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Easily Screenable Characteristics Associated with Cognitive Improvement and Dysfunction After Carotid Endarterectomy

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Keywords

Cerebrovascular Disease/Stroke; Cognitive Impairment; Risk factors; carotid endarterectomy; carotid stenosis; cognitive impairment; neuropsychometric assessment

Introduction & Background:

Carotid endarterectomy (CEA) has been shown to be an effective treatment for the prevention of stroke in asymptomatic or symptomatic patients with high grade carotid artery stenosis.^{1,2} Many studies of cognitive performance in the 1980s and early 1990s were directed at demonstrating improvement in cognitive performance after CEA.^{3,4} Our previous studies, however, demonstrated that patients may develop cognitive changes associated with CEA, either dysfunction or improvement.⁵ Our emphasis has been on patients who develop cognitive dysfunction (CD), because decreasing dysfunction is of clinical benefit. We evaluated early cognitive dysfunction (eCD) as dysfunction within 24 hours of surgery. The incidence of eCD was not trivial. It was about 25% compared to a surgical reference group.⁶

Early cognitive dysfunction was associated with a number of different patient characteristics, medications and genetic alleles: age, diabetes mellitus, statin usage, neurovascular anatomy, and certain alleles of ApoE, phosphodiesterase and complement.^{7–12} Of note, we found that

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statin usage dramatically decreased the incidence of new neurologic findings and eCD after CEA in asymptomatic patients, defined as those patients without a history of previous stroke or transient ischemic attack. This effect was less evident in symptomatic patients.¹³

Some patients have improved function.¹⁴ Cognitive improvement (CI) depends on similar characteristics as CD. One factor is the transcranial Doppler Pulsatility Index (PI), which is an approximation of peripheral cerebral resistance.¹⁵ The implication of this finding is that preoperative cognitive performance is limited by cerebral blood flow which is increased after CEA surgery.

The factors that contribute to CD and CI have been presented in previous publications by other authors.^{16–18} However, these cohorts have been small and in-depth analysis has been limited. Those smaller studies linked change in cognitive function to patient characteristics such as degree of stenosis, duration of carotid clamping, diabetes mellitus, operative mean arterial pressure, and statin use.^{10,13,19,20}

In the present study, we aim to determine the incidence of both eCD and early cognitive improvement (eCI) defined as cognitive performance within 24 hours of surgery in a large cohort of patients using a battery of neuropsychometric tests and the risk factors associated with each.

Materials and Methods:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients

This is a retrospective review of a prospective observational study. All of these patients have previously been reported in other publications.^{13,21} Five hundred eighty-five (585) patients were tested with a battery of neuropsychometric tests before surgery and again within 24 hours following surgery. The subjects were either symptomatic or asymptomatic and were enrolled with written informed consent in this IRB-approved observational study (www.clinicaltrials.gov: NCT00597883). A cohort of one hundred fifty-five (155) patients undergoing “simple” spine surgery defined as a microdiscectomy, or one or two level laminectomy who did not require a blood transfusion or intensive care postoperatively were used as a reference group to account for the trauma of surgery, effects of general anesthesia, and the practice effect of repeated neuropsychometric testing, as previously described.⁶ The CEA and reference groups were evenly matched in terms of age, BMI, and sex (Table 1). All patients underwent a series of neurocognitive tests immediately preoperatively and again on post-operative day one (POD1).

Anesthesia and Surgery

The surgical technique, anesthetic management, and surgical indications have remained constant throughout the study period as previously described.⁶ Vascular surgeons typically closed the endarterectomy site with a patch (autologous, xenographic, or synthetic), and the neurosurgeons used primary closure.

Cognitive Domains

The neuropsychometric tests included the Controlled Oral Word Association Test (COWAT), the Hopkins Verbal Learning Test (HVLt), the Buschke Selective Reminding Test (SRT), the Rey-Osterrieth Complex Figure Test (ROCF), the Trails Making Test (TMT), Rapid Finger Tapping Test, and the Grooved Pegboard Test. These tests are described in more detail.²² Some tests had multiple components and variations, and over time certain tests were changed. We substituted the HVLt for the SRT because the HVLt was tolerated better by patients than the SRT, and we eliminated the Rapid Finger Tapping Test because it was insensitive to changes in motor function compared to the Grooved Pegboard Test. To minimize the effects of differing tests on overall performance, we arranged the test results into four different cognitive domains: (1) Memory, (2) Executive Function, (3) Visuo-spatial Reasoning, and (4) Motor Function. The *memory* domain includes total recall and percent total retention scores from the HVLt, the immediate recall portion of the ROCF, and the consistent long term retrieval (CLTR) and long term retrieval (LTR) components of the SRT. The *executive* domain is composed of the COWAT and Trails B tests. The *visuo-spatial* domain is composed of the copy portion of the ROCF and the *motor* domain is determined by the grooved pegboard and finger tapping test. All of these tests provide numeric scores. The ranges of the raw score changes for both the CEA group and the reference group are included in Table 2.

