



ASSOCIATION BETWEEN $APOE-\epsilon_4$ CARRIER STATUS AND QUALITATIVE NEUROIMAGING CHARACTERISTICS IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

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ABSTRACT

Background: The pathogenesis of mild cognitive impairment (MCI) is multifactorial and includes the presence of genetic variants such as the ϵ_4 allele of the apolipoprotein E gene ($APOE-\epsilon_4$). Association between the $APOE-\epsilon_4$ carrier status and deleterious structural and functional changes on magnetic resonance imaging (MRI) has been previously described in individuals with Alzheimer's disease. However, the central nervous system changes may possibly develop in earlier stages of cognitive impairment, as reflected in MCI. **Objective:** The objective of the study was to determine the association between $APOE-\epsilon_4$ carrier status and qualitative changes on MRI (medial temporal and parietal atrophy), as well as the detection of white matter hyperintensities (WMH) in older adults with MCI, in the memory clinic of a tertiary care hospital in Mexico City. **Methods:** A cross-sectional study of 72 adults aged 60 years or above who underwent an exhaustive clinical, neuroimaging, and neuropsychological evaluation. Multivariate logistic regression models were constructed to determine the association between $APOE-\epsilon_4$ carrier status and qualitative/quantitative changes on MRI. **Results:** Mean age was 75.2 years (± 7.2) and 64% were female. Twenty-one participants were cognitively normal and 51 had MCI. Almost 56% were $APOE-\epsilon_4$ carriers and were associated with medial-temporal atrophy according to the Scheltens scale (odds ratio [OR]: 20.0, 95% confidence intervals [CI]: 3.03-131.7), parietal atrophy according to the Koedam's score (OR: 6.3; 95% CI 1.03-39.53), and WMH according to the Fazekas scale (OR: 11.7, 95% CI: 1.26-108.2), even after adjusting for age, educational level, and cardiovascular risk factors. **Conclusion:** The $APOE-\epsilon_4$ carrier status was associated with medial temporal and parietal atrophy, as well as WMH. Our findings support the hypothesis suggesting the contribution of this genotype to neurodegeneration and cerebral vascular pathology. (REV INVEST CLIN. 2022;74(2):113-20)

Keywords: Mild cognitive impairment. $APOE-\epsilon_4$ carrier status. Magnetic resonance imaging. Mexican mestizo older adults.

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INTRODUCTION

Mild cognitive impairment (MCI) is a clinical and neuropsychological syndrome reflecting an intermediate state between normal cerebral aging and dementia¹. Older age, a lower educational level, the presence of cardiovascular diseases (hypertension, diabetes, dyslipidemia, obesity, smoking history, stroke, and small vessel disease), and specific genetic variants (apolipoprotein E gene allele ϵ_4 [*APOE- ϵ_4*]) are considered risk factors in the progression from MCI to dementia, particularly Alzheimer's disease².

There is evidence that the *APOE- ϵ_4* isoform has toxic effects on the central nervous system (CNS) including neuronal damage, altered synaptic plasticity, mitochondrial dysfunction, hyperphosphorylation of tau proteins, and reduced cerebral β -amyloid (A β) clearance, all fostering neurodegeneration³ and functional changes in the hippocampus, parahippocampus, subiculum, entorhinal cortex, amygdala, and gray matter⁴. A previous study suggested that the right hippocampus is the most vulnerable area to the toxic effects of *APOE- ϵ_4* , leading to medial-temporal atrophy (MTA), a sensitive marker of AD^{5,6}. However, there are limited data on the association between the *APOE- ϵ_4* carrier status and structural CNS changes in earlier stages of cognitive impairment such as MCI⁷. Therefore, this study aimed to determine the association between the *APOE- ϵ_4* carrier status and medial-temporal and parietal atrophy as well as WMH in older adults with MCI.

METHODS

Design and participants

This is a cross-sectional study that included adults aged 60 years or above, conducted in the memory clinic of a tertiary care center in Mexico City, between March 2018 and February 2020. All participants underwent a comprehensive clinical evaluation by a neurologist or geriatrician and a neuropsychological evaluation by an expert neuropsychologist. Exclusion criteria included uncontrolled or untreated depressive symptoms (> 5 in the 15-item Geriatric Depression Scale)⁸, delirium, visual or hearing impairment,

illiteracy, a history of neurological or psychiatric disease (Parkinson's, cerebrovascular disease, and/or dementia), uncontrolled hypertension, untreated thyroid disease, high blood levels of glycosylated hemoglobin ($\geq 9\%$), a history of severe hypoglycemia, the presence of severe heart failure, recent traumatic brain injury, and prior placement of metallic objects or devices, or unsafe conditions to obtain an MRI.

