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Elevations in Preoperative Monocyte Count Predispose to Acute Neurocognitive Decline After Carotid Endarterectomy for Asymptomatic Carotid Artery Stenosis

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Abstract

Background and Purpose—Although the incidence of major stroke attributable to carotid endarterectomy (CEA) is low (1% to 2%), ≈25% of patients experience subtle postoperative neurocognitive dysfunction. This study examines whether preoperative leukocyte profiles predict cognitive outcome in asymptomatic CEA patients.

Methods—Sixty-nine asymptomatic CEA patients underwent neuropsychometric testing preoperatively and on postoperative day 1 (POD1). Preoperative white blood cell counts and differentials were obtained. Logistic regression was performed for risk factors for neurocognitive decline. Variables achieving univariate $P < 0.10$ were included in multivariate analysis.

Results—Eighteen (26%) patients experienced neurocognitive decline on POD1; multivariate analysis demonstrated that preoperative monocyte count ($P = 0.011$) and age ($P = 0.02$) independently predicted outcome.

Conclusions—Preoperative monocyte count and age are independently associated with acute neurocognitive decline after CEA for asymptomatic stenosis.

Keywords

carotid endarterectomy; ischemia; neuropsychology

Carotid endarterectomy (CEA) prevents stroke in appropriately selected patients with asymptomatic carotid artery stenosis.¹ Although the incidence of major stroke after CEA is low, recent studies suggest that a battery of neuropsychometric tests (NPMTs) detects subtle neurocognitive deficits in ≈25% of patients postoperatively.² Evidence indicates this decline may be ischemic in nature, caused by dislodged microemboli or transient cerebral hypoperfusion during endarterectomy.³

Studies demonstrate that leukocyte count independently predicts ischemic risk.^{4,5} We hypothesized that a preoperative proinflammatory state increases risk of acute neurocognitive decline after CEA by rendering cerebral tissue vulnerable to ischemic injury, or indicating

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plaque instability.^{6,7} This study prospectively evaluates the predictive value of preoperative leukocyte profiles in an asymptomatic CEA cohort.

Methods

Study Cohort

Sixty-nine prospectively enrolled patients with preoperative white blood cell (WBC) counts/differentials underwent CEA for asymptomatic carotid artery stenosis in this institutional review board–approved study. Patients were enrolled in an ongoing NPMT investigation; data from 37 patients were analyzed in a previous NPMT study.² No subjects underwent previous ipsilateral endarterectomy.

Anesthesia/Surgery

All patients received general anesthesia with routine monitoring/intraoperative electroencephalography, as described previously.² One patient was selectively shunted. Surgical times averaged 149.0±43 minutes.

NPMTs/Statistics

Patients were assessed preoperatively and on postoperative day 1 (POD1) using a battery of 5 NPMTs (Boston Naming, Halstead-Reitan Trails A/B, Controlled Oral Word Association, and Copy Portion of Rey Complex Figure). Tests were scored individually for CEA and control (56 contemporaneous lumbar laminectomy) patients. Changes in individual test scores were converted to z-scores as described previously.² Neurocognitive decline was defined as scores >2 SD above mean total cognitive changes of controls. NPMT outcomes were expressed as dichotomous variables (“injured”/“uninjured”).

Univariate logistic regression was performed for variables in the left column of Table 1. Variables achieving univariate $P<0.10$ were included in multivariate analysis using logistic regression with a backward selection process. Data are presented as odds ratio per SD increase in cell count for white cell data and per year for age. The remaining risk factors are presented as categorical variables, with odds ratios representing risk of having the condition. All data are expressed as mean±SD (odds ratio, 95% CI, P value) or with $P<0.05$ considered significant.

Results

Cohort Characteristics

Demographic/intraoperative variables for CEA and control patients are presented in Table 2. Eighteen (26%) patients experienced neurocognitive decline on POD1. There was no significant difference in age or anesthesia between the experimental/control groups or percent ipsilateral carotid stenosis between the injured/uninjured cohorts. No patients experienced radiographically/clinically apparent major postoperative stroke.

Statistics

Leukocyte analysis demonstrated no statistically significant differences between injured/uninjured groups, with the exception of monocytes. Mean preoperative monocyte counts were 0.70±0.19cells/nL in the injured and 0.52±0.18 cells/nL in the uninjured group ($P<0.001$).