Of 585 patients, six (6) patients were excluded due to insufficient neuropsychometric testing data. Of the remainder, 49% were evaluated in 4 of 4 domains, 46% in 3 of 4 domains, 4% in 2 of 4 domains, and 1% dropped out.

Neurocognitive Change Assessment

Performance on neuropsychometric tests was calculated by a method similar to one described previously.¹³ Each patient's individual test performance was evaluated based on the change in neuropsychometric test score. We compared neuropsychometric performance after CEA (the CEA group) or after "simple" spine surgery (the reference group) to each patient's baseline performance. We used the neuropsychometric performance of the reference group to generate Zscores of patients in the CEA group, where we subtracted the mean score change in the reference group and divided the standard deviation of the score change in the reference group. Patients in the CEA group are considered to have eCD if: patients had Z-scores ≤ -2 in two or more cognitive domains or patients had mean Z-scores across all 4 domains ≤ -1.5 . Patients are considered to have eCI if: they had Z-scores ≥ 2 in two or more cognitive domains or they had mean Z-scores across all 4 domains ≥ 1.5 . All other patients' cognitive performance was considered "no change". In summary, CEA patients' cognitive performance was defined with three levels: eCD, "no change", and eCI.

Statistical Analyses

In order to ensure comparability between the CEA group and the reference group, we first compared patient characteristics using Pearson's chi-squared test for categorical variables and two-sample t-test for continuous variables. We then used the proportional odds model to model the associations between the ordinal categorical cognitive performance outcomes (eCD, "no change", and eCI) and explanatory variables of interests such as use of statins or

aspirin, presence of diabetes mellitus, and years of education, as well as other patient characteristics, univariately and multivariately. These characteristics were chosen because they are easily accessible and routinely encountered in standard patient management or they have been shown to be associated with cognitive dysfunction or decline. An odds ratio (OR) greater than 1 demonstrated that the explanatory variable was associated with patients having worse cognitive function towards the direction of eCD and an odds ratio less than 1 showed that the variable was associated with patients having better cognitive function towards the direction of eCI. A p-value .05 was considered statistically significant. Statistical analysis was performed using the JMP® 10 Statistical Discovery from SAS (Cary, NC).

Results:

Of the 585 subjects enrolled in the study, six did not complete any postoperative neuropsychometric testing and three suffered postoperative strokes and were excluded from analysis. Of the remaining 576 subjects, 344 (59.8%) were asymptomatic and 232 (40.2%) were symptomatic for cerebrovascular accidents prior to surgery. 139 (24.1%) suffered eCD, 38 (6.6%) displayed eCI, and 399 (69.3%) had “no change” on postoperative day 1 (POD 1). Although it is theoretically possible, there was no overlap between patients who had eCD and patients who had eCI.

While all patients with high Z-scores in any of the four domains were more likely to reach the criteria for eCI, patients who had eCI were most likely to see higher Z-scores in the executive domain (OR=0.29, $p < 0.01$), followed by the motor (OR=0.31, $p < 0.01$), visuo-spatial (OR=0.33, $p < 0.01$), and memory (OR = 0.39, $p < 0.01$) domains. Figure 1 shows the average Zscore for patients in each of the cognitive domains.

Regression covariates and results from univariate proportional odds model analysis are presented in Table 3. It shows greater levels of education (OR=0.95 [0.90:1.00], $p=0.04$) and no co-morbid diabetes (OR=0.8 [0.65:0.99], $p=0.04$) are associated with better cognitive performance towards eCI. While statin naïve (OR=1.23[1.03:1.48], $p=0.02$) and female (OR=1.27[1.06:1.53], $p=0.02$) are associated with worse cognitive performance towards eCD.

Multivariate analysis using the proportional odds model shows that statin therapy, diabetes, and female sex were significant predictors for cognitive changes (Table 4). Statin naïve patients (OR=1.22[1.02:1.48], $p=0.03$) and women (OR=1.23[1.02:1.49], $p=0.03$) were more likely to have worse cognitive performance towards eCD. Non-diabetic patients (OR=0.80[0.65:0.99], $p=0.04$) were more likely to have better cognitive performance favoring eCI.

