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Evidence of shared risk for Alzheimer's disease and Parkinson's disease using family history

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Abstract

This case-control study examined the potential for a common etiology of Parkinson's disease (PD) and Alzheimer's disease (AD) using reported family history. Structured interviews were used to collect AD and PD family history from subjects ($n=1531$) with AD, PD, AD/PD, or controls. Intergroup analysis compared reported AD and PD family histories in the three case groups to the histories reported in the control group. Intragroup analysis stratified each diagnostic group based on positive family history of AD, then compared the subgroups for a family history of PD. Subjects with AD had a higher risk of having a family history of AD [odds ratio (OR) 2.3; 1.5–3.4] and subjects with PD had a higher risk of having a family history of PD (OR 2.2; 1.2–4.0) as compared to control subjects. Intergroup analyses revealed no significant crossed risk, increased risk of subjects with AD having a family history of PD vs controls and vice versa. Intragroup analysis found that subjects with PD and a family history of AD were more likely to have a family history of PD (OR 1.7; 1.1–2.6) when compared to subjects with PD and no family history of AD. A similar trend was found for subjects with AD (OR 1.7; 0.9–3.1). AD and PD cases each have an increased familial risk of their respective disease. Probands with AD or PD and a family history of either disease have a higher crossed risk of a family history of the other disease. These findings suggest the existence of common genetic and/or environmental factors that predispose to both AD and PD in the subset of cases with positive family history of both neurodegenerative diseases.

Keywords

Neurodegenerative diseases; Familial dementia; Odds ratio; Risk assessment; Family tree

Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) have markedly different clinical and pathological features. AD is the prototypical dementing illness, associated with cortical dysfunction, amyloid plaques, neurofibrillary tangles, and cholinergic basal forebrain degeneration. In contrast, PD is a common akinetic movement disorder, associated with basal ganglia dysfunction, Lewy bodies, and degeneration of the substantia nigral dopaminergic

neurons. Rare Mendelian forms of AD and PD have led to identification of a growing list of distinct genes for both diseases [1–9] reinforcing long held notions that distinct pathophysiological processes lead to the two diseases.

However, it is now well established that AD and PD share numerous epidemiological, clinical, neurochemical, and neuropathologic similarities. Clinically, 20–50% of patients with AD have extrapyramidal signs, particularly rigidity and bradykinesia, and almost 80% of patients with PD ultimately develop dementia [10]. Pathologically, one quarter to one third of AD patients show concomitant PD changes [11]. Thirty-three to 97% of PD patients with dementia have co-occurring AD at autopsy [12–14]. In addition, cortical Lewy bodies have been associated with dementia in both AD [15,16] and PD [17,18]. Thus, the overlapping features of these conditions raise questions about whether AD and PD in their “classical” forms are different diseases with distinct pathophysiologies that coincidentally overlap or alternatively indicate shared common pathophysiologies.

If AD and PD have some shared pathogenic mechanisms, one would expect family studies to detect an increased risk for AD in the families of patients with PD and an increased risk for PD in the families of patients with AD (i.e., ‘shared-risk’). Evidence for a ‘shared-risk’ has been mixed with most research finding no such increased crossed familial risk, although two of these studies nearly reached significance [19–23]. These studies grouped all AD cases together and all PD cases together and/or excluded patients with PD and dementia. A limitation of this methodological approach is that the intermingling of cases and families with varying loads of genetic and environmental factors will lessen the power to detect either type of factor. For both diseases, there are families with a strong genetic contribution and cases that are sporadic, suggesting there may be distinct mechanisms among patients with the same disease.

In the current study, we tested the ‘shared-risk’ hypothesis for AD and PD capitalizing on a large clinic and research population of subjects with detailed family histories obtained from structured interviews. To avoid some of the methodological limitations of prior studies, we reasoned that stratification of the cases within each disease group based on family history might allow a more robust method for detecting shared mechanisms. We hypothesized that cases with a positive family history of either disease will enrich for common genetic risk factors. One study that used this approach found support for the ‘shared-risk’ hypothesis when PD cases were stratified by presence or absence of a family history of the disease [24]. We analyzed four separate diagnostic groups (AD, PD, mixed AD and PD, and healthy controls). In an intergroup analysis, we compared reported family history of AD and PD for the three case groups vs the control group. In an intragroup analysis, we stratified the AD and PD groups based on the presence or absence of a family history of AD, and then compared each of these two subgroups for differences in family history of PD.

