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Does Alzheimer's disease pathologic change underlie subjective cognitive complaints?

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Keywords

Alzheimer's disease; subjective complaint; memory; neuropathology

Introduction

Subjective memory complaints may serve as a harbinger of future cognitive impairment in persons who perform within the range of normal on objective testing of memory and other cognitive domains. The subsequent decline may ultimately meet diagnostic criteria for mild cognitive impairment or dementia, and risk of such progression may be increased among carriers of the apolipoprotein E (APOE) ε4 allele[1] and those with biomarker evidence supporting the diagnosis of Alzheimer's disease (AD).[2]

Cross-sectional studies suggest that persons with subjective complaints may be at increased risk to demonstrate abnormal AD biomarkers.[3] Relatively few studies have examined the relationship between subjective complaints and AD neuropathologic change. Neuropathology studies suggest that amyloid plaques,[1, 4] neurofibrillary tangles,[4] and fulfillment of diagnostic criteria for AD[5] are more frequent at autopsy among those with subjective complaints, compared to those lacking complaints. In this study, we tested the hypothesis that, among participants in the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS), subjective memory complaints would be associated with AD pathologic change at autopsy. To test this hypothesis, we implemented criteria approximating the recent National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for pathological diagnosis for AD.[6]

Methods

We used data from the NACC UDS, a repository for longitudinal data collected from approximately 30 current or previously NIA-funded AD Centers nationwide that emphasize

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follow-up through autopsy confirmation of diagnosis (www.alz.washington.edu).[7] The UDS was initiated in 2005. These analyses examined data collected on or before September 2014. We limited our analyses to subjects who were determined to be cognitively normal control participants at all visits that had a clinical visit within two years of death and subsequent autopsy-derived neuropathological data. Normal cognitive status was based on the UDS diagnosis form (which utilizes expert or consensus diagnosis) and the additional requirement of global Clinical Dementia Rating Scale[8] of zero at the last UDS visit. We identified 3214 subjects with neuropathologic data. Of these, 287 demonstrated normal cognition at last UDS visit; 257 had a UDS visit within two years of death; 227 had complete neuropathologic data, based on the NIA-AA criteria; and 197 had complete data on subjective complaint.

In accord with the recent guidance,[6] AD neuropathologic change was scored using the *ABC criteria*. The "A score" reflects diffuse amyloid (Aβ) pathology based on Thal staging.. Since the NACC Neuropathology Data Set does not currently include Thal scores, here we approximated Thal scores using diffuse plaque staging, as has been done previously.[9] The presence of sparse plaques approximates an A score of 1 (Thal phase 1 or 2); the presence of moderate plaques approximates an A score of 2 (Thal phase 3), and the presence of frequent plaques approximates an A score of 3 (Thal phase 4 or 5). The "B score" reflects the Braak stage of neurofibrillary tangle pathology; with a B score of 1 equating to Braak stage I or II, 2 equating to Braak stage II or IV, and 3 equating to Braak stage V or VI. The "C score" reflects the neuritic plaque burden; a C score of 1 equates to a CERAD neuritic plaque score of sparse, 2 equates to moderate, and 3 equates to frequent. For A, B, and C scores, a score of 0 equates to an absence of neuropathology. Additionally, an "AD neuropathologic change" (AD NPC) score examined the frequency of subjects having no, low, intermediate and high AD NPC. We examined the proportion of participants who demonstrated at least intermediate AD NPC: A≥1; C≥2; and B≥2,[6] with the same caveats for A scores as noted above.

Subjective complaints were defined based on a UDS item in which the clinician is asked to record whether the participant reports a decline in memory. Descriptive statistics were used to compare demographic, clinical, and neuropathological variables (Table) in NACC UDS subjects who did and did not have subjective complaints at their final UDS visit. We did not control for multiple comparisons. Though we anticipated performing logistic regression models to examine predictors of AD neuropathology controlling for covariates, such models were underpowered and are not reported. One post-hoc analysis repeated comparisons in those who were and those who were not carriers of APOE ε4.

Written informed consent, including autopsy consent, is obtained from all willing participants in the NACC UDS. The UCLA IRB deemed this study "not human subjects research."

