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Apolipoprotein E-ε4 polymorphism and cognitive dysfunction after carotid endarterectomy

Eric J. Heyer[a,b,*], **Joanna L. Mergeche**[a], **Yaakov Stern**[b], **Hani R. Malone**[c], **Samuel S. Bruce**[c], **Justin T. Ward**[a], and **E. Sander Connolly**[b,c]

[a]Department of Anesthesiology, Columbia University, 630 West 168th Street, P&S Box 46, New York, NY 10032, USA

[b]Department of Neurology, Columbia University, New York, NY, USA

[c]Department of Neurological Surgery, Columbia University, New York, NY, USA

Abstract

Approximately 25% of patients undergoing carotid endarterectomy (CEA) exhibit cognitive dysfunction (CD) 1 day and 1 month after CEA. The apolipoprotein E (apoE)-ε4 polymorphism has been previously identified as a robust independent risk factor for CD 1 month after CEA. We aimed to determine whether the apoE-ε4 polymorphism is also an independent risk factor for CD as early as 1 day after CEA and to confirm the previous findings at 1 month. Patients undergoing elective CEA (n = 411) were enrolled with written informed consent in this follow-up observational study. CD was evaluated via an extensive neuropsychometric battery. apoE-ε4 carriers exhibited significantly more CD 1 day (30.1% *versus* 17.9%, $p = 0.01$) and 1 month (25.7% *versus* 9.8%, $p = 0.001$) after CEA compared to non-carriers. Multivariate regression models were generated to determine independent predictors of CD. At 1 day, apoE-ε4 was significantly associated with higher risk of CD (odds ratio [OR]: 2.24 [1.29-3.84], $p = 0.004$), while statin use was significantly associated with lower risk (OR: 0.40 [0.24-0.67], $p < 0.001$). At 1 month, apoE-ε4 was significantly associated with higher risk of CD (OR: 3.14 [1.53-6.38], $p = 0.002$), while symptomatic status was significantly associated with lower risk (OR: 0.45 [0.20-0.94], $p = 0.03$). The apoE-ε4 polymorphism is an independent risk factor for CD as early as 1 day after CEA and is confirmed to be an independent risk factor for CD at 1 month as well.

Keywords

Apolipoprotein E; Carotid endarterectomy; Cognition; Cognitive dysfunction

1. Introduction

Patients with high-grade carotid artery stenosis may undergo carotid endarterectomy (CEA) for carotid revascularization and prevention of stroke[1, 2]. We previously demonstrated that

*Corresponding author. Tel: 212 305 9072; fax: +1 212 305 8287., ejh3@columbia.edu (E.J. Heyer). .

Conflicts of Interest/Disclosures

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the incidence of cognitive dysfunction (CD), a subtler form of neurologic injury than stroke, is approximately 25% 1 day and up to 23% 1 month after CEA[3-6]. Our previous work has also confirmed that CD at 1 day is associated with elevations in the S100B biomarker of neuronal injury[7, 8] and currently unpublished data demonstrates a higher risk of early mortality in those patients that demonstrate CD at 1 day. Work by other groups demonstrates that CD observed 1 week and 3 months after non-cardiac surgery is predictive of early disability, retirement, and death[9].

The apolipoprotein E (apoE) gene plays an important role in lipid metabolism and is implicated in the regulation of processes including the immune response and neuronal repair and regeneration[10, 11]. There are three isoforms of apoE – ε2, ε3, and ε4 – which have respective carrier rates of approximately 8%, 78%, and 14% in the general population[12]. The apoE-ε4 allele is a risk factor for atherosclerosis[13], accelerated cognitive decline[14-17], Alzheimer's disease[18], and decreased capacity for cognitive recovery after neurologic insult[10]. These risks occur in a gene-dosage pattern[19]; in order from the least to the most risk: apoE-ε4 non-carriers, carriers of one apoE-ε4 allele, and carriers of two apoE-ε4 alleles.

