effects of age and MMSE on UPDRS3, we used linear regression analysis. For all analyses described, significance was established at $p < 0.05$.

Results

Of 262 eligible Amish subjects aged 60 or greater on prevalence data May 1, 2001, 213 consented to participate (81%). Four died before they could be screened. The remainder of subjects or caregivers refused participation. The demographics of this population by diagnostic category are in table 1. The prevalence of clinically definite PD in all subjects over age 60 was 5,703 per 100,000 (95% confidence interval: 5,095–6,225). The prevalence of PD in this population increased with every 10-year age strata (table 2).

Occupations of these Amish research subjects reflected the rural environment in which they reside. Nearly all men were farmers (crop and/or livestock), but approximately 50% had additional manual labor occupations such as carpentry, factory work, or other agricultural related occupations. The overwhelming majority of women were homemakers (94%) and the remainder performed clerical work for local businesses. All subjects resided in a remote, rural Midwestern farm region and used well water during their lives, although professional water and wastewater systems ('rural water') were being introduced into the community during the course of this study. According to Amish customs, none of the subjects use electricity so all home heating and lighting used propane. There were no living spouse pairs with PD although 1 woman with PD had a husband who died with idiopathic PD prior to the prevalence date for this study. Only 2 of the residents in this community with PD were first-degree relatives (father-son).

The mean UPDRS3 score in the community was 9.4 ± (SD) 10.8. Parkinsonism in the community, as measured by UPDRS3 scores, increased with age. The correlation between UPDRS3 and age was $r = 0.438$ ($p < 0.001$). Bradykinesia ($r = 0.406$, $p < 0.001$) and axial signs ($r = 0.481$, $p < 0.001$) moderately correlated with age. There was a weak correlation between rigidity ($r = 0.265$, $p < 0.001$) and age. There was a negative correlation between cognitive status, as measured by the MMSE, and age ($r = -0.557$, $p < 0.001$). The parkinsonian phenotype subgroups were negatively correlated with MMSE (more parkinsonian patients had worse cognitive function): bradykinesia, $r = -0.587$ ($p < 0.001$); rigidity, $r = -0.393$ ($p < 0.001$), and axial signs, $r = -0.485$ ($p < 0.001$). Using linear regression, MMSE and age produced an adjusted R^2 of 0.364 ($F = 60.01$, $p < 0.001$) for the prediction of UPDRS3 scores. MMSE was the strongest predictor of UPDRS3 scores ($\beta = -0.455$, $t = -7.582$, $p < 0.001$).

Table 1. Demographics features of Amish studied

	Age		Gender	
	mean	SD	male	female
All	71.42	8.51	121	141
Normal	66.51	4.8	18	27
Subjects not examined	73.25	9.98	22	27
Definite PD	78.46	8.24	6	9
UPDRS >9[a]	75.78	7.71	29	44
MMSE <25[b]	75.03	9.38	21	22
UPDRS >9 and MMSE <25	77.05	8.61	10	20

[a] UPDRS >9 includes subjects with PD.
[b] MMSE <25 excludes subjects with PD.

Table 2. Crude prevalence (per 100,000) of clinical categories

Age strata	Subjects n	Cases, n		
		PD prevalence	UPDRS >9 prevalence	MMSE <25 prevalence
60–69	132	2 1,515	16 12,121	16 12,121
70–79	85	7 8,235	36 42,353	15 17,647
80–89	39	5 12,820	20 51,282	10 25,641
90+	6	1 16,666	1 16,666	2 33,333

Definite PD only (prevalence rate is a minimum and assumes nonparticipants were normal).

Pairwise kinship coefficients demonstrated that the normal control group was more related than subjects with UPDRS >9 when analyses included first-degree relatives (table 3). To minimize the bias from having more first-degree relative comparisons in the normal subjects, we performed the same analyses excluding all comparisons between first-degree relatives within these diagnostic categories. Normal subjects were more related to each other than subjects with clinically definite PD, UPDRS3 >9 and MMSE <25 when first-degree relatives were excluded. To ensure that the kinship results were not affected by subjects who refused to participate, we performed an additional kinship calculation adding all subjects not seen to the normal subjects and compared

Table 3. Kinship coefficients for diagnostic categories

	Kinship comparisons n	Mean kinship coefficient[1]	SD	p value[2]
Normal	990	0.0119	0.0266	
Without 1st-degree relatives	983	0.0102	0.0169	
Definite PD	78	0.0078	0.0262	0.1315
Without 1st-degree relatives	77	0.0054	0.0100	0.00003
UPDRS >9	2,211	0.01	0.0282	0.0398
Without 1st-degree relatives	2,026	0.0076	0.0155	0.00001
MMSE <25	1,225	0.0105	0.0266	0.1499
Without 1st-degree relatives	1,217	0.0090	0.0180	0.00003
UPDRS >9/MMSE <25	406	0.0106	0.0284	0.2941
Without 1st-degree relatives	398	0.0083	0.0162	0.01597

[1] For comparisons between all subjects meeting diagnostic criteria for each category.
[2] Compared to normal.

kinship coefficients between this group and all diagnostic groups. Including these subjects in the 'normal' category did not change the results in table 3.