Results

Neuropathological data were available for 197 subjects meeting study inclusion criteria; 33 (17%) cases were documented as having subjective memory complaint at their final UDS

visit, 164 (83%) had no complaints. The Table describes the demographic, clinical, and neuropathologic findings comparing those with subjective complaints to those who lacked them. There were no differences between the groups in the proportions of ages at death, frequency of family history of dementia, or the make up of the sample based on sex, race, ethnicity, or level of education. The frequency of geriatric depression scores greater than six was no different between the groups. Participants with subjective complaints were twice as likely to be APOE ε4 carriers, although this difference did not reach statistical significance (X^2 test; p=0.06).

We found no differences in the frequencies of diffuse plaque scores between those with and those without subjective complaints. Subjects with subjective complaints demonstrated higher B scores (Table). For example, 67% of cases with subjective complaints had a B score≥2 (were Braak III-IV or higher), compared to 42% of those lacking complaints. When we examined the proportions of the groups fulfilling criteria approximating probable AD, as outlined in Montine et al,[6] 39% of cases with a subjective complaint, compared to 24% of those lacking complaint, met criteria for at least intermediate AD neuropathologic change (X^2 test; p=0.06). No differences between the groups were observed for vascular or Lewy body pathology.

When we repeated our analyses limited to those who were and those who were not APOE ε4 carriers, we observed significant differences between subjects with and without subjective complaints only for B scores and only in non-carriers (data not shown).

Discussion

These results add to a modest literature on the potential association between subjective memory complaints and AD neuropathology.[1, 4–5] We found a greater frequency of AD neuropathologic change in cognitively normal research participants with subjective complaints, compared to cognitively normal research subjects who lacked complaints. In contrast to the results of Kryscio and colleagues,[1] we did not find increased neuritic plaque burden in those with subjective complaints, despite comparable frequencies of at least intermediate neuritic plaque burden being observed in those with subjective complaints in the two studies; 37% in Kryscio et al. and 33% in our study. Whereas Kryscio and colleagues found no difference in tangle burden between those with subjective complaints and those without, the Memory and Aging Study at Rush University reported an association between increased memory complaint scoring and both amyloid plaque and neurofibrillary tangle burden in non-demented participants, when controlling for covariates.[4] In our study, two-thirds of those with subjective complaints but less than half of those who lacked them had a neurofibrillary tangle burden approximating that of mild dementia.[10] Similarly, 15% of subjects with subjective complaints, compared to 1% of those without subjective complaints, had a tangle burden associated with moderate to severe dementia.[10] Interestingly, the observed differences in tangle pathology appear to be driven by effects limited to non-carriers of the APOE ε4 allele, although a very small number of cases with subjective complaints were ε4 carriers.

Though our results are suggestive, they are limited by the use of a single-item assessment of subjective complaints; an up to two-year interval between clinical and neuropathological assessments, during which AD pathology may have developed;[11] a small sample size (of those with complaints); a lower proportion of participants with complaints than has been observed in some other studies;[12] and an inability to control for covariates or multiple comparisons. Of particular concern is the inability to discern potential effects of age and APOE ε4 carrier status. Age has previously been shown to predict neurofibrillary tangle burden,[13] while APOE has been previously shown to be associated with amyloid pathology.[1] Lack of differences between the groups in other known AD risk factors, such as family history and education, however, support the conclusion that subjective complaints may be associated with AD neuropathology. It is also the case, that NIA-AA criteria include Thal staging of diffuse plaques, which are based on anatomical distributions. Our data did not account for anatomy, though this concern may be minimized given a lack of findings related to amyloid pathology.

These results support the hypothesis that subjective memory complaints may indicate the presence of, or at least signal increased risk for, underlying AD neuropathologic change. Further understanding of this relationship is needed, including biomarker and neuropathological studies. Subjective memory complaints may serve an important role in designing efficient clinical trials to test therapies for preventative efficacy and may offer clinicians the opportunity to work with patients to reduce risk and plan for the future.

