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Framingham Risk Score and the Risk of Progression from Mild Cognitive Impairment to Dementia

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Abstract.
Background: Mild cognitive impairment (MCI) often represents the clinical manifestation of cognitive deterioration preceding Alzheimer's disease (AD). Currently, there are no reliable approaches for an objective evaluation of the risk of developing AD in MCI patients.
Objective: The aim of this study was to verify whether the Framingham cardiovascular risk profile (FCRP) could be useful to identify patients at the highest risk of conversion from MCI to AD.
Methods: Patients with amnestic MCI (aMCI) were carefully investigated to assess their vascular risk profile. They were also submitted to a comprehensive neuropsychological evaluation. The FCRP was calculated for each patient and the apolipoprotein E (ApoE) genotype was determined from peripheral blood cells. The main outcome was defined as a conversion to AD within 24 months after inclusion.
Results: 385 consecutive aMCI subjects were included. Age, FCRP, and vascular age showed a fairly predictive value on conversion to AD. Selecting the subpopulation of ApoE ε4 carriers, we observed that FCRP had an increased performance in predicting the conversion. The rate of conversion increased from 12.5% in the FCRP low-risk group to 43.2% in the high-risk group ($p < 0.0001$). ApoE ε4 carriers had a 3.7-times increased probability of conversion with respect to the other subjects ($p < 0.0001$).
Conclusions: FCRP assessment could be considered a reliable approach to predict conversion to AD in aMCI subjects. The presence of ApoE ε4 increases significantly the risk of conversion. These data confirm the narrow relationship between genetic and vascular risk factors in influencing the evolution of cognitive impairment.

Keywords: Alzheimer's disease, apolipoproteins, cognitive dysfunction, dementia, risk factors

INTRODUCTION

Mild cognitive impairment (MCI) is a clinical condition characterized by slight cognitive alterations not interfering with patients' ability to maintain autonomy in daily living [1, 2]. This condition is defined as a "pre-dementia state"; the annual conversion rate to dementia, particularly Alzheimer's disease (AD), ranges from 5% to 20% [2]. Several studies have been performed in the attempt to identify and correct possible factors responsible for the conversion. Genetic factors are relevant, in particular the presence of apolipoprotein E (ApoE) ε4 allele [3, 4]. Different investigations suggest that vascular risk factors could also be implicated. Several studies have been conducted to evaluate the impact of each

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single vascular risk factor therapy on the progression of cognitive impairment, but data obtained has turned out to be contrasting [5–8]. Some investigations have shown that a clustering of different vascular risk factors could predispose to conversion [9–11]. At the moment, it is still not possible to reliably identify MCI patients with increased risk of evolution to AD. In a previous study, we demonstrated that Framingham cardiovascular risk profile (FCRP) could be useful to predict cognitive deterioration in AD patients [12]. FCRP is a composite measure of general cardiovascular risk used to predict the risk of acute vascular events in a 10-year period [13, 14].

The aim of this study was to evaluate whether an increased FCRP score could be used to predict a conversion in MCI patients. We also assessed the role of ApoE in this setting to obtain insights about the relevance of the relationships between genetic aspects and vascular phenotype.

