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Maternal Transmission of Alzheimer Disease

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Abstract

Some propose maternal Alzheimer disease (1) inheritance. We compared dementia family histories in AD cases and cognitively normal controls. We expected more mothers to have AD in both groups. If maternal risk was not only due to female longevity more AD cases' than controls' mothers should be demented. We matched 196 AD cases to 200 controls by gender and age. We obtained parent dementia status and age of death for 348 AD and 319 control parents. 24 (12%) controls' fathers, 26 (13%) AD patient fathers, 58 (29%) controls' mothers and 55 (28%) AD mothers had memory difficulty. More mothers than fathers had memory problems in both groups and the statistical significance persisted after adjusting for parent age at death and APOE for controls (OR=2.40, p=0.004) but not cases (OR=1.63, p=0.14), although results are qualitatively similar. There was no evidence of a real difference between the two groups in interaction analysis (p=0.41). Mothers of both cases and controls were more often affected than fathers, even after adjusting for age. Cases' mothers were no more often demented than controls' mothers, which does not support the maternal AD transmission. Rather, the increased number of affected mothers relates, at least in part, to female longevity.

Keywords

Alzheimer disease; Inheritance; Genetics; Maternal

1. Introduction

Other than advanced age, having a family history of Alzheimer disease is the biggest risk factor for developing this disease. Based on twin studies, 60–80% of AD risk is genetic (2). Some studies estimate that the ε4 allele of the APOE gene may account for up to 25% (3) and variants of additional genes such as Clu, PICALM and BIN1 are currently being investigated as Late Onset genetic risk factors http://www.alzgene.org/. Yet much of the genetic risk remains unexplained.

More women are affected with AD than men (1) and in one study of parents of affected individuals, the age adjusted maternal to paternal relative risk was estimated at 2.8 (95% confidence interval from 1.1 to 7.7) (4). To explain these findings, researchers have explored genetic mechanisms thought to be related specifically to maternal AD transmission. These include epigenetic imprinting, chromosome × mutations, and mitochondrial DNA-mediated transmission. The studies investigating these mechanisms have not yet yielded conclusive results (5). Brain imaging studies have provided potential support for AD maternal transmission. Mosconi and colleagues (6) found greater brain glucose metabolism reduction and Honea and colleagues(7) found increased atrophy of AD sensitive areas in cognitively

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normal subjects with a maternal history of AD. Andrawis and colleagues(8) report in the Alzheimer Neuroimaging Initiative sample that MCI and AD patients with AD maternal history had smaller hippocampi at baseline and greater atrophy at follow-up.

Family history studies investigating maternal AD transmission have yielded mixed results. Edland and colleagues (4) found dementia patients' mothers have a higher age-adjusted risk of Primary Progressive Dementia than fathers. Ehrenkrantz and colleagues(9) found conflicting evidence that AD patients' mothers are not more likely than fathers to be demented or have affected offspring. We found no studies that directly compared AD probands' family histories with those of cognitively normal controls matched by gender and age strata.

The present study compared parental dementia frequency in AD cases and cognitively normal controls matched by gender and age strata. We obtained family history data using patient information forms and medical record review. We expected that both cases and controls would have more mothers who had been affected with dementia than fathers. The goal of this study was to further investigate the maternal transmission hypothesis. If it is correct then we would expect, after adjusting for parent age, a higher odds ratio for maternal to paternal dementia among parents of AD cases than for parents of controls.

2. Methods

200 AD cases were identified along with 200 controls frequency matched by gender and 5 year age strata. The controls were from a longitudinal biomarker study. Volunteers undergo initial neurological and neuropsychological examination and then are seen annually with neuropsychology testing. None were spouses of the cases and were not related to the cases. Four of the AD cases were subsequently excluded because their data were unavailable. With family history forms and medical record review, dementia status and age of death were obtained for as many of the parents as was possible. Although all parents were deceased at the time of the study father's age of death was unknown for 29 controls and 16 cases and mother's age of death was unknown for 37 controls and 16 cases. Numerical variables were summarized with the sample median, interquartile range, minimum, and maximum. Categorical variables were summarized with the number and percent. Comparisons of patient characteristics and family history of memory problems between cases and controls were performed using either a Wilcoxon rank-sum test (numerical variables) or Fisher's exact test (categorical variables). Separately for parents of AD cases and parents of controls, single variable and multivariable logistic regression models fit via generalized estimating equations to account for the correlation among parents of each case or control were used to examine associations of patient and parent characteristics with memory problems in parents. Estimated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were computed. Further logistic regression models were used to investigate interactions. P-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS (version 9.2; SAS Institute Inc., Cary, NC).