The study protocol was approved by the local Research and Ethics Committees (GER-2416-18-20-1). All participants signed an informed consent form and all procedures were performed per the Declaration of Helsinki and local regulations. This study was supported by the *Consejo Nacional de Ciencia y Tecnología* (FOSISS 2017-1 290406 2017).

Mild cognitive impairment

An MCI diagnosis was established following Petersen et al. criteria, which include the following variables: self-reported subjective memory complaints – subsequently confirmed by an informant, preserved activities of daily living, normal global cognitive function according to a standard neuropsychological test, and the absence of a dementia diagnosis^{1,9}.

Cognitive and functional assessment

The Montreal Cognitive Assessment (MoCA) with a resulting score between 24 and 26 was also included in the study^{10,11}. The brief Neuropsychological Evaluation in Spanish (NEUROPSI), previously standardized in the Mexican population¹², was used to assess specific domains compromised in cerebral impairment. The cognitive domains evaluated in various subtests of the NEUROPSI include orientation, attention, and concentration, language, memory, executive functions, reading, writing, and calculation abilities. A composite score of 1.5 standard deviations (SD) below the adjusted mean for age and education was considered compatible with MCI.

The Katz Index and the Lawton Brody Index were used to assess basic (ADL) and instrumental (IADL) activities of daily living, respectively^{13,14}. Participants were considered dependent if the score was ≤ 5 on the ADL scale and ≤ 7 for women, and ≤ 4 for men

on the IADLs scale. Participants who denied memory complaints and had normal cognitive performance on neuropsychological tests (standardized by age, sex, and level of education) were considered cognitively normal (CN).

Brain magnetic resonance imaging (MRI) and visual rating

MRIs were evaluated by an expert neuroradiologist blinded to the participants' clinical status. Three visual rating scales were used: the Scheltens scale ([SS] hippocampal atrophy)¹⁵, the Koedam scale ([KS] parietal atrophy), and the Fazekas scale ([FS] that quantifies white matter hyperintensities [WMH])¹⁶.

The degree of MTA was assessed in coronal slices and T1-weighted sequences according to the SS¹⁷ as follows: 0 (no atrophy), 1 (mild atrophy), 2 (mild/moderate atrophy), 3 (moderate/severe atrophy), and 4 (severe atrophy). Parietal atrophy was assessed in sagittal and T1-weighted sequences with the use of the KS¹⁸, consisting of the following stages: 0 (no atrophy), 1 (mild atrophy), 2 (moderate atrophy), and 3 (severe atrophy).

Hyperintensities were evaluated in axial and in T2-weighted and FLAIR sequences using the FS¹⁹ and scored based on the following findings: 0 (no lesions), 1 (non-confluent lesions), 2 (confluent lesions), and 3 (diffuse lesions).

Visual scale results were further dichotomized to identify cases with normal or abnormal results based on the following scores: SS = 0 (normal), 1-4 (abnormal); KS = 0 (normal), 1-3 (abnormal); and FS: 0 (normal), 1-3 (abnormal).

APOE genotype

DNA was extracted using the salting-out method. The *APOE* genotype was determined by polymerase chain reaction (PCR) after collecting 10 mL of peripheral blood from each participant. DNA was extracted from leukocytes and amplified using the oligonucleotide primers F4 (5'-ACAGAATTCGCCCCCGGCCTG-GTAcACACAC-3') and F6 (5'IAAGCITGGCACGGCTGn = cAAG'). The sample was denatured and subjected

to 30 amplification cycles that yielded approximately 300 ng of *APOE* sequences. Next, 5 units of HhaI (New England Biolabs, Ipswich, MA, USA) were added for the digestion of *APOE* sequences. Each sample was combined with polyacrylamide for electrophoresis to detect the different genotypes: $\epsilon_2 \epsilon_2/\epsilon_2$, ϵ_3/ϵ_3 , ϵ_3/ϵ_3 , ϵ_4/ϵ_4 , ϵ_4/ϵ_4 , ϵ_2^{20} . For the purposes of our study, results were operationalized as a binomial variable: the presence of one or two *APOE-ε₄* alleles versus no *APOE-ε₄* alleles.

Sociodemographic and clinical variables

Age, sex, educational level, and the presence or absence of the following cardiovascular risk factors (CVRFs) were included: hypertension, obesity, dyslipidemia, diabetes, and smoking. CVRFs were conglomerated and treated as a continuous variable.