MATERIALS AND METHODS

Study population and FCRP calculation

We considered all patients evaluated for mild cognitive deficits at the Neurological Clinic of Marche Polytechnic University, during a ten-year period (from January 2006 to January 2016), who had a diagnosis of MCI according to international guidelines [1]. We only collected amnestic MCI (aMCI) because, according to literature, this subtype has the highest risk of conversion to AD [15, 16]. Each subject was submitted to general and neurological physical exams and blood pressure determination. Data about the presence of vascular risk factors such as cardiopathy or non-valvular atrial fibrillation, hypertension, diabetes, dyslipidemia, or smoking habits were collected. Medications, i.e., antiplatelet, anticoagulant, antihypertensive, statins, or antidiabetic drugs, and a possible familiarity for dementia were also evaluated. A subject was considered as smoker in the presence of an active smoking habit for at least one year before our evaluation. We also investigated the presence of vascular diseases. According to the Framingham Heart Study [17], we considered as prior vascular disease coronary heart disease (myocardial infarction, coronary insufficiency, or angina), heart failure, peripheral vascular disease (intermittent claudication), and cerebrovascular disease (transient ischemic attack, ischemic or hemorrhagic stroke). Following international guidelines, we divided the pressure values (mean of the two collections) in five classes of hypertension: optimal: systolic = 120 mmHg, diastolic = 80 mmHg; normal blood pressure: systolic = 120–129 mmHg, diastolic = 80–84 mmHg; high normal blood pressure: systolic = 130–139 mmHg, diastolic = 85–89 mmHg; hypertension stage I: systolic = 140–159 mmHg, diastolic = 90–99 mmHg; hypertension stage II-IV: systolic $\geq$160 mmHg or diastolic $\geq$100 mmHg [17, 18].

Then, we obtained a complete blood collection, considering in particular total and high-density lipoprotein (HDL) cholesterol and fasting blood glucose. We performed a comprehensive laboratory work-up to exclude metabolic or deficiency alterations compatible with other forms of dementia differing from AD.

According to a previous study [12], we divided total and HDL cholesterol in different classes. Total cholesterol ranges were: <160 mg/dL, 160–199 mg/dL, 200–239 mg/dL, 240–279 mg/dL, and $\geq$280 mg/dL; HDL cholesterol ranges were: <35 mg/dL, 35–44 mg/dL, 45–49 mg/dL, 50–59 mg/dL, $\geq$60 mg/dL.

Presence of diabetes was considered when fasting blood glucose values were 126 mg/dL; alternately, a patient was considered diabetic if he/she regularly assumed insulin or oral hypoglycemic medications. Hypertension was defined on the basis whether antihypertensive medications were being used or on their presence in clinical history. Based on these clinical and laboratory findings, we are able to calculate the FCRP score for all subjects included, according to the definition offered by D'Agostino et al. [17]. We obtained the Estimated 10-year global CVD risk, the Risk Category, and the Estimated Vascular Age.

Neuropsychological assessments

During the first evaluation (T_0), all the patients were submitted to a complete neuropsychological battery. Inclusion criteria were a diagnosis of aMCI according to international guidelines [1] and a value of 0.5 at the Clinical Dementia Rating sum of boxes (CDR-SB), a general measure of cognitive functions [19].

Radiological and ultrasonographic examination

Brain computed tomography (CT) scan or magnetic resonance imaging (MRI) to include only patients with no relevant cerebral vascular

impairment was performed. According to Wahlund classification, we included in the study only subjects with grade 0 (no vascular lesions) or grade 1 (small subcortical focal lesions, defined as areas with high signal intensity on T2 but isointense with normal brain parenchyma on T1) [20]. Each patient was also submitted to an ultrasonographic evaluation by a pulsed wave Doppler and echo-color Doppler (iU22 Philips ultrasound, Bothell, WA, USA) to exclude subjects with occlusion or severe stenosis of carotid vessels, factors associated with severe risk to progression toward dementia [21, 22]. We also performed an electrocardiogram and, in selected cases, a transthoracic or transesophageal echocardiography to exclude patent forame ovale or other cardiac embolic diseases.

APOE phenotype definition

Finally, we obtained ApoE genotype from the blood sample collection with a nucleic acid isolation system (QuickGene-810, Fujifilm, Japan) and with a real-time polymerase chain reaction amplification in the ApoE polymorphic gene region using an automated rotary thermocycler (Rotor-Gene 6000, Corbett Research, Australia). Gene counting calculated the different frequencies of the ε2, ε3, and ε4 alleles.

Exclusion criteria

Exclusion criteria were a diagnosis different from MCI or a CDR-SB score more than 0.5; alterations of physical or neurological examination; presence of relevant cerebral vascular derangement classified as a Wahlund score more than 1; occlusion or significant stenosis of carotid vessels at ultrasonographic evaluations; severe co-pathologies or cardiac embolic disease.