Discussion

In this community we found a high prevalence of PD. This high prevalence could have resulted by chance or could be due to the relatively small population over age 60, but we feel that this is unlikely given the nearly 10-fold greater prevalence compared to a previous American door-to-door study [20]. It is also possible that screening by movement disorders specialists could increase prevalence due to a more sensitive examination. Previous studies suggest that non-neurologist screenings detect parkinsonism with good sensitivity [21], but no one using similar methodology has compared surrogate screening methods to movement disorders specialist examination. In addition, the religious prohibition of smoking may contribute to the higher prevalence of PD given the strong evidence of a protective effect of tobacco on incident PD [22, 23]. Although we do not have detailed information about caffeine use in this population, there is no specific prohibition against caffeine use in the Amish, and the protective effects of caffeine on parkinsonism [24] and PD [25] do not appear to be as profound as those of tobacco.

The original hypothesis of this study was that PD in this Amish population would be due to recessive genetic factors, based upon the high prevalence of inbreeding in Amish communities. This population-based study was an attempt to replicate the methodology used in a previous study in Iceland where subjects with PD were found to be more related than normal subjects from the same population, resulting in the discovery of the PARK 10 locus [7]. However, our community-based study of elderly Amish demonstrates that clinically definite PD subjects were less related than normal subjects, implying that environmental factors may be important in the pathogenesis of PD in this population. Similarly, subjects with parkinsonism as defined by UPDRS3 score were not more related to each other than normal subjects, consistent with studies relating parkinsonism in elderly populations with environmental factors [26]. This does not necessarily mean that there are no genes contributing to PD or parkinsonism in this population, since most 'sporadic' PD cases are thought to be due to environment-gene interactions [27, 28]. It is still possible that there may be a subgroup of subjects with a monogenetic form of PD and the higher prevalence of parkinsonism in this community may result from phenocopies of the genetic parkinsonisms, confounding detection of linkage. Nevertheless, the findings in this study are consistent with a potential environmental etiology of the parkinsonian phenotypes in this Amish community, underscoring the likely diverse etiologies contributing to the pathogenesis of PD.

The population-based kinship methods we employed provide indirect evidence for potential environmental factors leading to PD. Since familial aggregation can occur due to a common living environment and Amish tend to reside on the family farm in adulthood, the find-

ing that subjects with PD were not more related than normal subjects potentially implicates a nonresidential environmental exposure in the pathogenesis of PD. Given the limited number of occupations represented in this and other Amish populations, detailed work history reconstruction may lead to a source of PD and parkinsonism in this community. Although the small number of clinically definite PD subjects may preclude detecting an environmental risk factor, parkinsonism, as defined by the UPDRS3, was substantially more common and may prove to be a useful case definition for a future case-control study of environmental risk factors in this population.

We found that MMSE <25 did not appear to have a genetic component, since those with low MMSE scores were not more related than reference subjects with normal MMSE scores. The results did not change when a lower MMSE score was selected (data not shown), although one might have expected that this would select a group of subjects with likely Alzheimer's disease. Follow-up of subjects with a clinical dementia rating or similar assessment may yet select a more related cohort appropriate for linkage analysis. Sequencing the apolipoprotein E gene, the most common genetic risk factor for Alzheimer's disease [29, 30], would provide confirmation of the validity of our methodology, as we would predict that apolipoprotein A alleles would not be associated with the dementia phenotype in this community since subjects with dementia were not more related than normal subjects.

Finally, there are several important caveats to this study. Since the prevalence of PD increases with age for sporadic PD and the prevalence of PD is typically age-dependent in genetic forms [31, 32], this cross-sectional study may misclassify subjects as normal who later develop PD. Unfortunately, this confound is unavoidable without prolonged follow-up of subjects or use of a biomarker of nigrostriatal dysfunction [33]. Second, phenocopies of PD such as multiple system atrophy or progressive supranuclear palsy may be mistaken for PD in cross-sectional studies. Once again, long-term follow-up of affected subjects minimizes the likelihood of misdiagnosis. We believe that the misclassification risk in this cohort is relatively small since most of the clinically definite PD subjects have been examined on multiple occasions. Even negative genetic linkage studies would not necessarily preclude genes of major effect in this genetically complex cohort. The pedigree that we created to link all subjects in this community contains over 100 inbreeding loops. Current computer technology precludes genetic analysis of this community-based pedigree without breaking most of the loops, resulting in a loss of potentially important genetic information. Finally, the sample size in this study is relatively small and should be confirmed in a larger sample. There are over 200,000 Amish in North America but all live in geographically isolated regions. Even with the availability of the electronic pedigree information at the National Institutes of Health [18], many individuals will still need to be linked to common ancestors through the use of multiple regional family history books, a process that can be quite laborious.

Despite these caveats, we believe that our study provides preliminary evidence of a potential environmental contribution to the etiology of PD in this population. Given the similarities between Amish communities, it may be possible to use these methods to study the various rural Amish communities throughout the United States. Geographic isolation and reticence to cooperate with researchers are both limiting factors that can be addressed in future research by using community-based recruiters and conducting home-based screenings over several days. This larger sample size from throughout the rural United States may provide substantial power to detect associations between the PD phenotype and specific toxins, such as specific pesticides/herbicides and well water contaminants. Similarly, the limited number of manual labor occupations may provide greater power to discriminate specific work exposures associated with the PD or parkinsonian phenotypes. Finally, our work with this and other Amish communities provides a foundation for the study of genetic and environmental risk factors for other neurodegenerative diseases.

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