3. Results

Characteristics of AD cases and controls are summarized in Table 1. For both cases and controls, median age was 79 years and 35% were male. Compared to controls, cases had a higher prevalence of APOE ε4 (64% vs. 27%, $p<0.001$). No other statistically significant differences between cases and controls were observed, though not surprisingly the median ages at death of mothers were greater than those of fathers for both cases and controls. Associations of patient and parent characteristics with dementia of parents are summarized in Table 2 for the 348 parents of AD cases and 319 parents of controls for whom data was complete with respect to age at death, dementia status, and APOE genotype of offspring. In

single variable analysis, there was evidence that mothers are more likely to have been reported as having a history of dementia compared to fathers for both cases (OR=2.33, p=0.004) and controls (OR=2.96, p<0.001) and parents who live longer are more likely to have dementia for both cases (OR [10 year increase]=1.98, p<0.001) and controls (OR[10 year increase]=2.01, p<0.001). Although not statistically significant the data was consistent with an increase in the odds of dementia in the parent when the child had APOE ε4; this was more apparent in parents of controls than cases (OR=1.78, p=0.054).

The statistical significance of the association between parent gender and dementia persisted after adjusting for parent age at death and APOE ε4 for controls (OR=2.40, 95% CI: 1.32–4.38, p=0.004) but not cases (OR=1.63, 95% CI: 0.87–3.05, p=0.14), although the results are qualitatively similar. Analysis of interactions yielded no evidence of differences between cases and controls with respect to whether their mothers had more memory problems than their fathers (P=0.41). It was estimated that overall, after adjusting for parent age and APOE genotype and AD status of an adult child, mothers have about twice the odds of being reported as having memory problems compared to fathers (OR=2.39, 95% CI: 1.30–4.41, p=0.005).

4. Discussion

Mothers of both cases and controls lived longer than fathers and even after adjusting for age at death were more than twice as likely to have memory difficulties reported. This is consistent with previous research (1, 4). However, cases' mothers were no more often demented than controls' mothers. After adjusting for APOE ε4 and parent age, there was statistically significant evidence that the risk of dementia for controls' mothers was higher than for fathers; the same relationship was apparent for AD cases though to a lesser degree that was not statistically significant in this study.

Using a very large sample size and controlling for age structure and longevity, Ehrenkrantz and colleagues (9) also found no evidence for increased maternal AD transmission. Unexpectedly, they estimated the cumulative risk of Primary Progressive Dementia to be higher in offspring of affected fathers than those with affected mothers. Despite the findings of this study, there is a body of evidence which could support the maternal transmission of AD. Functional and structural imaging studies have shown AD cases and cognitively normal controls with a maternal AD history have increased brain atrophy of AD sensitive areas and increased glucose hypometabolism compared to subjects with either no AD parental history or a paternal history. (6–8)This also could indicate that a maternal AD history may influence earlier onset and rate of progression but not necessarily implicate a special role of maternal transmission in disease etiology. Prospective longitudinal studies may help resolve this issue.

Edland and colleagues (4) investigated maternal AD transmission using cognitively normal spouses as the primary source of family history information and as controls. The age adjusted relative risk of dementia was nearly 3 times higher for cases' mothers than fathers. They also found an increased risk in the control spouse mothers which was not significant but they pointed out there were only 14 affected parents (10 mothers and 4 fathers) and suggested a larger study.

One of the limitations of the present study includes not evaluating separately Early Onset Alzheimer's Disease (EOAD) and Late Onset Alzheimer's Disease (LOAD). EOAD and LOAD are thought to be mediated by different genetic mechanisms. If the relationship between AD maternal/paternal transmission was examined separately for EOAD and LOAD, maternal AD transmission may be more prominent in one or the other. Another limitation was the reliance on cases and controls' medical records for parental information.