Follow-up

We performed a regular clinical or telephonic follow-up for each patient every 6 months until a final visit 24 months after the first evaluation (T_1). During this last face-to-face follow-up visit, each aMCI patient repeated the same neuropsychological battery of the first evaluation and we calculated the CDR-SB score. Diagnosis of AD was established, according to guidelines [23], on neuropsychological evaluation results, on clinical history and on a global CDR score $\geq$1.

Clinical, neurosonological, and neuropsychological operators were blinded to each other's data. The study was approved by the ethics committee of Marche Polytechnic University. All participants and/or caregivers gave their informed written consent according to the Declaration of Helsinki.

Statistical analysis

Sex, hypertension, diabetes, dyslipidemia, smoke, cardiopathy, non-valvular atrial fibrillation, familiarity for AD, and the presence of ApoE ε4 allele were recorded as dichotomous variables. Use of statins, antihypertensive, antidiabetic, antiplatelet, and anticoagulant drugs was synthesized in different dichotomous variables. Age, scholarity, Mini-Mental State Examination (MMSE) score, Framingham vascular risk, vascular age, total and HDL cholesterol were recorded as continuous variables. We also prepared an ordinal variable by subdividing the sample into low, intermediate, and high vascular risk according to the FCRP score: subjects were considered at low risk if their Framingham risk was <10%, at intermediate risk if between 10 and 19%, and at high risk if >20%. The main outcome was defined as conversion to AD at 24 months, and this variable was coded as binary. To evaluate the conversion toward AD, the CDR-SB was used [19]. In particular, aMCI subjects obtained a global CDR score of 0.5, while a mild state of dementia was targeted with a score of 1.

Ordinal and binary variables were cross tabulated and compared with the chi-square test. Continuous variables were compared with the *t*-test for independent variables. We used a ROC curve analysis adopting the main outcome variable, FCRP score, and the vascular age to assess the predictive value of these variables in the setting of mild cognitive impairment evolution. The same test was run in the overall sample as well as in the subpopulation carrying only the ApoE ε4 allele.

Power analysis underlined that a sample size $\geq$377 could allow us to exclude the H_0 hypothesis that the effects observed in binary logistic regression were due to chance, with an α level <0.05, a power (1-β) of 95% and an odds ratio $\geq$1.6.

The probability of conversion to AD was then assessed with a binary logistic regression model adopting the conversion to AD variable as main outcome, the ordinal variable containing the vascular risk as the main predictor and ApoE genotype, age, sex, scholarity, cardiopathy, and non-valvular atrial fibrillation as covariates.

Then we adopted the same model, without the ApoE genotype, only in the population carrying the e4 allele in order to evaluate the risk added by vascular impairment in this specific population. Statistical analysis was performed with SPSS 13.0 for Windows Systems, and power analysis was performed with G*Power for Windows Systems.

RESULTS

From 465 patients initially recruited, 38 died before the final evaluation. In 6 cases, we changed the diagnosis during the follow-up, and 36 did not accept to participate in the study. We obtained a final sample of 385 consecutive subjects. Baseline characteristics are synthesized in Table 1. Subdividing the population in subjects who evolved to AD (group 1, n. 142) and subjects who remained cognitively stable (group 2, n. 243), we observed that age ($p = 0.006$, *t*-test), FRCP ($p = 0.002$, *t*-test) and vascular age ($p = 0.006$, *t*-test) turned out to be significantly higher in group 1 with respect to group 2, while MMSE at T_0 was not different between the two groups, as shown in Table 2.

In the overall sample, both Framingham estimated vascular risk (AUC:0.592; 95%CI:0.534–0.649; $p = 0.003$) and estimated vascular age of the subjects (AUC:0.605; 95%CI:0.547–0.663; $p = 0.001$) showed a fairly predictive value on conversion to AD at T_1 (Fig. 1a). Selecting the subpopulation of ApoE ε4 carriers, we observed that FRCP had an increased performance in predicting cognitive deterioration (AUC:0.682; 95%CI:0.577–0.786; $p = 0.001$), while the estimated vascular age maintained a similar performance (AUC:0.610; 95%CI:0.501–0.719; $p = 0.050$).