We previously demonstrated in a cohort of 75 CEA patients that the apoE-ε4 polymorphism is a strong independent risk factor for CD 1 month after CEA[4]. No previous studies have determined whether the apoE-ε4 polymorphism is an independent risk factor for CD as early as 1 day after CEA. It is important to address these issues given the evidence that CD at 1 day is associated with the elevation of markers of neuronal injury, early mortality, and poor quality of life.

In this follow-up study, we aimed to determine whether the apoE-ε4 polymorphism is an independent risk factor for CD as early as 1 day after CEA and confirm the previous findings at 1 month[4] in a much larger patient cohort. We hypothesized that the apoE-ε4 polymorphism is an independent risk factor for CD as early as 1 day in addition to 1 month.

2. Methods

2.1 Patients

Four hundred and eleven (411) patients with high-grade carotid artery stenosis undergoing elective CEA were enrolled with written informed consent in this Institutional Review Board approved observational study. Seventy-five patients were included in a previous publication[4]. Eligible patients were scheduled for elective CEA, English-speaking, had no axis I psychiatric disorders, and were able to complete the neuropsychometric battery preoperatively and postoperatively. The surgical technique and indications for CEA have remained constant at this institution, as previously described[3, 6, 20]. All of the procedures were performed by eight senior neurological and vascular surgeons. All patients received general anesthesia with standard hemodynamic and temperature monitoring, as previously described[3, 6, 20]. One neurosurgical anesthesiologist administered 62.5% of the general anesthetics.

2.2 Cognitive measures

The outcome of CD was evaluated using a battery of neuropsychometric tests preoperatively and within 24 hours postoperatively by a single clinical coordinator under the supervision of a neuropsychologist. The outcome of CD is binary and patients were designated to either have or not have CD. All patients completed the neuropsychometric tests preoperatively and at 1 day postoperatively. Three hundred and six patients also completed the tests at 1 month.

The neuropsychometric tests evaluated four cognitive domains – verbal memory (Hopkins Verbal Learning Test, Controlled Oral Word Association Test, Buschke), visuo-spatial organization (Rey-Osterrieth Complex Figure Copy and Recall), motor function (Grooved Pegboard and Finger Tapping Test), and executive action (Halstead-Reitan Trials A and B). The criteria for CD are based on difference scores calculated for each test by subtracting the preoperative test performance from the postoperative test performance at 1 day. Similar to previous studies[21, 22], a Z-score was generated based on a surgical reference group's performance to account for practice effect, trauma of surgery, and the surgical experience.

The surgical reference group was composed of 156 patients ≥ 60 years of age undergoing lumbar level laminectomy or microdiscectomy on ≤ 2 levels without fusion, no tumor/cyst, or blood loss necessitating transfusion. These patients experienced similar surgical and anesthetic times as well as a similar general anesthetic to the CEA patients. The mean difference score of the surgical reference group was subtracted from the difference score for the CEA patients and then divided by the standard deviation (SD) of the surgical reference group ([Difference $_{CEA}$ − Mean Difference $_{Reference}$]/Standard Deviation $_{Reference}$). Therefore, each test is evaluated in units of standard deviation of the surgical reference group's change in performance. CEA patient domains were evaluated to account for both focal and global/hemispheric deficits: (1) ≥ 2 SD worse performance than the surgical reference group in two or more cognitive domains or (2)≥ 1.5 SD worse performance than the surgical reference group in all four cognitive domains. The neuropsychometric tests, their scoring, and performance calculations are described in greater detail in previous works[3, 6, 20, 23, 24]. The surgical reference group was only used to generate Z-scores; therefore, they were not included in any other analysis or reported otherwise in this study.

Factors that affect the risk of CD, age > 75 years, diabetes mellitus, and statin use [5, 22], were included in all statistical analyses. Other factors that may affect the risk of CD, but have not been previously demonstrated to do so, were included in all analyses to account for any potential effects: sex, years of education, body mass index (BMI), history of smoking, peripheral vascular disease (PVD), hypertension, symptomatic status of prior transient ischemic attack or stroke, and duration of cross-clamp.