Statistical analysis

Variables were described with arithmetic means and SD. To determine the association between the *APOE-ε₄* carrier status and cognitive status according to the neuroimaging characteristics, multivariate logistic regression models were constructed whereby four mutually exclusive groups were created by combining each of the three visual scales and the *APOE ε₄* carrier or non-carrier status: Fazekas 0 with a normal image and *APOE-ε₄* negative; Fazekas 1 with a normal image and *APOE-ε₄* positive; Fazekas 2 with an abnormal image and *APOE-ε₄* negative; and Fazekas 3 with an abnormal image and *APOE-ε₄* positive.

0: Scheltens with a normal image and *APOE-ε₄* negative; 1: Scheltens with a normal image and *APOE-ε₄* positive; 2: Scheltens with an abnormal image and *APOE-ε₄* negative; and 3: Scheltens with an abnormal image and *APOE-ε₄* positive.

0: Koedam with a normal image and *APOE-ε₄* negative; 1: Koedam with a normal image and *APOE-ε₄* positive; 2: Koedam with an abnormal image and *APOE-ε₄* negative; and 3: Koedam with an abnormal image and *APOE-ε₄* positive.

The models were adjusted for age, educational level, and CVRF, and the odds ratios (OR) were estimated.

$p < 0.05$ was considered statistically significant, and 95% confidence intervals (CIs) were provided. All statistical analyses were performed in the SPSS version 25 for Windows® (Chicago, IL, USA).

RESULTS

Among the 72 recruited participants, 21 (29%) were CN and 51 (71%) had MCI. Their mean age was 75.2 years (± 7.2) and 64% were female. Hypertension was the most frequent CVRF (62.9%) followed by dyslipidemia (48.6%) and diabetes (30%). The mean number of CVRF was 3.2 (± 1.4). The mean score for depressive symptoms was 2.6 (± 2.3). Compared with CN participants, those with MCI had a lower educational level (14.0 ± 3.8 vs. 10.1 ± 5.36 ; $p < 0.01$), a lower score in NEUROPSI (111.3 ± 5.0 vs. $91.1, \pm 14.0$; $p < 0.01$), and lower MoCA scores (27.2 ± 1.9 vs. $21.4, \pm 3.9$; $p < 0.01$). Participants with MCI versus CN had a higher frequency of hypertension (79.5% vs. 20.5%; $p = 0.020$) and dyslipidemia (82.4% vs. 16.6%; $p = 0.02$). In addition, the MCI group had more frequent abnormal results in the FS 1-3, 65% versus 35% ($p < 0.01$); SS 1-4 84% versus 16% ($p < 0.01$); and KS 1-3 78 % versus 22% ($p = 0.03$) in comparison with the CN group (Table 1).

As to the *APOE* genotype, 40 (55%) individuals in the sample harbored ϵ_4 (homo or heterozygous), particularly in the MCI group in comparison with the CN population (55% vs. 45%, $p < 0.03$).

Table 2 shows the participant subgroup with an MRI in the MCI group and an established *APOE*- ϵ_4 carrier status: (FS 0: 13 [39%] vs. FS 1-3: 21 [61%], $p < 0.05$), (SS: 0 1 [3%] vs. 33 [97%], $p < 0.01$), (KS 0: 7 [21%] vs. 27 [79%], $p < 0.18$).

Table 3 shows the multivariate logistic regression analysis assessing the independent association between an *APOE*- ϵ_4 carrier status and the detected neuroimaging features. We observed a statistically significant association between the FS and the carrier status (OR: 15.3, 95% CI: 1.3-17, $p = 0.03$), and the SS (OR: 19.8, 95% CI %: 2.2-175, $p < 0.01$), as well as the KS (OR 6.3, 95% CI: 1.03-39.5, $p = 0.05$) in participants with MCI, after adjusting for age, educational level, and CVRF.

DISCUSSION

The *APOE*- ϵ_4 carrier status was associated with medial-temporal and parietal atrophy, as well as WMH. Our findings support the hypothesis suggesting this genotype's contribution to neurodegeneration and cerebral vascular pathology in patients with MCI. These results reflect those reported in the CVRF, Aging, and Incidence of Dementia (CAIDE) study, in which participants with more CVRF had a greater MTA and vascular injury burden, suggesting that a positive *APOE*- ϵ_4 carrier status and the presence of cardiovascular factors could play a role in the pathogenesis of neurodegeneration and its progression to Alzheimer's disease²¹.