Considering all the subjects, we observed that the proportion of aMCI-affected patients undergoing a conversion to AD increased along with the vascular risk, as assessed by FRCP (Fig. 2a), with a rate of conversion ranging from 12.5% in the low-risk group to 40.3% in the intermediate-risk group to 43.2% in the high-risk group ($p < 0.0001$ at chi-square test). Running the same cross tabulation in the subgroup of patients carrying the ApoE ε4 genotype, we observed that the MCI-affected patients undergoing a conversion to AD were more sensitive to an increased vascular risk (Fig. 2b). In fact, the rate of conversion ranged from 10.0% in the low-risk group to 43.8% in the intermediate-risk group to 69.4% in the high-risk group ($p < 0.0001$ at the chi-square test).

Binary logistic regression analysis confirmed that the risk of conversion to AD increased with the increase in vascular risk in the overall MCI population even after correction for covariates (Fig. 3a). In this model, subjects with intermediate vascular risk had a 5.4-times increased probability if compared

Table 1
Baseline characteristics of the sample

Neuropsychological Variables	
Mini-Mental State Examination at T0 (±SD)	26.7 (±2.18)
Number of subjects evolved to AD (n. %)	142 (36.9%)
Epidemiological Variables	
Age (±SD), years	72.29 (±7.79)
Male Sex (n. %)	195 (50.6%)
Scholarity (±SD), years	8,03 (±4.32)
Vascular Variables	
Mean IMT (±SD), mm	0.90 (±0.17)
Framingham Risk Score (±SD), %	21.49 (±8.51)
Estimated Vascular Age (±SD), years	74.88 (±8.58)
Risk Factors for AD	
AD Familiarity (n. %)	99 (25.7%)
ApoE ε4 carrier (n.%)	111 (28.8%)
Hypertension (n.%)	200 (51.9%)
Vascular Risk Factors	
Diabetes (n. %)	54 (14.0%)
Dyslipidemia (n. %)	153 (39.7%)
Cigarette smoking (n. %)	137 (35.6%)
Cardiopathy (n. %)	72 (18.7%)
Non-valvular Atrial Fibrillation (n. %)	29 (7.5%)
Drugs	
Use of Statins (n. %)	117 (30.4%)
Use of Anti-hypertensive drugs (n. %)	217 (56.4%)
Use of Antidiabetic drugs (n. %)	47 (12.2%)
Use of Antiplatelet drugs (n. %)	144 (37.4%)
Use of Oral Anticoagulant drugs (n. %)	18 (4.7%)
Population, divided by Framingham Risk	
Low Framingham Risk Score (n. %)	72 (18.7%)
Intermediate Framingham Risk Score (n. %)	72 (18.7%)
High Framingham Risk Score (n. %)	212 (62.6%)

Table 2
Baseline differences between continuous variables

	Evolved to AD	Not Evolved to AD	*p*
Age (±SD)	73.70 (±6.79)	71.47 (±8.21)	0.006
Mini-Mental State Examination (T0) (±SD)	26.95 (±2.25)	26.64 (±2.13)	0.179
Framingham Risk Score (±SD)	23.28 (±7.32)	20.44 (±8.99)	0.002
Estimated Vascular Age (±SD)	76.68 (±6.09)	73.83 (±9.59)	0.002