When patients with significant carotid stenosis were separated based on whether they were symptomatic or asymptomatic, different factors showed significance. For symptomatic stenosis, years of education (OR=0.90[0.83:0.99], $p = 0.03$) were correlated with higher scores as was the case for the CEA group as a whole. For asymptomatic stenosis, older age

(OR=1.03[1.00:1.06], $p = 0.05$), women (OR=1.33[1.05:1.70], $p = 0.02$), and patients not on aspirin therapy (OR=1.37[1.03:1.82], $p = 0.03$) were more likely to do poorly.

Discussion:

The Proportional Odds Model (also called Ordered Linear Regression) is a statistical method used to model ordinal outcomes given a known variable. In the present study, the ordinal outcomes are eCD, “no change”, and eCI. We sought to create a model which would predict which cognitive performance outcome group a patient would fall into given known factors available from the patient’s medical history. Previous studies have looked at cognitive change as a binary outcome (e.g. cognitive dysfunction or no cognitive dysfunction), but we believe there are actually many separate outcomes which lie along a spectrum. The proportional odds model is the best way to account for these multiple outcomes and uncover how each of these factors interact together and where they may have the greatest impact.²³ We understand that by using the proportional odds model, we assume that predictors for dysfunction and improvement have the same strength. In the absence of evidence that this assumption is without merit, we believe that this model is sufficient to assess the odds of cognitive change after CEA.

In the intervening years since Heyer et al showed that a significant portion of patients suffer from eCD within 24 hours after CEA, cognitive assessments for over 20 more CEA patients have been added to the database. The number of patients with eCD has remained consistent at 25%, but we were also interested in cognitive improvement following carotid revascularization surgery. We have also found that nearly 6% of patients have eCI. It is thought that cognitive change after CEA is due to postoperative hemodynamic changes within the cerebral arterial system.²⁴ Using perfusion weighted magnetic resonance imaging, Wang et al showed that subjects were more likely to have cognitive improvement following CEA if their perfusion indexes improved post procedure.²⁵ On the opposite end of the spectrum, while patients who develop new neurologic deficits after carotid revascularization surgery are thought to be due to microemboli²⁶, we think that microemboli may not account for eCD. We were unable to correlate evidence of emboli using diffusion weighted MRI in patients who had eCD after CEA.²⁷ On the other hand, patients lacking both posterior communicating arteries (PCOMs) had a significantly higher incidence of eCD implying an underlying ischemic etiology.⁸ Although it has been shown that early cognitive change after CEA may not be sustained at later points and patients often return to baseline, we believe that the detection and prevention of eCD to be of vital importance.²⁰ We theorize that much of this recovery may be due to compensation which often occurs after neurocognitive injury which allows the patient to return to a “normal” level of cognition, while the underlying injury remains. Previously, we found that eCD in patients not on statin therapy was predictive of shorter survival compared to those without eCD or those on statin therapy regardless of the presence or absence of eCD.²¹ Additionally, patients who suffer eCD may have subclinical neuronal damage as determined by increased serum levels S100B.²⁸ To date there is little research on the effects of delayed cognitive dysfunction after CEA.

Consistent with our previous findings, non-diabetics and those on statin therapy were shown to have decreased incidence of cognitive dysfunction. Patients who were both non-diabetic

and on statins were also more likely to have cognitive improvement. Education and sex play significant roles in the development of cognitive change after CEA. In univariate analysis, every 5 years of education accounted for 24% increased odds that the patient would have some cognitive improvement after the surgery. One theory is that education is a surrogate for cognitive reserve which allows patients to accommodate for some cognitive impairment with some form of cognitive compensation.²⁹ Sex also had a predictive effect on CD. Women fared much worse than their male counterparts in terms of likelihood of developing eCD. All of the women in this cohort were post-menopausal. It is believed that reduced estrogen production by postmenopausal women increases their risk for metabolic dysregulation and inflammation.³⁰ While we did not measure circulating estrogen, we speculate that this post-menopausal inflammatory state may be responsible for the discordant rates of post-CEA eCD between men and women.

Since the surgical indications for CEA in asymptomatic and symptomatic carotid stenosis differ, we decided to look for differences in the rates of eCD and eCI in these two subgroups.³¹ We failed to see any difference in the incidence of cognitive change between the groups. Since we previously found that statins benefited asymptomatic patients, we looked at whether different factors were protective or harmful between symptomatic and asymptomatic patients. Interestingly, the groups had differing results. Similar to the univariate whole group analysis, female sex as well as increasing age and aspirin non-use were associated with poorer cognitive function in the asymptomatic group. Only years of education reached significance in the symptomatic group and was associated with cognitive improvement. Antiplatelet therapy has long been standard treatment for preventing recurrent stroke and vessel reocclusion, but additionally preoperative platelet activity reduction does lead to decreased incidence of microembolic events perioperatively and therefore is speculated to have a protective effect against eCD.^{32,33} While we believe that each of these factors would become significant given sufficient power, education as a surrogate for cognitive reserve was especially important for symptomatic patients who have demonstrable structural damage.