The data was not always complete and parent dementia status was based on family members' recollections rather than a formal diagnosis. Recall bias could have occurred. Without the assistance of caregivers, demented patients may be less able to recall parental dementia status. Conversely, controls less often retrospectively view parental memory difficulties as significant. Men in the parental generation may also be less likely to report cognitive decline than women. It is possible that men in the parental generation had more education and thus may have benefited from a greater cognitive reserve. There is evidence suggesting demented men have greater reduction in cerebral metabolism than in women who are equally demented (10) and is in keeping with the hypothesis of higher cognitive reserve in the men. Similarly Barnes et al. found greater clinical dementia expression in women compared to men with comparable AD pathology (11)

The results of the present study do not support maternal AD transmission. Other approaches to this issue still raise the possibility that increased maternal transmission is plausible. Future studies should include prospective longitudinal determination of AD transmission, rate of progression and evaluation of early and late onset AD. In this way the apparently conflicting findings may be explained.

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Table 1

Characteristics of AD patients and age and gender matched controls

Variable	AD Cases (N=196)	Controls (N=200)	P-value [4]
Gender (male)	69(35%)	70(35%)	NA
Age (years)[1]	79 (75 –83) (65–96)	79 (75 –83) (65–94)	NA
ApoE4			<0.001
Yes	126 (64%)	53 (27%)	
No	67 (34%)	145 (73%)	
Unknown	3 (2%)	2 (1%)	
Father's age at death (years) [1 2]	72 (62 –82) (35–100)	76 (64 –87) (32–115)	0.11 [5]
Father had known memory problems			0.88
Yes	26(13%)	24(12%)	
No	160(82%)	158(79%)	
Unknown	10(5%)	18(9%)	
Mother's age at death (years) [1 3]	81 (69 –88) (28–104)	84 (73 –90) (24–108)	0.086 [5]
Mother had known memory problems			0.74
Yes	55(28%)	58(29%)	
No	137(70%)	132(66%)	
Unknown	4(2%)	10(5%)	

[1] Sample median, interquartile range and minimum and maximumare given to summarize numerical variables.

[2] Father's age of death was unknown for 29 controls and 16 cases.

[3] Mother's age of death was unknown for 37 controls and 16 cases.

[4] P-values result from Wilcoxon rank-sum tests for numerical variables and Fisher's exact test for categorical variables, where unknown values were excluded.

[5] Anadditional model adjusting for parent gender does not provide statistically significant evidence that parents of controls live longer than cases (P=0.10).

Table 2

Associations of patient and parent characteristics with memory problems in 348 parents of AD cases and 319 parents of controls.

Variable	Single or multiple variable model [2]	Parents of AD cases (N=348parents of 181cases) [1]		Parents of controls (N=319parents of 169controls)[1]	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Gender of AD patient or control(female)	*single*	0.75 (0.48–1.17)	0.21	0.96 (0.54–1.69)	0.95
	multiple	0.72 (0.44–1.18)	0.20	1.34 (0.69–2.61)	0.38
Presence of APOE ε4in AD patient or control(present vs. not present)	*single*	1.31 (0.81–2.12)	0.28	1.78 (0.99–3.20)	0.054
	multiple	1.54 (0.91–2.62)	0.11	2.16 (1.11–4.20)	0.023
Parent's age at death (10-year increase)	*single*	1.98 (1.59–2.46)	<0.001	2.01 (1.62–2.51)	<0.001
	multiple	1.96 (1.57–2.45)	<0.001	2.03 (1.63–2.54)	<0.001
Parent's gender (female) [3]	*single*	2.33 (1.31–4.14)	0.004	2.96 (1.74–5.05)	<0.001
	multiple	1.63 (0.87–3.05)	0.14[3]	2.40 (1.32–4.38)	0.004[3]

[1]The analysis included 176 mothers and 172 fathers of 181 AD cases and 156 mothers and 163 fathers of 169 controls.

[2]Estimated odds ratios (ORs), 95% confidence interval (CIs), and p-values result from logistic regression models using generalized estimating equations to account for correlations among parents of the same family. Multivariable analysis adjusted for all variables shown in the table.

[3]In an additional multivariable model that incorporated both parents of AD cases and parents of controls, with an interaction term between parent's gender and AD status of 'child', there was no evidence of a difference of the maternal vs. paternal effect in parents of AD cases versus controls (p=0.52).