2.3 Genotyping

DNA was extracted from buffy coats of whole blood samples. Bi-allelic genotyping results were generated using the Kompetitive Allele-Specific Polymerase chain reaction (PCR) based assay (LGC Genomics, Middlesex, UK). For rs429358, 5′CGCGGACATGGAGGACGTGT3′ was the sense primer and 5′GCGGACATGGAGGACGTGC3′ the antisense primer. For rs7412, 5′GATGCCGATGACCTGCAGAAGT3′ was the sense primer and 5′ATGCCGATGACCTGCAGAAGC3′ the antisense primer. Samples were plated into 1536 well PCR plates in duplicate. Only wild-type apoE-ε3/ε3, heterozygous apoE-ε3/ε4, and homozygous apoE-ε4/ε4 were evaluated in this study. Patients with at least one apoE-ε 4 allele were considered carriers.

2.4 Statistical analyses

Statistical analysis was performed using R environment (R Development Core Team, Vienna, Austria). For univariate analyses, Student's *t*-test, Wilcoxon rank sums test, Fisher's exact test, Pearson's chi-squared test, and simple logistic regression were used where appropriate. Multiple logistic regression models were constructed to identify independent predictors of CD at 1 day and at 1 month. All factors with $p < 0.20$ in a simple univariate logistic regression were entered into the final models.

Model fit and calibration of the multivariate regression model were confirmed with the likelihood ratio test, Hosmer-Lemeshow goodness-of-fit test, and receiver operating characteristic analysis. Multivariate imputation by chained equations was in the event of missing data using the fully conditional specification method, as described[25]. The R package mice[26] with predictive mean matching for continuous variables and logistic regression for categorical variables was used to perform the imputation. p 0.05 was considered significant.

3. Results

The presence of the apoE-ε4 polymorphism in our patient cohort was comparable to that observed in several other healthy populations and large-scale population studies[27, 28]. apoE-ε4 distribution was consistent with Hardy-Weinberg equilibrium (ε3/ε3 74.9%, ε3/ε4 23.4%, ε4/ε4 1.7%; $p = 0.99$). Patient characteristics are presented in Table 1. The previously identified factors that affect CD were not significantly different between apoE-ε4 carriers and non-carriers: age > 75 years (32.0% *versus* 27.6%, $p = 0.39$), diabetes mellitus (18.6% *versus* 21.4%, $p = 0.52$) and statin use (70.9% *versus* 66.6%, $p = 0.42$). All other patient characteristics and medical history parameters were not significantly different. Baseline neuropsychometric test scores were not significantly different between apoE-ε4 carriers and non-carriers (Table 1).

Eighty-six (20.9%) CEA patients demonstrated CD at 1 day and 41 (13.4%) demonstrated CD at 1 month. apoE-ε4 carriers exhibited a significantly higher incidence of CD at 1 day (30.1% *versus* 17.9%, $p = 0.01$) and 1 month (25.7% *versus* 9.8%, $p = 0.001$) than non-carriers. Based on simple univariate regression with CD at 1 day, age > 75 years, years of education, BMI, statin use, and the apoE-ε4 polymorphism were included in the multivariate regression model for predictors of CD at 1 day. The final multivariate regression model for CD at 1 day demonstrated the apoE-ε4 polymorphism was significantly associated with higher risk of CD (OR: 2.24 [1.29-3.84], $p = 0.004$), while statin use was significantly associated with lower risk of CD (OR: 0.40 [0.24-0.67], $p < 0.001$) (Table 2).

Based on simple univariate regression with CD at 1 month, age > 75 years, hypertension, diabetes mellitus, PVD, symptomatic status, and the apoE-ε4 polymorphism were included in the multivariate regression model for predictors of CD at 1 month. The final multivariate regression model for CD at 1 month demonstrated that the apoE-ε4 polymorphism was significantly associated with higher risk of CD (OR: 3.14 [1.53-6.38], $p = 0.002$), while symptomatic status was significantly associated with lower risk of CD (OR: 0.45 [0.20-0.94], $p = 0.03$) (Table 3). Patients who were evaluated for CD at 1 month were not significantly different from those patients who were lost at follow-up and were not evaluated at 1 month.