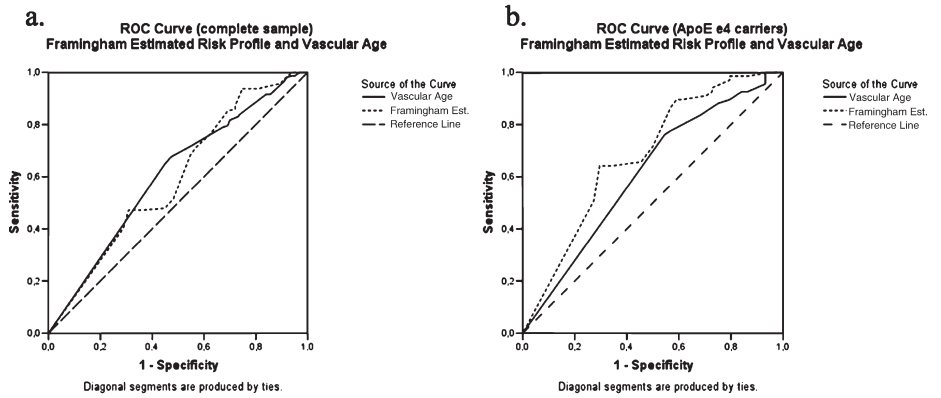

Fig. 1. ROC Curve Analysis in (a) the complete sample and in (b) the subpopulation of ApoE ε4 carriers.

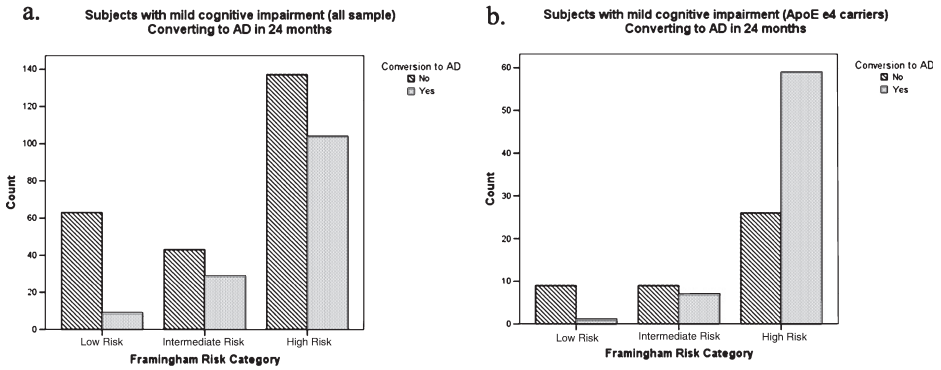

Fig. 2. Differences in the distribution of subjects evolving to AD in the low, intermediate, and high risk according to the Framingham risk score (a) in the overall sample (b) in the subpopulation of subjects with ApoE ε4 allele.

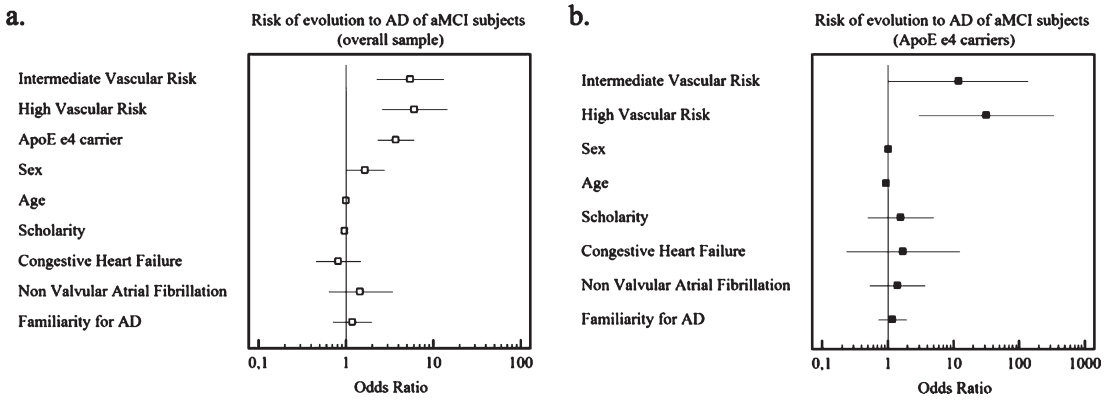

Fig. 3. Risk of evolution from MCI to AD (a) in the overall sample (b) in the subpopulation of subjects with ApoE ε4 allele.

