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Risk factors for amyloid positivity in older people reporting significant memory concern

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Abstract

Objective: The goal of this study is to identify risk factors for the presence of amyloid accumulation in the brains of patients reporting subjective cognitive decline (SCD). Identifying such risk factors will help better identify patients who ought to receive neuroimaging studies to confirm plaque presence and begin intervention, as well as enhancing the study of the pathogenesis of Alzheimer's disease.
Methods: Ninety-nine SCD participants (72.2 ± 5.6 years, 57.6% female) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) underwent florbetapir PET. Logistic regression analysis was conducted to examine the relationship between the presence of an increased amyloid signal (amyloid positivity) and several potential risk factors, including: demographics, APOE ε4 genotype, family history of dementia, history of hypertension, history of cigarettes smoking, cognitive function and depressive symptoms.
Results: Being female was a significant risk factor for amyloid positivity (OR = 4.915, 95% CI = 1.709–14.139), as was being an APOE ε4 carrier (OR = 2.985, 95% CI = 1.084–8.219) and having a history of cigarette smoking (OR = 4.091, 95% CI = 1.483–11.285).
Conclusion: Our study demonstrates that female gender, APOE ε4 genotype, and history of cigarettes smoking are associated with amyloid positivity in patients with SCD.

1. Introduction

Subjective cognitive decline (SCD) [1], also known as significant memory concern (SMC), is a self-perceived cognitive decline in the absence of objective cognitive impairment. This is commonly reported by older people, but may reflect an internal appreciation of loss of function which the patient is able to adequately compensate for on testing. Emerging evidence supports the notion that SCD may be a harbinger of future progression into clinically observable states of impairment; namely, mild cognitive impairment (MCI) and dementia [2–4]. Recent studies have also suggested that SCD is related with increased amyloid accumulation [5–10], although some inconsistencies exist [11,12]. As amyloid appears to be the initial driver in the development of Alzheimer's disease (AD) [13], the identification of amyloid positive subjects is critical for the clinical trials, especially those with amyloid-modifying therapies. Secondary prevention trials are also being conducted in amyloid-positive individuals with SCD; in these trials, documentation of amyloid status is indispensable for enrollment.

It is estimated that the prevalence of amyloid positivity in SCD individuals ranges from 12% to 43% [14], which may be affected by age and genetic background. Current methods

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such as CSF protein analysis and amyloid neuroimaging are not feasible at the large scale necessary to identify sufficient numbers of eligible subjects for clinical trials. Thus, identifying factors which strongly predict amyloid positivity in SCD would facilitate the process of clinical trial recruitment and provide a useful tool for studying AD pathogenesis. Although risk factors related with amyloid accumulation have been extensively reported in cognitively normal and cognitively impaired individuals [15–17], the risk factors for the unique category of patients reporting SCD, but testing normally, have not been well-studied. Thus, our current study aimed to examine, in patients reporting SCD, the relationship between amyloid positivity and the following relevant risk factors: demographics, APOE ε4 genotype, family history of dementia, history of hypertension, history of cigarettes smoking, cognitive function and depressive symptoms.

2. Materials and methods

2.1. ADNI dataset

Cross-sectional data used in the preparation of this paper were extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) during January 2017. The ADNI was founded in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary aim of ADNI has been to verify whether clinical and neuropsychological assessment, neuroimaging and other biomarkers can be integrated to measure the progression of MCI and early AD. Participants have been recruited from > 50 sites in the USA and Canada. For up-to-date information, see www.adni-info.org. The ADNI was conducted after institutional review board approval at each site. Written informed consent was abstained from all participants or their authorized representatives.

2.2. Participants

For the present analysis, participants were selected if they were diagnosed as having significant memory concern (SMC). In ADNI, SMC, rather than SCD, was used to denote this self-perceived cognitive decline – thus, we will use the term SMC when referring to this dataset. The eligibility criteria for selecting SMC have been described previously [18]. In brief, SMC participants had subjective memory concerns, quantified by using the Cognitive Change Index (CCI, positive if sum of first 12 items > 16) [19], a Clinical Dementia Rating (CDR) of 0, a Mini-Mental State Examination (MMSE) score ≥ 24,normal performance on the Wechsler Logical Memory Delayed Recall (LM-delayed), and no informant-reported memory complaints. (Further information about the ADNI cohort can be found at www.adni-info.org).

2.3. Florbetapir-F18 positron emission tomography

Florbetapir PET data were processed and acquired as described previously [20,21]. Mean florbetapir standard uptake value ratios (SUVRs) were created from cortical gray matter (lateral and medial anterior frontal, posterior cingulate, lateral parietal, and lateral temporal regions) and normalized to the whole cerebellum (gray and white matter). Amyloid positivity was defined as SUVRs >1.11 and amyloid negativity as SUVRs ≤1.11, as described previously [22]. More detailed information about PET protocols and data can be found on the ADNI website (http://adni.loni.usc.edu/methods/).