Materials and methods

Subjects

Participants ($n=1531$) were recruited as part of a research registry in Emory University’s Department of Neurology and Alzheimer’s Disease Research Center over a 13-year period between 1992 and 2005. Patients with AD ($n=592$), PD ($n=585$), and AD/PD ($n=126$) were recruited from the memory and movement disorder clinics sequentially. Control subjects ($n=228$) without a known history of neurological disease were recruited mostly from general medical clinics and community educational events. All subjects provided informed consent using an Institutional Review Board (IRB)-approved protocol.

Each subject was assigned a research diagnosis as either AD, PD, AD/PD, or control by (1) individual experienced neurologists subspecializing in cognitive or movement disorders, who

personally provided a comprehensive evaluation in clinic, or (2) by two or more subspecialty neurologists after reviewing all available medical information. For those patients with longitudinal clinical assessments, the most recent clinical impressions were utilized. The AD group included subjects with a diagnosis of AD, using widely accepted criteria including supportive neuropsychological testing [25], and were free of other neurological disease. The PD group included patients with a diagnosis of PD based on presence of two or more cardinal motor features of the disease [26,27] and the absence of features suggestive of other Parkinsonian syndromes or additional neurologic disease. The AD/PD group included several clinical diagnoses, including (1) both AD and PD (AD/PD), (2) Parkinson's disease with dementia (PDD), (3) AD with extrapyramidal symptoms (EPS), and (4) dementia with Lewy bodies (DLB). The control group had no reported medical history of a neurological disease (by exam where available, by self-report for all others), were 65 years of age or older, and had Mini Mental Status Exam (MMSE) scores of 25 or higher. Any control subject in this protocol related to any of the subjects in the three case groups was excluded to minimize recruitment bias.

Ascertainment of family history

Subjects in all study groups completed a structured family history interview in which they were asked to identify all family members with either AD or PD. Other family members helped to provide details for most AD and AD/PD cases and for a smaller percentage of the PD cases. Furthermore, they were required to specifically indicate which family member had the disease in question. In addition, a subset of subjects was also asked about cancer occurrence in their family to test for recall bias.

A family history of AD was considered positive if AD was reported in any specific, named family member. The same method was used to determine a positive family history of PD and to determine a positive family history of cancer. We did not include reports of memory loss, tremor, or other types of dementia as positive family histories. For those analyses utilizing extended family members to determine a positive family history, most of the extended family members included were second degree family members. None of the family members were examined.

Analyses

First, an analysis between the groups (intergroup analysis) was performed in which we compared incidence of family history of AD and family history of PD in each of the three case groups as compared to the control group. The results are the odds ratios (OR) for family history of AD and for family history of PD in the AD, PD, and AD/PD groups individually as compared to the control group. These analyses were multivariate and controlled for age, race, and gender. The size of the extended family would ideally also be included, but our data were insufficient to control for this variable. The analyses were also performed separately using information about all blood relatives (i.e., extended family) or first-degree relatives only.

Second, an analysis within each group (intragroup analysis) was performed after stratifying the diagnostic groups by family history (Fig. 1). Each case group was stratified by the presence or absence of a family history of AD in the extended family, and each subgroup was then compared to the other for family history of PD. Note that the analogous analysis with stratification by family history of PD and OR calculated for risk of family history of AD yields the same results (data not included; Fig. 2). All analyses were controlled for age, race, and gender. We did not perform the intragroup analysis on first-degree relatives only because of the relatively small numbers in these groups.

Statistical analyses were performed using SAS PROC LOGIST. Age, race, and gender were included in all analyses. Age was used as a continuous variable; race was Caucasian or African-American. Approximately 4% of the data were lost in multivariate analyses because of missing data for one or another covariate.

Results

The demographics of the subjects in each diagnostic group are shown in Table 1. As expected, the females predominate in the AD group, and the PD subjects are predominantly male and younger. Gender differences were also seen in the control group (female predominant) and the AD/PD group (male predominant). We performed a univariate *t* test for age and univariate chi-square tests for race and gender comparing the control group to the three case groups. See Table 1 for results.