Univariate analysis demonstrated a 12% increased risk of neurocognitive injury (1.12, 1.02 to 1.22, 0.02) for each year age increase. Each SD increase in monocyte count (SD=0.20 cells/nL) resulted in a 179% increase risk of neurocognitive injury (2.79, 1.46 to 5.35, 0.002). Neutrophil count trended toward significance in univariate analysis (1.64, 0.96 to 2.80, 0.07). Lymphocyte count and other stroke risk factors did not reach significance ($P<0.10$). Total

WBC count was not included in the multivariate analysis because of high correlation with neutrophil count (Pearson correlation [r]=0.89; $P<0.0001$).

Multivariate analysis included age, monocyte, and neutrophil count (Table 1). Age was predictive of outcome (1.12, 1.02 to 1.24, 0.02). Monocyte count remained highly significant (2.37, 1.21 to 4.62, 0.01), and neutrophil count a borderline predictor (1.78, 0.97 to 3.27, 0.06).

Discussion

Preoperative monocyte count and age independently predict acute neurocognitive outcome after CEA for asymptomatic stenosis. These associations persist when accounting for conventional stroke risk factors, including smoking, which is known to elevate WBC counts.

Acute post-CEA neurocognitive dysfunction is believed to be ischemic in nature attributable to cerebral hypoperfusion or microembolization of plaque. Previous work demonstrates an association between impaired post-CEA NPMT performance and elevated serum levels of S100b,⁸ a marker of glial cell death, supporting this hypothesis. NPMT testing offers a more detailed assessment of higher cortical functioning than traditional neurological examination. Thus, patients may experience cognitive decline attributable to subtle ischemia without the traditional radiographic or clinical characteristics of major stroke.

Our findings suggest an inflammatory component to acute post-CEA cognitive dysfunction. Atherosclerosis is viewed as a chronic inflammatory condition, with monocyte activation and infiltration implicated as initiating events,⁹ and plaque macrophage content independently associated with instability.⁷ Elevated preoperative monocyte counts may therefore indicate the presence of unstable plaque more prone to microembolize during CEA. Furthermore, a role for monocytes in stroke, independent of atherosclerosis, has been suggested. Interleukin-8, a monocyte release product, is elevated after stroke and serves as a strong neutrophil chemoattractant. This may “prime” patients for acute ischemic post-CEA neurocognitive decline by creating a favorable environment for neutrophil recruitment after disrupted cerebral blood flow during surgery.¹⁰

Further investigation is necessary to elucidate the mechanisms linking elevated monocyte counts with acute post-CEA cognitive dysfunction. Although previous data suggest that the majority of these patients will continue to experience impaired NPMT performance at 1 month,² additional investigations assessing the association of monocyte counts and delayed post-CEA cognitive decline are warranted.

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References

1. Executive committee for the asymptomatic carotid atherosclerosis study. Endarterectomy for asymptomatic carotid artery stenosis. *J Am Med Assoc* 1995;273:1421–1428.
2. Heyer EJ, Sharma R, Rampersad A, Winfree CJ, Mack WJ, Solomon RA, Todd GJ, McCormick PC, McMurtry JG, Quest DO, Stern Y, Lazar RM, Connolly ES. A controlled prospective study of neuropsychological dysfunction following carotid endarterectomy. *Arch Neurol* 2002;59:217–222. [PubMed: 11843692]
3. Wolf O, Heider P, Heinz M, Poppert H, Sander D, Greil O, Weiss W, Hanke M, Eckstein HH. Microembolic signals detected by transcranial doppler sonography during carotid endarterectomy and correlation with serial diffusion-weighted imaging. *Stroke* 2004;35:e373–e375. [PubMed: 15388901]

4. Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. *J Am Med Assoc* 1987;257:2318–2324.
5. Grau AJ, Boddy AW, Dukovic DA, Bugge F, Lichy C, Brandt T, Hacke W. Leukocyte count as an independent predictor of recurrent ischemic events. *Stroke* 2004;35:1147–1152. [PubMed: 15017013]
6. Chapman CM, Beilby JP, McQuillan BM, Thompson PL, Hung J. Monocyte count, but not C-reactive protein or interleukin-6, is an independent risk marker for subclinical carotid atherosclerosis. *Stroke* 2004;35:1619–1624. [PubMed: 15155967]
7. Alvarez Garcia B, Ruiz C, Chacon P, Sabin JA, Matas M. High-sensitivity c-reactive protein in high-grade carotid stenosis: risk marker for unstable carotid plaque. *J Vasc Surg* 2003;38:1018–1024. [PubMed: 14603210]
8. Connolly ES Jr, Winfree CJ, Rampersad A, Sharma R, Mack WJ, Mocco J, Solomon RA, Todd G, Quest DO, Stern Y, Heyer EJ. Serum s100b protein levels are correlated with subclinical neurocognitive declines after carotid endarterectomy. *Neurosurgery* 2001;49:1076–1082. [PubMed: 11846900]discussion 1082–1073
9. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999;340:115–126. [PubMed: 9887164]
10. Grau AJ, Reis A, Bugge F, Al-Khalaf A, Werle E, Valois N, Bertram M, Becher H, Grond-Ginsbach C. Monocyte function and plasma levels of interleukin-8 in acute ischemic stroke. *J Neurol Sci* 2001;192:41–47. [PubMed: 11701151]

TABLE 1
Risk Factors for Neurocognitive Decline After CEA. Logistic Regression

	Injured	Uninjured	OR	95% CI	P
Patients (n)	18 (26%)	51 (74%)
Age	75.2±5.3	69.2±8.5	1.12 [#]	(1.02, 1.24)	0.02*
Male gender	9 (50%)	32 (63%)
Obesity*	2 (11%)	9 (18%)
Smoking	12 (67%)	32 (63%)
Hypertension [†]	11 (61%)	39 (76%)
Diabetes mellitus	4 (28%)	11 (22%)
Hypercholesterolemia [‡]	11 (61%)	28 (55%)
Statin medication	11 (61%)	20 (40%)
Previous myocardial infarction	4 (22%)	18 (35%)
Previous contralateral CEA	0 (0%)	5 (10%)
Right operative side	10 (55%)	20 (39%)
Duration of surgery	143.4±31.6	147.9±47.1
Duration of cross-clamp	39.8±15.7	43.3±19.8
Shunt placement	1 (6%)	0 (0%)
WBC count	7.96±1.71	6.96±2.19
Neutrophil count	5.13±1.44	4.33±1.54	1.78 ^{**}	(0.97, 3.27)	0.06
Monocyte count	0.70±0.19	0.52±0.18	2.37 ^{**}	(1.21, 4.62)	0.01*
Lymphocyte count	1.84±0.57	1.86±0.95

* Obesity=body mass index ≥ 30

[†] hypertension=systolic blood pressure >140 and/or use of antihypertensives

[‡] hypercholesterolemia=cholesterol >200 and/or use of anticholesterol medication; odds ratios, CIs, and *P* values presented apply to multivariate logistic regression

[#] Age odds ratio: per year increase

** monocyte/neutrophil ORs: per SD increase in cell count (monocyte: 0.20 cells/nL; neutrophils: 1.5 cells/nL); no other variables achieved criteria for inclusion in multivariate analysis; continuous data presented as mean±SD.

TABLE 2

Demographic/Intraoperative Parameters

	CEA	Spine
Patients (n)	69	56
Age (y)	70.8±8.2	71.9±7.4
Male gender (%)	41 (59%)	33 (59%)
Obesity (%) [*]	11 (16%)	4 (7%)
Diabetes mellitus (%)	16 (23%)	4 (7%)
Hypertension (%) [†]	50 (72%)	31 (55%)
Hypercholesterolemia (%) [‡]	39 (56%)	14 (25%)
Previous myocardial infarction (%)	22 (32%)	8 (14%)
Previous contralateral CEA (%)	5 (7%)	2 (4%)
Duration of surgery (min)	146.8±43.4	148.7±54.5
Fentanyl (µg/kg)	2.4±1.4	2.4±1.1
Midazolam (mg/kg)	0.04±0.01	0.03±0.01

^{*} Obesity = BMI ≥ 30

[†] hypertension = SBP > 140/use of antihypertensives

[‡] hypercholesterolemia = cholesterol > 200/use of anticholesterol medication.