Further, we detected an association between the *APOE*- ϵ_4 carrier status and MTA in MCI participants, regardless of their age, lower educational level, and CVRF. A similar result was described by Claus et al.²², in which MTA was independently associated with the *APOE*- ϵ_4 carrier status in individuals with MCI. Another study including 273 participants (classified as CN, with amnesic MCI or dementia), reported that the SS was the only scale which differentiated the presence of MTA between cases with MCI and CN individuals²³. In 2017, another study also demonstrated the efficacy of SS as an MCI diagnostic tool²⁴. The SS has been shown to correlate significantly with qualitative hippocampal measurements and is of greater clinical relevance when associated with cognitive function²⁵. Its sensitivity and specificity are similar to automated methods measuring volume and cortical thickness volume²⁶. In contrast, Korf et al.²⁴, Flak et al.²⁵, and Rhodius-Meester et al. showed that *APOE*- ϵ_4 was not directly associated with MTA^{27,28}.

In the MCI group, we also detected that *APOE*- ϵ_4 carriers had a greater vascular injury load in comparison with non-carriers, as reported by Zlokovic et al.⁴ A meta-analysis including 29,965 participants, showed that a positive *APOE*- ϵ_4 carrier status increased the risk of an associated greater vascular burden²⁹. Similarly, Erten-Lyons, et al., referred an association between AD pathology and alterations in the integrity of cerebral white matter³⁰. These changes could be the result of Wallerian degeneration of myelinated axons leading to changes in cerebral white matter and disorganization of the

Table 1. Sociodemographic characteristics, cognitive assessment, comorbidity, and neuroimaging in the CN and MCI groups

	Total CN		MCI	p
	(n = 72)	(n = 21)	(n = 51)	
Age, years mean (SD)	75.2 (7.2)	73.1 (6.5)	76.1 (7.3)	0.09
Female n (%)	46 (63.9%)	15 (32.6%)	31 (67.4%)	0.73
Education, years mean (SD)	11.25 (5.2)	14.05 (3.8)	10.10 (5.3)	0.01
Katz mean (SD)	5.85 (0.3)	5.75 (0.4)	5.89 (0.3)	0.13
Lawton mean (SD)	6.78 (1.9)	7.30 (1.6)	6.55 (2.0)	0.15
MoCA mean (SD)	23.70 (4.3)	27.25 (1.9)	21.44 (3.9)	0.01
NEUROPSI mean (SD)	99.06 (14.3)	111.30 (5.0)	91.71 (13.1)	0.01
GDS mean (SD)	2.69 (2.3)	1.40 (1.6)	3.31 (2.4)	0.01
Cardiovascular risk factors				
Hypertension, n (%)	44 (62.9%)	9 (20.5%)	35 (79.5%)	0.02
Dyslipidemia, n (%)	34 (48.6%)	6 (17.6%)	28 (82.4%)	0.02
Diabetes, n (%)	21 (30.0%)	6 (28.6%)	15 (71.4%)	0.86
Obesity, n (%)	17 (23.6%)	5 (29.4%)	12 (70.6%)	0.95
Smoking status, n (%)	25 (34.7%)	9 (36.0%)	16 (64.0%)	0.41
CVRF media ± DE	3.21 (1.41)	2.81 (1.16)	3.37 (1.48)	0.12
Visual scales				
Fazekas, n (%) 1-3 white matter hyperintensities	40 (55.6%)	7 (35.3%)	33 (64.7%)	0.01
Scheltens, n (%) 1-4: medial temporal atrophy	55 (78.6%)	9 (16.4%)	46 (83.6%)	0.01
Koedam, n (%) 1-3 Parietal atrophy	50 (70.4%)	11 (22%)	39 (78.0%)	0.03

CN: cognitively normal; MCI: mild cognitive impairment; Katz: independence in activities of daily living index; Lawton: instrumental Activities of Daily Living Index; MMSE: mini-Mental State Examination; MoCA: Montreal cognitive assessment; NEUROPSI: brief Neuropsychological Evaluation in Spanish; GDS: geriatric depression scale; CVRF: cardiovascular risk factors. Categorical variables x2 (bilateral sig. 0.005); categorical and continuous variables independent samples t-test (bilateral sig. 0.005).

cytoskeleton, with subsequent formation of neurofibrillary tangles and neuronal degeneration³¹. In our study, the association of WMH and MTA with the *APOE-ε₄* carrier status was statistically significant, which could support the concept of mixed

pathophysiology mechanisms (neurodegeneration and cerebral vascular pathology).