to patients with low vascular risk (OR:5.468; 95%CI:2.232–13.392; $p < 0.0001$); subjects with high vascular risk had a 6.0-times increased probability compared to low vascular risk patients (OR:6.066; 95%CI:2.525–14.577; $p < 0.0001$). In this model, ApoE ε4 carriers had a 3.7-times increased probability of conversion to AD with respect to the other subjects (OR:3.705; 95%CI:2.272–6.042; $p < 0.0001$). Running the same model only in the ApoE ε4 carrier group, we observed that the probability of deterioration increased (Fig. 3b). In the intermediate-risk group, the probability was 11.9 times more than in the low-risk group (OR:11.951; 95%CI:1.026–139.277; $p = 0.048$) and,

in the high-risk group, the odds ratio reached 31.55 if compared to the low-risk group (OR:31.556; 95%CI:2.909–342.341; $p = 0.005$). The magnitude of effects of both binary logistic analyses was consistent with the *a priori* power analysis and confirmed the expected power of the study.

Conclusions

Data emerging from our study suggest that the association between ApoE genotype and vascular phenotype significantly increases the risk of a possible conversion from aMCI to AD. Specifically, aMCI patients with a cluster of vascular risk factors, corresponding to a growing extent of vascular impairment, show an increasing risk of conversion to AD. ApoE ε4 genotype increases this effect, probably acting on both neurodegenerative and vascular factors. Several studies have shown that vascular risk factors and cerebral micro- and macrovascular vessel derangement are implicated in AD onset and progression. Among the different hypothesized mechanisms, an alteration of cerebral microvascular unit and a chronic cerebral hypoperfusion seem to play the most relevant role. Moreover, in a recent study, FCRP turned out to be a reliable predictor of progression of cognitive impairment in AD patients [12]. The possibility that vascular processes may be significantly involved in sustaining age-related cognitive worsening has been widely investigated [24]. Vascular risk factors may promote cerebral atrophy and it has been suggested that brain atrophy can result from an ischemic process [25]. Recently, a large amount of evidence emerged to suggest the hypotheses of an additive or a synergistic effect between cerebrovascular impairment and neurodegeneration as the main determinant of dementia occurrence [26]. MCI is a recognized stage of predementia, and several studies suggest some possible approaches to predict the rate of conversion. A large amount of evidence comes from cerebrospinal fluid (CSF) biomarkers, i.e., levels of $A\beta_{1\text{-}42}$ are typically reduced in AD. Different investigations demonstrate that this decrease is present many years before symptoms' onset and presents a high positive predictive value for the progression from MCI to AD [27, 28]. A number of evidence arising from amyloid positron emission tomography abnormalities, CSF fluorodeoxyglucose-positron emission tomography hypometabolism, volume and atrophy rate markers derived from structural MRI in MCI patients suggest the possibility to use functional and anatomic cerebral changes to predict a conversion to AD [29–31]. Recent findings, moreover, show that AD progression is associated with progressive changes of biomarkers impairment more than with their presence[32–34].

All these data are interesting and accurate, and they were introduced in the last diagnostic criteria for AD [23, 32]. However, these evaluations are very complex and expensive and require advanced instruments and skilled personnel so that their applicability is limited. On the other hand, AD is the most diffused dementia, and the number of patients is projected to increase dramatically. FCRP evaluation and ApoE genotype are widely available and could be helpful to suggest the subgroup of aMCI patients who will benefit most from second-level examination. The association between AD and high vascular scores from the Framingham study has already been studied. Jefferson et al. investigated the association between FCRP and deterioration of cognitive assessment in cognitively healthy subjects and patients with MCI [35], while the Framingham Offspring Study showed a correlation between FCRP and cognitive impairment in APOE ε4 carriers with several cardiovascular risk factors [36, 37]. Another relevant aspect is that, as opposed to genetic and liquoral biomarkers, vascular and metabolic alterations are modifiable factors. A correct management of hypertension and diabetes and the adoption of a correct and healthy lifestyle should be particularly encouraged in subjects at increased risk of developing dementia. In a previous study, we demonstrated that vascular derangement tends to reinforce genetic predisposition to dementia and suggested that a possible approach to delay AD progression could be an aggressive intervention on vascular modifiable risk factors [4]. Moreover, different studies demonstrated that risk factors for embolic pathologies as microembolism could be involved in AD onset [38].