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Table

Demographic, clinical, and neuropathological characteristic for subjects meeting all inclusion criteria

	Subjective Complaint					
Demographic characteristic	**No, n (%)**		**Yes, n (%)**		**All**	**p-value[a]**
Total n	**164 (83%)**		**37 (18%)**		**197 (100%)**	
Age at death						.46*
<60	4	(2%)	0	(0%)	4 (2%)	
60–69	5	(3%)	0	(0%)	5 (3%)	
70–79	24	(15%)	4	(12%)	28 (14%)	
80–89	60	(36%)	9	(27%)	69 (35%)	
90–99	65	(40%)	17	(52%)	82 (42%)	
100+	6	(4%)	3	(9%)	9 (5%)	
Family history of dementia[b]	63	(40%)	11	(33%)	74 (39%)	.47
Female sex	103	(63%)	20	(61%)	123 (62%)	.81
White race	155	(95%)	32	(97%)	187 (95%)	>.999*
Hispanic ethnicity[c]	5	(3%)	0	(0%)	5 (3%)	.31*
At least some college education[d]	131	(81%)	27	(82%)	158 (81%)	.90
Clinical characteristic						
Hypertension[e]	109	(67%)	19	(58%)	128 (65%)	.31
Diabetes[f]	26	(16%)	3	(9%)	29 (15%)	.42*
GDS >6[g]	16	(11%)	5	(16%)	21 (12%)	.48
APOE e4 carrier[h]	21	(14%)	9	(28%)	28 (14%)	.06
Neuropathological characteristic						
Diffuse plaque frequency (A score approximation)[i]						.89
None (approximating A score 0)	53	(35%)	10	(32%)	63 (35%)	
Sparse (approximating A score 1)	34	(23%)	6	(19%)	40 (22%)	
Moderate (approximating A score 2)	29	(19%)	6	(19%)	35 (19%)	

Demographic characteristic	Subjective Complaint: No, n (%)		Subjective Complaint: Yes, n (%)		All		p-value[a]
Total n	**164 (83%)**		**37 (18%)**		**197 (100%)**		
Frequent (approximating A score 3)	34	(23%)	9	(29%)	43	(24%)	
B score (Braak stage)							.0004*
0 (Not present)	15	(9%)	2	(6%)	17	(9%)	
1 (I–II)	81	(49%)	9	(27%)	90	(46%)	
2 (III–IV)	67	(41%)	17	(52%)	84	(43%)	
3 (V–VI)	1	(1%)	5	(15%)	6	(3%)	
C score (Neuritic plaque frequency)							.34
0 (None)	71	(43%)	14	(42%)	85	(43%)	
1 (Sparse)	41	(25%)	8	(24%)	49	(25%)	
2 (Moderate)	38	(23%)	5	(15%)	43	(22%)	
3 (Frequent)	14	(9%)	6	(18%)	20	(10%)	
AD NPC approximation[l]							.06*
Not AD	49	(30%)	10	(30%)	59	(30%)	
Low	76	(46%)	10	(30%)	86	(44%)	
Intermediate	38	(23%)	11	(33%)	49	(25%)	
High	1	(1%)	2	(6%)	3	(2%)	
Presence of Lewy bodies[j]	14	(11%)	4	(17%)	18	(12%)	.48
Presence of Vascular pathology[k]	119	(94%)	23	(100%)	142	(95%)	.60

[a] Chi square test for difference in proportion between those with and without subjective complaint. Fisher's exact test used for comparisons with at least one cell n<5.

[b] 7 subjects (all without subjective complaint) were missing data on family history of dementia

[c] 1 subject (without subjective complaint) was missing data on Hispanic ethnicity

[d] 2 subjects (both without subjective complaint) were missing data on education

[e] 1 subject (without subjective complaint) was missing data on hypertension, 8 subjects with a remote/inactive history of hypertension were included in the "Yes" group

[f] 1 subject with a remote/inactive history of diabetes was included in the "Yes" group

[g] 21 subjects (20 without subjective complaint, 1 with) were missing data on GDS score

[h] 17 subjects (16 without subjective complaint, 1 with) were missing data on APOE genotype

[i] 16 subjects (14 without subjective complaint, 2 with) not assessed for diffuse plaques

[j] 2 subjects (both without subjective complaint) not assessed for Lewy bodies and 3 subjects with unspecified Lewy bodies excluded

[k] 1 subject (without subjective complaint) not assessed for vascular pathology

[l] see methods

[*] Denotes Fisher's exact test used instead of Chi square test