We purposefully did not include any analysis pertaining to the length of surgery, cross-clamp duration, or anesthesia provider as we have shown in previous studies that they have no effect on the more subtle cognitive dysfunction that we seek to investigate in the present study.¹³ Likewise we did not complete any analysis looking into the change in incidence of eCD or eCI over time. We know that the prevalence of statin use has increased over time and due to that increase, we believe the incidence of eCD after CEA has decreased.

The most important characteristics associated with cognitive change, whether improvement or dysfunction, were statin therapy, female sex, and diabetes as determined by multivariate analysis. Characteristics like statin use and diabetes have been previously recognized as having an association with cognitive dysfunction after CEA. Statins have shown a protective effect mostly likely caused by their anti-inflammatory properties which reduce the activation and migration of immune cells.²⁸ Diabetes, as well, has been shown to contribute to the neuroinflammatory burden after CEA and increase rates of cognitive dysfunction.³⁴

Our current analysis shows that sex is also an important risk factor in the development of worse cognition after CEA. In previous studies of revascularization surgery for asymptomatic carotid stenosis such as the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST), a meta-analysis showed that women had no benefit in terms of 5 year reduction in stroke or perioperative death compared to men.³⁵ Women with symptoms are also less likely to benefit from revascularization surgery as shown in pooled data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Aspirin and Carotid Endarterectomy Study (ACE).³⁵ Stelagowski et al showed that men and women have separate risk factors for perioperative stroke following CEA with hypercholesterolemia being a more influential risk factor in men than in women.³⁶ While we were unable to demonstrate any significant factors which would explain the higher rates of eCD in women, outcome differences based on sex remain an unresolved issues in carotid revascularization studies.

We acknowledge that our analysis has some limitations. Firstly, we do not have a true control group as this was an observational study and there was no randomization or placebo group. Therefore we acknowledge that our reference group (the spine group) is entirely not comparable to the CEA group with respect to risk factors, but they are comparable with respect to the trauma of surgery, anesthetics, and practice effect, which were the factors that we were accounting for. While our threshold of ≥ 2 SD in 2 or more cognitive domains for diagnosing eCD or eCI is admittedly arbitrary, we wanted to use a highly stringent measure of change. Given the fact that some of our patients were only fully tested in 2 of the 4 domains, we consider the reported incidence of eCD/eCI to be a conservative estimate of cognitive change after carotid revascularization surgery.

Conclusion:

Patients having CEA may develop eCD or eCI within the first 24 hours after surgery. The risk factors associated with development of eCD or eCI within the first 24 hours after CEA surgery depend on the medications that the patient is taking as well as patient characteristics including genetic factors. In general, women are more likely to develop eCD. More years of education decreases the incidence of eCD and increases the incidence of eCI. The only medications likely to decrease eCD are statins and aspirin. Both are correlated most strongly in asymptomatic patients. Women may derive less benefit from surgery than men, but more robust sex-specific studies are needed.

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Abbreviations List

ACAS	Asymptomatic Carotid Atherosclerosis Study

ACE	Aspirin and Carotid Endarterectomy Study
ACST	Asymptomatic Carotid Surgery Trial
ApoE	Apolipoprotein E
BMI	Body Mass Index
CD	Cognitive Dysfunction
CEA	Carotid Endarterectomy
CI	Cognitive Improvement
CLTR	Consistent Long Term Retrieval
COWAT	Controlled Oral Word Association Test CP, Cognitive Performance eCD – Early Cognitive Dysfunction eCI, Early Cognitive Improvement
HVLT	Hopkins Verbal Learning Test
IRB	Institutional Review Board
LTR	Long Term Retrieval
MRI	Magnetic Resonance Imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial
OR	Odds Ratio
PCOM	Posterior Communicating Artery
PI	Pulsatility Index
POD	Post-operative Day
ROCF	Rey-Osterrieth Complex Figure Test
SD	Standard Deviation
SRT	Buschke Selective Reminding Test
TMT	Trails Making Test

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Highlights

- Carotid endarterectomy patients may have cognitive changes within 24 hrs of surgery
- Of 576 CEA patients, 24% suffered early cognitive dysfunction and 6% improvement
- Women were more likely to have worse cognitive outcomes
- Non-diabetics were more likely to have better cognitive outcomes

Fig 1: Average Z-Scores by Cognitive Domain.