Several large trials have investigated the possibility to delay AD onset by treating vascular risk factors, but the results have been contrasting. A possible explanation for this could be the enrolment of AD patients without an accurate assessment of vascular and genetic profiles. Recently, Weekman et al. published an interesting study on a mouse model of dementia showing that anti-Aβ immunotherapy, besides maintaining the efficacy in clearing Aβ from the brain, was not able to delay cognitive impairment when dementia was associated with vascular comorbidity. The authors hypothesized that the positive effect of anti-Aβ antibodies in the mouse and the poor results in clinical trials could be, at least partially, explained by the interference of the

vascular components of cognitive impairment [39]. More generally, classifying MCI patients in subgroups with different probability to convert could help physicians to recognize when the use of aggressive therapeutic resources is more likely to be successful. In other words, it is probable that the stratification of patients according to their prognosis could improve the therapeutic approach. Moreover, considering the absence of realistic disease-modifying therapies, treatment of vascular risk factors, including an aggressive employment of antihypertensive drugs [5] or statins [40], should take a pivotal role in the management of AD patients.

Furthermore, it is relevant to underline that no single vascular risk factor but a cluster of them can be responsible for the final vessel derangement, and only a global comprehensive vascular evaluation could be useful for clinicians [41]. Under this light, FCRP could represent a useful instrument, because it is able to assess the global vascular risk of each single patient. Moreover, it can be calculated also in an ambulatory care or a non-specialist center. Other studies have investigated similar predictive approaches. In the CAIDE study, Kivipelto and colleagues calculated a "dementia risk score" able to predict dementia in subjects submitted to a 20-year follow-up [42, 43]. They showed that, among the most significant predictive factors for dementia, hypertension, dyslipidemia, and obesity had a similar impact of old age and low education levels [43]. This score was quite different from FCRP because it takes into consideration different risk factors as age, education, sex, total cholesterol, body mass index, physical activity, ApoE ε4 status and systolic blood pressure and calculated the risk of dementia. FCRP analyses more in depth the vascular profile of the patients, taking into account factors as smoking or prior vascular disease.

We also evaluated the impact of ApoE ε4 allele on the risk of AD progression, and found that carrier subjects with vascular derangement had a very high risk. This finding is not surprising as ApoE is implicated in lipid metabolism and storage and several studies have shown that the presence of ApoE ε4 causes a worsening of VLDL metabolism. The final impact on cerebral vessels is a faster impairment and a more significant atherosclerosis development in cerebral vessels [4]. Moreover, ApoE ε4 is associated with lower $A\beta_{1-42}$ levels in the CSF [27] and with greater brain atrophy rates [44].

A limitation of this study is that we decided to consider only aMCI because they presented most relevant probability to convert to AD. Larger studies including all the different typology of MCI, especially multidomain MCI, could offer a more complete evaluation about the very complex issue about factors involved in the modulation of the risk of conversion in dementia. Currently, a patient with a diagnosis of MCI is not receiving any specific treatment and different studies have shown that the use of anti-cholinesterase drugs do not interfere with the progression to dementia [45]. Identifying possible patterns of treatable risk factors or sub-groups of MCI patients to be followed and more strictly treated could be a reliable target for the management of cognitive impairment and could help to reduce the percentage of future dementing subjects.

In conclusion, AD will affect millions of people in the future, and a valid therapeutic option is lacking. Prevention is the only realistic way to delay the onset and progression from a pre-dementing stage to the cognitive function fall. The correction of vascular risk factors besides preventing cardiovascular events, which are among the most diffused causes of death in industrialized countries, could also reduce the risk of developing AD especially in subjects with a genetic predisposition.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/17-0160r1).

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