2.4. Clinical and genetic data

ADNI participants underwent comprehensive clinical and neurocognitive assessments. In the present analysis, data on demographics, APOE ε4 genotype, medical history, family history of dementia, MMSE and Geriatric Depression Scale (GDS-15) were obtained from ADNI database. Because the GDS has a "complaint" question (do you feel you have more problems with memory than most?), we created an adjusted GDS removing that question. We did not include participants with inconclusive family histories of dementia (n = 6). Participants without imaging data were also excluded (n = 3). The final sample for the present analysis was comprised of 99 older people with SMC.

2.5. Statistics analysis

Our variables of interest were the following: demographics, APOE ε4 genotype, history of hypertension, history of cigarettes smoking, family history of dementia, MMSE scores, depressive symptoms, and amyloid positivity. These were summarized using descriptive statistics. Logistic regression models were used to assess predictors of amyloid positivity. Univariate regression models were used for the analysis of age, gender (male or female), education, marital status (married, never married, divorced, widowed), APOE ε4 genotype (carrier or non-carrier), history of hypertension (yes or no), history of cigarettes smoking (yes or no), family history of dementia (yes, or no), MMSE scores, depressive symptoms with different amyloid status. Then, we constructed a multivariate logistic regression model using a forward LR sequence. The significant predictors identified in the univariate logistic regression models were then entered in another multivariate logistic regression model which controlled for the potential impacts of age and educational level. All analyses were completed using SPSS version 22.

3. Results

3.1. Participants' characteristics

The characteristics of the 99 SMC participants with a Florbetapir PET scan are summarized in Table 1. The median age of the sample was 71.3 years, ranging from 60 to 90 years. Forty-two (42.4%) participants were men. The median years of schooling were 17, ranging from 8 to 20 years. 69 (69.7%) were married, 10 (10.1%) never married, 8 (8.1%) were divorced and 12 (12.1%) were widowed. There were 60 (60.6%) participants

Table 1
Characteristics of the study sample.

Characteristics	n = 99
Age, years	71.3 (67.2–76.5)
Male, n (%)	42 (42.4)
Education years	17 (16–19)
Married, n (%)	69 (69.7)
APOE ε4 positive, n (%)	30 (30.3)
Family history of dementia, n (%)	60 (60.6)
MMSE points	29 (28–30)
Adjusted GDS-15 points	0 (0–1)
History of cigarettes smoking, n (%)	47 (47.5)
Hypertension, n (%)	44 (44.4)
Global florbetapir PET (SUVR)	1.13 ± 0.18
Amyloid positive, n (%)	34 (34.3)

Abbreviations: MMSE: Mini-Mental State Examination; GDS: Geriatric Depression Scale.
Continuous variables are presented as median (interquartile range).

with a family history of dementia, 30 (30.3%) with at least 1 APOE ε4 allele, 47 (47.5%) having a history of cigarettes smoking and 44 (44.4%) had a history of hypertension. The median (interquartile range, IQR) MMSE scores and GDS scores were 29 (28–30) and 0 (0–1), respectively. 34 (34.3%) had florbetapir retention ratio > 1.11.

3.2. Predictors of amyloid positivity

Table 2 provides summaries of univariate logistic regression models. Female gender, APOE ε4 carrier status and history of cigarettes smoking were significantly associated with amyloid positivity. Then these three factors, while controlling for age and education, were entered in the multivariate logistic regression model. Table 3 provides summaries of multivariate logistic regression model. We found that amyloid positivity was associated with these three predictors, including female gender (adjusted OR = 4.915, 95% CI = 1.709–14.139), APOE ε4 carrier status (adjusted OR = 2.985, 95% CI = 1.084–8.219) and history of cigarettes smoking (adjusted OR = 4.091, 95% CI = 1.483–11.285).

Table 2
Summary of univariate logistic regression models.

Characteristics	Outcome: amyloid positivity	
	OR (95% CI)	p
Age, years	1.050	0.202
Gender		
Male	1.0	
Female	3.565 (1.406–9.034)	0.007
Education years	0.924	0.342
Marital status		
Married	1.0	
Never married	1,424 (0.365–5.564)	0.611
Divorced	1.282 (0.281–5.851)	0.749
Widowed	1.526 (0.435–5.349)	0.509
APOE ε4 status		
Negative	1.0	
Positive	4.0 (1.616–9.90)	0.003
Family history of dementia		
No	1.0	
Yes	0.893 (0.383–2.081)	0.793
MMSE scores	0.97	0.861
Adjusted GDS-15	0.651	0.081
History of cigarettes smoking		
No	1.0	
Yes	3.572 (1.485–8.590)	0.004
Hypertension		
No	1.0	
Yes	0.679 (0.291–1.582)	0.370

MMSE: Mini-Mental State Examination; GDS: Geriatric Depression Scale.