Table 2 shows the number of participants in each study group with positive family histories of AD and PD. Including all known relatives in the analysis, the frequency of reported AD family history was higher in the AD case group (33.5%) than in the other three study groups (25.9% for controls, 21.4% for AD/PD, and 21.0% for PD). This frequency difference is significant between the AD group and all three other groups: PD ($p<0.001$), AD/PD ($p<0.008$), and control ($p<0.04$). In addition, the frequency of AD family history is higher in the control group (25.9%) than in the PD case group (21.0%) and in the AD/PD case group (21.4%); however, this difference is not statistically significant with *p* values of 0.14 and 0.35, respectively. Similarly, the frequency of reported PD family history was significantly higher in the PD case group (27.2%) than in the other three study groups (15.1% for AD/PD $p<0.005$, 12.3% for control $p<0.0001$, and 7.6% for AD $p<0.0001$). The frequency of PD family history was significantly higher in the control group (12.3%) than in the AD case group (7.6%; $p<0.04$).

Logistic regression analysis was used to calculate the OR for the family history of AD or PD in the three case groups compared to controls (Table 2). As expected, AD subjects had a significantly increased risk of having a positive family history of AD when compared to the control subjects [1.9; 1.3–2.7 95% confidence interval (CI)]. Similarly, the PD patients had a significantly increased risk of a family history of PD when compared to controls (2.4; 1.5–3.9 95% CI). There was no crossed risk of either AD or PD; that is, AD cases did not show an increased risk of a family history of PD, and PD cases did not show an increased risk of a family history of AD. In fact, PD patients had a lower risk of familial AD than controls (0.6; 0.4–0.9 95% CI). AD/PD subjects showed no differences in risk of family history of either AD or PD as compared to control subjects.

As the reliability of reported medical information may be dependent upon the distance between the proband and relatives, a separate analysis of crossed risk of AD and PD was performed using only the data from the first-degree relatives (Table 2). Multivariate results were generally unchanged when comparing the analyses including only first-degree relative family history to the analyses including all relatives, although there were the expected lower frequencies of positive family histories for both diseases when only including first-degree relatives. Three of the univariate results changed when comparing analyses including only first-degree relative to those including all relatives. The AD family history reported in the PD case group was significantly lower than in the control group ($p<0.03$) when only first-degree relatives were included. When including all relatives, this difference was not significant ($p<0.14$). The PD family history reported in the AD/PD case group was significantly different from that reported by the PD case group when including only first-degree relatives ($p<0.005$) vs ($p<0.2$) when all relatives were included. And lastly, the AD case group did report significantly less PD family history than controls when only first-degree relatives were included ($p<0.04$) vs ($p<0.27$) when all relatives were included. These changes in significance do not alter the conclusions drawn

from this analysis. Hence, the results of the intergroup analysis showed that AD and PD subjects have substantial increased risks of having the same disease in their family, but among all cases, there was no evidence for increased crossed risk.

To investigate the possible presence of a subset of cases with increased susceptibility to both AD and PD, we stratified the subjects in each diagnostic group by presence or absence of AD in their family history (including all relatives). We then performed an intragroup analysis comparing the frequency of a family history of PD in those with or without a family history of AD. As shown in Table 3, for probands with either AD or PD, those with a family history of AD were more likely to have a family history of PD. For example, AD cases with a positive family history of AD also exhibited an increased frequency of a positive family history of PD [11.1 vs 5.8%; OR 1.7 (0.9–3.1, 95% CI)] when compared to AD cases without a family history of AD. The increased crossed risk was also observed for PD cases with a positive family of AD [35.8 vs 24.9%; OR 1.7 (1.1–2.6, 95% CI)] when compared to PD cases without a family history of AD. The crossed risk was also observed in control cases, but the results did not reach statistical significance [17% vs 10.7%; OR 1.7 (0.7–4.1, 95% CI)]. No crossed risk of AD and PD was observed for those cases with AD/PD overlap syndrome, suggesting that either these are mechanistically distinct cases, a mixture of cases with several causes, or that the sample size was insufficient to detect a true difference [14.8 vs 15.2%; OR 0.8 (0.2–3.0, 95% confidence interval)].

The sensitivity of a family history report is dependent upon the recall and knowledge of the informant. As the identity of the informant was not recorded for all subjects, we are unable to analyze that data for the entire cohort. To address the possibility of bias based on the identity of the informant among groups, we examined this information for a random 20 subjects in each group. The subject was the sole provider of the family history for 100% of the controls, 70% of the PD subjects, 15% of the AD subjects, and 25% of the AD/PD subjects. The other 30% of PD subjects were assisted by at least one other family member. In the AD and AD/PD groups, 65% were assisted by at least one other family member. In the remaining 20% of AD cases and 10% of AD/PD cases, another family member was the sole provider. These results provide evidence for a notable difference in informants between the four study groups. Given the reduced involvement of the proband in reporting their family history, we would expect the family history reported in the AD and AD/PD groups to be less complete than in the PD and control groups.