4. Discussion

CD is a subtler form of neurologic injury than stroke present in approximately 25% of patients 1 day and in up to 23% of patients 1 month after CEA[3-6]. CD at 1 day is associated with elevated levels of S100B, a glial protein marker of neuronal injury [7], and currently unpublished data demonstrates CD at 1 day is predictive of earlier mortality. Previous studies demonstrate the apoE-ε4 polymorphism is a strong independent risk factor for CD 1 month after CEA[4], but no studies have evaluated the apoE-ε4 polymorphism in the context of CD at earlier time points such as at 1 day. This study presents a larger patient cohort of 411 patients to determine whether the apoE-ε4 polymorphism is an independent risk factor for CD as early as 1 day and to confirm the previous findings at 1 month.

This study confirms that the apoE-ε4 polymorphism is a strong independent risk factor for CD at 1 month and demonstrates that the apoE-ε4 polymorphism is also a strong independent risk factor for CD as early as 1 day. Statin use was significantly associated with less risk of CD at 1 day, which is consistent with previous work done on asymptomatic CEA patients that demonstrate a significantly lower risk of CD at 1 day when taking statins[22]. Based on these findings and those of previous studies, it is reasonable to consider that the pleiotropic effects of statins may be able to improve the ability to recover from neurologic injury after CEA or maintain a lower inflammatory burden[29]. This notion could be of particular importance in apoE-ε4 carriers who have impaired neurologic recovery[10, 30, 31]. Further prospective randomized research will be necessary to delineate whether statin type, statin dose, or duration of statin use are important considerations and whether this observation is sustained at later time points such as at 6 months and 1 year.

Symptomatic status was unexpectedly associated with lower risk of CD at 1 month. This finding is unclear and we cannot offer an adequate explanation of the finding at this time though we speculate it may be a function of loss to follow-up. We anticipate a future study with stronger patient retention can investigate and explain this finding.

We acknowledge the limitations of our study. Only 306 patients completed neuropsychometric evaluation at 1 month and it is unclear whether this had an impact on the findings. There were no significant differences between those who completed and missed the evaluation, but we speculate the reduced number of patients at 1 month may have influenced the findings at 1 month, especially with respect to symptomatic status and lower risk for CD. This study is retrospective and single center.

In conclusion, the apoE-ε4 polymorphism is not only a strong independent risk factor for CD at 1 month, but also for CD as early as 1 day after CEA.

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Table 1

Patient characteristics and cognitive measures outcomes before carotid endarterectomy

	All CEA patients n = 411	ε4 carriers n = 103	Non-carriers n = 308	*P*
Age > 75 years	28.7%	32.0%	27.6%	0.39
Sex, male	66.2%	65.6%	68.0%	0.66
Education, years	14.7 ± 3.3	14.9 ± 3.5	14.6 ± 3.3	0.44
BMI, kg/m^2	27.1 ± 4.5	26.7 ± 5.3	27.2 ± 4.2	0.44
History of smoking	69.8%	71.8%	69.2%	0.61
Hypertension	57.7%	64.1%	55.5%	0.13
Statin use	67.6%	70.9%	66.6%	0.42
Diabetes mellitus	20.7%	18.6%	21.4%	0.52
PVD	28.0%	30.1%	27.3%	0.58
Symptomatic history†	41.6%	47.6%	39.6%	0.16
Cross-clamp duration, minutes	44.3 ± 16.2	42.9 ± 14.8	44.8 ± 19.1	0.38
Baseline COWA	40.2 ± 13.1	41.6 ± 14.1	39.8 ± 12.7	0.28
Baseline Boston Naming	54.3 ± 5.1	55.1 ± 4.3	54.1 ± 5.3	0.13
Baseline Hopkins Total	20.9 ± 6.2	20.6 ± 5.9	21.0 ± 6.4	0.72
Baseline Rey Copy	28.4 ± 5.6	28.3 ± 5.2	28.5 ± 5.7	0.78
Baseline Rey Recall	11.5 ± 5.9	11.5 ± 5.3	11.6 ± 6.1	0.92
Baseline Trails A	49.9 ± 25.8	50.3 ± 23.8	49.8 ± 26.5	0.88
Baseline Trails B	122.4 ± 80.7	129.3 ± 91.6	120.3 ± 76.7	0.33
Baseline Pegboard Dominant	113.0 ± 50.8	111.4 ± 36.1	113.6 ± 55.0	0.74
Baseline Pegboard Non-Dominant	131.2 ± 64.9	123.4 ± 39.6	134.0 ± 71.6	0.19