Data represents the average Z-scores of the subjects in each of the 4 cognitive domains for the 3 cognitive performance outcome groups (eCD, “no change”, and eCI) following neuropsychometric testing 24hrs post-CEA.

Table 1:

Patient Characteristics between the CEA group and the reference group

Patient Characteristics	Carotid (N = 576)			Spine (N = 155)			p-value
	Mean (SD)	Min - Max	% Total	Mean (SD)	Min - Max	% Total	
Age	70.7 (8.6)	43 – 95		71 (7.2)	48 – 89		0.70
Years of Survival	8.7 (5.3)	0.01 – 19.17		11.1 (5.0)	2.8 – 17.7		< 0.01
Years of Education	14.6 (3.3)	5 – 25		15.6 (3.6)	5 – 30		< 0.01
BMI	26.6 (4.6)	17.8 – 49.9		26.5 (4.3)	16.8 – 40.4		0.51
Sex (Male)	65.2			64.5			0.95
Hypertension	57.6			44.5			< 0.01
DM	21.4			8.4			< 0.01
Symptomatic	40.2			N/A			N/A
Statin	62.7			29.7			< 0.01
Aspirin	82.5			52.9			< 0.01
PVD	30.7			14.8			< 0.01

Table 2:

Neuropsychometric Raw Test Score Change from Pre-op to Post-op Day 1

Test	Change Score Range	
Memory Domain	Carotid	Reference
ROCF Recall	-22 — 26	-5 — 14
HVLT Total Recall	-13 — 15	-6 — 10
HVLT % Retention	-110 — 125	-46 — 40
SRT- LTR	-80 — 42	-46 — 23
SRT - CLTR	-92 — 35	-31 — 28
Executive Domain		
COWAT	-21 — 32	-19 — 34
TMT B	-223 — 162	-75 — 69
Motor Domain		
PB Dominant	-190 — 195	-43 — 41
PB NonDominant	-414 — 200	-70 — 56
Finger Tapping Dominant	-23.8 — 32.6	-13 — 17
Finger Tapping NonDominant	-27.6 — 22.3	-16.2 — 18.2
Visuo-Spatial Domain		
ROCF Copy	-77 — 17.5	-10 — 9

ROCF: Rey-Osterrieth Complex Figure Test; HVLT: Hopkins Verbal Learning Test; SRT: Buschke Selective Reminding Test; LTR: Long Term Retrieval; CLTR: Consistent Long Term Retrieval; COWAT: Controlled Oral Word Association Test; TMT: Trails Making Test; PB: Pegboard

Table 3:

Univariate Analysis on cognitive performance using proportional odds model

Univariate Analysis					
Patient Characteristic	Coefficient	OR	95% CI	p value	CP*
Age	0.0122	1.01	0.99 : 1.03	0.24	
Years of Education [†]	-0.281	0.76	0.57 : 0.99	0.04	eCI
No Diabetes Mellitus	-0.2178	0.8	0.65 : 0.99	0.04	eCI
No Hypertension	-0.097	0.91	0.76 : 1.08	0.29	
No Statin Use	0.208	1.23	1.03 : 1.48	0.02	eCD
Female	0.2412	1.27	1.06 : 1.53	0.01	eCD
No Peripheral Vascular Disease	0.0863	1.09	0.90 : 1.32	0.38	
No Aspirin	0.1945	1.21	0.97 : 1.52	0.09	

* Cognitive Performance;

[†] Year of Education: per 5-year increment.

Table 4:

Multivariate Analysis on cognitive performance using proportional odds model

Multivariate Analysis					
Patient Characteristic	Coefficient	OR	95% CI	p value	CP*
Age	0.0121	1.01	0.99 : 1.03	0.26	
No Statin Use	0.2059	1.22	1.02 : 1.48	0.03	eCD
No Aspirin	0.2165	1.24	0.99 : 1.56	0.06	
No Diabetes Mellitus	-0.2256	0.8	0.65 : 0.99	0.04	eCI
Asymptomatic Carotid Stenosis	0.0670	1.07	0.89 : 1.28	0.47	
Years of Education	-0.0362	0.96	0.91 : 1.02	0.21	
Female	0.2098	1.23	1.02 : 1.49	0.03	eCD
No Hypertension	-0.1291	0.88	0.74 : 1.05	0.17	

* Cognitive Performance