Discussion

AD and PD each have well-established familial risks, with about 15–35% of all cases having an affected relative with the same disease [22,23,28–33]. We found that, as a group, AD subjects have no increased familial risk of PD and that, as a group, PD subjects are significantly less likely to have a family history of AD than controls. However, our intragroup analysis reveals an interaction between family history of AD and family history of PD in both the AD and the PD groups. This finding supports the ‘shared-risk’ hypothesis; that is, there is a subset of families presenting with both AD and PD, and then there are other families in which the respective diseases appear to occur sporadically. Thus, for at least a subset of families, our results suggest a shared pathophysiological mechanism for AD and PD.

Our intergroup analysis was very similar in methodology and results to other studies that examined familial risk for AD and for PD [28,31]. Inclusion in case groups was based on clinical diagnosis following accepted diagnostic criteria. In all cases, the risk for AD was higher in families with a history of AD, and the risk for PD was higher in families with a history of PD [19–21,34]. These same studies also failed to find any crossed risk of AD or PD using intergroup analyses.

Our intragroup analysis, with methodology similar to the study of Van Duijn et al. [24], found support for the shared-risk hypothesis. These analyses were performed by splitting each diagnostic group into two subgroups based on reported family history of AD and then determining if one subgroup had a larger family history of PD than the other. Both AD and PD are complex diseases with a variety of genetic and environmental influences. Separating the subjects with a probable higher degree of genetic predisposition for a disease, i.e., familial cases, allowed us to find correlations using family history, which may be masked when including sporadic cases. Past studies that refuted the correlation between AD and PD [34, 35] did not distinguish probands with familial disease from probands with sporadic disease. This approach to stratify cases of neurodegenerative disease by family history may be a key to finding common risks between the diseases. Families with members affected by either AD or PD might either be crucial to understanding the shared risk of AD and PD or they might have a different disease pathophysiology than sporadic cases. We performed our intragroup analysis two ways: (1) by creating subgroups based on reported family history of AD and then calculating the OR for having a family history of PD and (2) by creating subgroups based on reported family history of PD and then calculating the OR for having a family history of AD. We did not report the results of the second analysis because they are identical to those derived in the first analysis. See Fig. 2 for further illustration.

Recall bias is a potential limitation of the study. Previous studies have detected a recall bias for a specific disease if the proband has the disease [36]. To minimize the influence of recall bias, we performed the intergroup analysis using the family history of only first-degree relatives and the family history of the extended family and observed similar results using both strategies. We also tested for this bias by performing an intragroup analysis searching for an interaction between family history of AD and family history of cancer and between family history of PD and family history of cancer, including all family members. This analysis included 60% of the subjects in the AD and PD groups who had been specifically asked about their family history of cancer in addition to family history of AD or PD during their structured interview. None of the intragroup analyses involving family history of cancer had statistically significant results. Hence, our results do not appear to be caused by recall bias, rather, they likely reflect a true sharing of risk for both AD and PD in some families.

Other limitations of the study include limited or no physical exams performed on control subjects, no exams or medical records collected on family members reported to have disease, and referral bias. AD and PD family history, most notably in the control group, is higher than the histories reported in most literature. It is possible that subjects were more likely either to be referred to the study or to be interested in participating in the study if they had a family history of AD or PD. Although this limitation affects the results of the intergroup analysis, it should not alter the intragroup analysis findings. In addition, as many of the family histories for AD and AD/PD subjects were not collected from the proband, the specificity of family histories collected for these groups may be reduced [36]. Given the memory problems encountered by our AD and AD/PD subjects and not wanting to limit these groups to individuals in the early stages of the disease, this was a limitation we accepted. However, the sensitivity of these histories should not have been affected based on studies conducted by Elbaz et al. [36] and Li et al. [37]. Age, race, and gender of our four study groups were also different and may have affected the family history reported.

Interestingly, inter- and intragroup analyses showed no significantly increased risk for a family history of AD or of PD in subjects with AD/PD when compared to controls. Individual subjects in our AD/PD group had various diagnoses involving AD and PD-like symptomatology, including (1) separate AD and PD diagnoses (AD/PD), (2) DLB, (3) AD with EPS or gait disorder, and (4) PDD. Previous studies examining crossed risk of AD and PD have tended to exclude these overlap cases [35]. This lack of increased incidence of AD or PD family histories

in the AD/PD group suggests that DLB and PDD may not share etiologies with “pure” forms of AD and PD, although clinical and pathological features are similar. However, these results should be interpreted cautiously, particularly as the number of subjects in the AD/PD group was much smaller than in the AD and PD groups. Examining a larger group of AD/PD subjects and perhaps examining separately the various disease categories included in this group, using both inter- and intra-group analyses, is an important follow-up to this study.