Data are presented as mean ± standard deviation or percentage.

BMI = body mass index, CEA = carotid endarterectomy, COWA = Controlled Oral Word Association, HDL = high-density lipoprotein, LDL = low-density lipoprotein, PVD = peripheral vascular disease.

†History of stroke or transient ischemic attack.

Table 2

Logistic regression model for cognitive dysfunction at 1 day after carotid endarterectomy

	Univariate odds ratio	*P*	Multivariate odds ratio	*P*
Age > 75 years	1.44 (0.86–2.38)	0.16	1.31 (0.75–2.25)	0.33
Sex, male	1.06 (0.96–1.26)	0.74		
Education, years	1.08 (1.00–1.16)	0.06	1.08 (1.00–1.18)	0.06
BMI, kg/m^2	1.0 (0.98–1.10)	0.19	1.02 (0.97–1.09)	0.43
History of smoking	0.93 (0.56–1.57)	0.78		
Hypertension	0.97 (0.60–1.57)	0.89		
Statin use	0.41 (0.25–0.66)	< 0.001	0.40 (0.24–0.67)	< 0.001
Diabetes mellitus	1.43 (0.81–2.47)	0.22		
PVD	1.07 (0.63–1.79)	0.80		
Symptomatic history†	1.14 (0.70–1.84)	0.56		
Cross-clamp duration, minutes	1.00 (0.99–1.02)	0.52		
apoE-ε4 polymorphism	1.98 (1.18–3.29)	0.01	2.24 (1.29–3.84)	0.004

apoE = apolipoprotein E, BMI = body mass index, PVD = peripheral vascular disease.

†History of stroke or transient ischemic attack.

Table 3

Logistic regression model for cognitive dysfunction at 1 month after carotid endarterectomy

	Univariate odds ratio	*P*	Multivariate odds ratio	*P*
Age > 75 years	1.58 (0.78–3.12)	0.20	1.60 (0.76–3.28)	0.22
Sex, male	1.07 (0.35–1.37)	0.36		
Education, years	1.06 (0.96–1.17)	0.27		
BMI, kg/m^2	0.99 (1.07–1.01)	0.75		
History of smoking	1.06 (0.53–2.26)	0.87		
Hypertension	1.57 (0.80–3.21)	0.20	1.44 (0.71–3.02)	0.32
Statin use	0.85 (0.43–1.72)	0.64		
Diabetes mellitus	1.58 (0.73–3.23)	0.22	1.78 (0.79–3.87)	0.16
PVD	1.82 (0.90–3.58)	0.09	1.62 (0.78–3.29)	0.20
Symptomatic history[†]	0.54 (0.25–1.10)	0.10	0.45 (0.20–0.94)	0.03
Cross-clamp duration, minutes	1.01 (0.99–1.04)	0.21		
apoE-ε4 polymorphism	3.21 (1.60–6.37)	0.001	3.14 (1.53–6.38)	0.002

apoE = apolipoprotein E, BMI = body mass index, PVD = peripheral vascular disease.

[†]History of stroke or transient ischemic attack.