Our study also detected an association of the *APOE-ε₄* carrier status with parietal atrophy according to the

Table 2. Effect of *APOE-ε₄* carrier status on MRI according to the Fazekas, Scheltens, and Koedam scales, in the CN and MCI groups

	CN (n = 21) (%)		p	MCI (n = 51) (%)		P
	<i>APOE-ε₄</i> carrier (n = 6)	Non- <i>APOE-ε₄</i> carrier (n=15)		<i>APOE-ε₄</i> carrier (n = 34)	Non- <i>APOE-ε₄</i> carrier (n=17)	
Fazekas						
0: no white matter hyperintensities	5 (84%)	9 (60%)	0.30	13 (39%)	5 (30%)	0.05
	1 (16%)	6 (40%)		21 (61%)	12 (70%)	
Scheltens						
0: no medial- temporal atrophy	4 (67%)	8 (54%)	0.57	1 (3%)	2 (12%)	0.01
1-4: medial-temporal atrophy	2 (33%)	7 (46%)		33 (97%)	15 (87%)	
Koedam						
0: no parietal atrophy	3 (50%)	7 (46%)	0.89	7 (21%)	4 (23%)	0.18
1-3 parietal atrophy	3 (50%)	8 (54%)		27 (79%)	13 (76%)	

CN: cognitively normal; MCI: mild cognitive impairment. Categorical variables x2 (bilateral sig. 0.005).

Table 3. Association of *APOE-ε₄* carrier status and visual neuroimaging scales in MCI

Fazekas		Scheltens				Koedam					
Model 1 OR (CI: 95%)	p	Model 2+ OR (CI: 95%)	p	Model 1 OR (CI: 95%)	p	Model 2+ OR (CI: 95%)	p	Model 1 OR (CI: 95%)	p	Model 2+ OR (CI: 95%)	p
<i>APOE-ε₄</i> carrier status + normal NI											
1.1 (0.3-6.0)	0.60	1.0 (0.1-6.3)	0.9	0.5 (0.04-6.0)	0.5	0.2 (0.01-4.3)	0.3	0.78 (0.1-5.1)	0.7	0.3 (0.04-3.5)	0.3
Non-<i>APOE-ε₄</i> carrier status + abnormal NI											
3.0 (0.8-10.8)	0.09	2.7 (0.5-12.6)	0.2	7.4 (1.7-32.0)	0.01	5.1 (0.9-28.2)	0.06	2.0 (0.5-7.3)	0.2	2.2 (0.4-10.6)	0.3
<i>APOE-ε₄</i> carrier status and abnormal NI											
11.7 (1.2-108.2)	0.03	15.3 (1.3-175)	0.03	20.0 (3.0-131.7)	0.01	19.8 (2.2-175)	0.01	4.6 (0.9-22.4)	0.06	6.3 (1.03-39.53)	0.05

Carrier status: participants with the presence of at least one *APOE-ε₄*; neuroimaging: NI; normal neuroimaging: visual scales with a score of 0; abnormal neuroimaging: visual scales equal to or greater than 1; OR: odds ratio; CI: confidence interval; +Model 1: binomial line regression between visual scales with *APOE-ε₄* carrier state; +Model 2: binomial linear regression adjusted for age, education level, and cardiovascular risk factors (composed of cardiovascular diseases reported by participants when the brain MRI was obtained); MCI: mild cognitive impairment.

KS in the MCI group. The previous studies have demonstrated the influence of *APOE-ε₄* carrier status on the anatomical areas compatible with parietal atrophy^{32,33}. According to Braak and Braak's pathological stratification, neurofibrillary changes begin in the medial temporal lobe and extend to the neocortical association areas, suggesting that cortical brain atrophy could be strongly correlated with the clinical progression of MCI³⁴.

The limitations of our study pertain to the sample size and the cross-sectional design, which does not allow us to establish cause and effect relationships. Difficulty was also encountered when recruiting volunteers since they had to be in a preclinical state and positive to the *APOE-ε₄* carrier status. However, the main strength of our study is that it compensates for some of the dearth of Latin American or Mexican studies analyzing the association between *APOE-ε₄* carrier status and neuroimaging findings in older adults with MCI.

Older adults with MCI and *APOE-ε₄* carriage presented an association with MTA and WMH according to the SS and FS, respectively. Moreover, after controlling for age, educational level, and CVRF, an association with parietal atrophy was also established. Early detection of these neuroimaging findings would allow for more accurate differentiation between MCI and AD dementia. Therefore, it is pivotal to control CVRF by establishing timely control and prevention strategies to delay progression toward dementia.

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