Finding support for a shared risk for AD and PD provides new directions for research into the causes for these diseases. Familial risk of disease could in principle be due to genetic influences or shared environmental exposures. Our study did not evaluate the cause for this correlation of AD and PD family histories. As our findings were observed in extended families and in only first-degree relatives, we hypothesize that genetic factors are more likely responsible for increased crossed risk of AD and PD. Past genetic studies, looking at AD and PD separately, have determined that some genes, like MAPT, are involved in the presentation of both diseases [38,39] The alzgene.org and pdgene.org websites have made it easier to identify the currently known genes that may fit best with the conclusions of this study.

Future genetic association studies might profit from recognizing the differences between the pure AD subjects with no family history of AD, pure AD subjects with a family history of just AD, and pure AD subjects with a family history of both AD and PD. The same differentiation can be made for PD subjects. Segregating these subjects into these categories may enrich for genetically loaded cases and facilitate discovery of genes that confer a risk for both diseases.

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Fig. 1.
Schematic of intragroup analysis for shared risk of AD and PD

Fig. 2.

Odds ratios for intragroup analysis are equivalent whether AD or PD is used as the initial stratifying factor (AD group used as example)

Table 1

Demographics by diagnostic study group

	AD	PD	AD/PD	Control
Sample size	592	585	126	228
Average Age ($\pm$ SD)	78.6 ($\pm$ 9.5)	68.0 ($\pm$ 11.0)	77.5 ($\pm$ 8.4)	76.4 ($\pm$ 6.3)
Significance of difference from control group	$p<0.0001$	$p<0.0001$	$p<0.22$	
Gender				
Female (n)	65.2% (386)	37.1% (217)	43.7% (55)	61.8% (141)
Male (n)	34.8% (206)	62.9% (368)	56.3% (71)	38.2% (94)
Significance of difference from control group	$p<0.37$	$p<0.0001$	$p<0.0009$	
Race				
African-American	30.1% (178)	6.7% (39)	11.9% (15)	14.5% (33)
Caucasian	69.9% (414)	93.3% (546)	88.1% (111)	85.5% (194)
Significance of difference from control group	$p<0.0001$	$p<0.0004$	$p<0.49$	

Table 2
Familial risk of AD and PD (intergroup analysis)

Subjects (<i>n</i>)	Risk of AD		Risk of PD	
	Positive family history AD (<i>n</i>)	Odds ratio ^a (95% CI)	Positive family history PD (<i>n</i>)	Odds ratio ^a (95% CI)
All relatives included				
AD (592)	33.5% (198)	1.9 (1.3–2.7)	7.6% (45)	0.6 (0.4–1.1)
PD (585)	21.0% (123)	0.6 (0.4–0.9)	27.2% (159)	2.4 (1.5–3.9)
AD/PD (126)	21.4% (27)	0.8 (0.5–1.4)	15.1% (19)	1.3 (0.7–2.5)
Control (228)	25.9% (59)		12.3% (28)	
First-degree relatives only				
AD (592)	27.7% (164)	2.3 (1.5–3.4)	5.4% (32)	0.8 (0.4–1.5)
PD (585)	11.8% (69)	0.6 (0.3–0.9)	15.6% (91)	2.2 (1.2–4.0)
AD/PD (126)	18.3% (23)	1.1 (0.6–2.1)	11.1% (14)	1.5 (0.7–3.3)
Control (228)	17.5% (40)		7.5% (17)	

^aOdds ratio vs control and adjusted for age, race, and gender

Table 3

Shared risk of AD and PD among those with family history of neurodegenerative disease (intragroup analysis)

Group	Family history of PD among those with family history of AD	Family history of PD among those with NO family history of AD	Odds ratio ^a (95% confidence interval)
AD	11.1% (22/198)	5.8% (23/394)	1.7 (0.9–3.1)
PD	35.8% (44/123)	24.9% (115/462)	1.7 (1.1–2.6)
AD/PD	14.8% (4/27)	15.2% (15/99)	0.8 (0.2–3.0)
Control	17.0% (10/59)	10.7% (18/169)	1.7 (0.7–4.1)

^a Odds ratio of those with and without a family history of AD, respectively, and adjusted for age, race, and gender