Table 3
Summary of multivariate logistic regression model.

Characteristics	Outcome: amyloid positivity	
	OR (95% CI)	p
Gender		
Male	1.0	
Female	4.915 (1.709–14.139)	0.003
APOE ε4 status		
Negative	1.0	
Positive	2.985 (1.084–8.219)	0.034
History of cigarettes smoking		
No	1.0	
Yes	4.091 (1.483–11.285)	0.007

4. Discussion

In the present study, we aimed to identify potential factors of amyloid positivity in older people with SMC. Our findings showed that female gender, APOE ε4 genotype and history of cigarette smoking were associated with amyloid positivity among individuals with SMC.

We found sex differences in amyloid burden among SMC individuals, with more amyloid positivity in females. Some epidemiologic studies have suggested that females have a higher prevalence [23] and incidence [24] of AD, and our data indicate that sex may contribute to AD pathogenesis through amyloid-β (Aβ) dependent pathway. In line with our findings, previous animal studies have shown that females have more amyloid deposition than their male counterparts [25,26], providing direct evidence that sex differences in amyloid accumulation may play the critical role in AD pathogenesis. However, in human postmortem studies, the results were conflicting and inconclusive [27,28], and these discrepant findings may be due to, at least in part, the fact that several potential confounding factors, like age, education, APOE ε4 genotype and cardiovascular risk factors, were not adequately adjusted. Recent study using amyloid neuroimaging suggested that females deposit more amyloid in the brain than males in a community-based cohort without dementia [29], although some inconsistencies exist here as well [14,30]. Further study is needed to elucidate the exact relationship between sex and amyloid pathology.

As expected, we found that the presence of APOE ε4 genotype increased the odds of amyloid positivity among SMC individuals. Being homozygous for APOE ε4 appears

to be the largest genetic risk factor for AD [31], and our findings suggest that this correlates with amyloid accumulation even in SMC. Previous animal studies have demonstrated that the impacts of APOE ε4 on amyloid-β aggregation [32,33] and clearance [34] may play the critical role in the AD pathogenesis, which is in line with our findings. Additionally, results of neuropathological studies in AD patients indicated that APOE ε4 carriers possessed elevated levels of Aβ, Aβ oligomers and plagues depositions in the brain [35–37]. Neuroimaging studies have also shown that APOE ε4 genotype portends increased amyloid accumulation both in cognitively normal older people [38] and in mild cognitive impairment (MCI) patients [39], although studies in AD subjects have yielded contradictory results [39,40]. Further, studies have suggested that APOE ε4 carriers possess more amyloid burden than APOE ε4 non-carriers among SMC individuals [18,41]. Findings from brain imaging studies and animal models indicate that blood-brain barrier (BBB) dysfunction may precede onset of neurodegeneration and cognitive impairment, thereby contributing to the pathogenesis of AD [42]. Emerging evidence shows that APOE play a critical role in the maintenance of BBB integrity in an isoform dependent manner and that lack of APOE results in BBB breakdown [43,44]. In comparison with APOE ε3 knock-in mice, BBB permeability is elevated in APOE ε4 knock-in mice [43,44]. By activating a proinflammatory CypA–nuclear factor-kB-matrix-metalloproteinase-9 pathway in pericytes, investigators found that APOE ε4 knock-in mice, but not APOE ε2 and APOE ε3, have a damaged BBB [44]. Importantly, BBB breakdown also leads to impaired amyloid-β clearance, and oligaemia in turn increases amyloid-β production [45]. Taken together, our findings are largely consistent with APOE ε4 literature, supporting the notion that APOE ε4 may result in decreased amyloid-β clearance and thus enhance the development of AD.

In this study, history of cigarettes smoking was found to be associated with increased amyloid burden in SMC individuals. This finding was consistent with in vitro [46], animal model [47], human postmortem [48] and epidemiological studies [49] demonstrating that smokers have significantly increased amyloid pathology and risk of AD. However, the exact mechanisms by which smoking exerts its detrimental effect in AD remain elusive. Several potential pathways may be involved, including smoking related oxidative stress, neuroinflammation, altered mitochondrial respiratory chain function induced by some cigarettes combustion products, dysfunction of the proteostasis machinery, impairments of blood-brain barrier (BBB) and so on. Further investigations are needed to elucidate the exact mechanisms by which smoking affects the pathophysiology of AD.

Our findings should be interpreted with caution because the study sample was relatively small; thus, further investigations with larger sample size are needed to increase the statistical power to elucidate the exact relationship between these factors and amyloid positivity. While our study could not provide this level of granularity, the relationship between these risk factors and differential accumulation of amyloid across brain regions would be of great interest. Further study will be needed to clarify this association.

In conclusion, our findings revealed that female gender, APOE ε4 genotype and history of cigarettes smoking were associated with amyloid positivity among individuals with SMC.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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