Inflammation and Cognitive Dysfunction in Type 2 Diabetic Carotid Endarterectomy Patients

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OBJECTIVE—Type 2 diabetic patients have a high incidence of cerebrovascular disease, elevated inflammation, and high risk of developing cognitive dysfunction following carotid endarterectomy (CEA). To elucidate the relationship between inflammation and the risk of cognitive dysfunction in type 2 diabetic patients, we aim to determine whether elevated levels of systemic inflammatory markers are associated with cognitive dysfunction 1 day after CEA.

RESEARCH DESIGN AND METHODS—One hundred fifteen type 2 diabetic CEA patients and 156 reference surgical patients were recruited with written informed consent in this single-center cohort study. All patients were evaluated with an extensive battery of neuropsychometric tests. Preoperative monocyte counts, HbA_{1c}, C-reactive protein (CRP), intercellular adhesion molecule 1, and matrix metalloproteinase 9 activity levels were obtained.

RESULTS—In a multivariate logistic regression model constructed to identify predictors of cognitive dysfunction in type 2 diabetic CEA patients, each unit of monocyte counts (odds ratio [OR] 1.76 [95% CI 1.17–2.93]; $P = 0.005$) and CRP (OR 1.17 [1.10–1.29]; $P < 0.001$) was significantly associated with higher odds of developing cognitive dysfunction 1 day after CEA in type 2 diabetic patients.

CONCLUSIONS—Type 2 diabetic patients with elevated levels of preoperative systemic inflammatory markers exhibit more cognitive dysfunction 1 day after CEA. These observations have implications for the preoperative medical management of this high-risk group of surgical patients undergoing carotid revascularization with CEA.

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The incidence of ischemic stroke is significantly higher in type 2 diabetic patients (1,2), as type 2 diabetes is an independent risk factor for stroke and its recurrence (3,4). Carotid artery stenosis is a major cause of ischemic stroke and can be surgically treated with carotid endarterectomy (CEA). In previous work, we have demonstrated that ~25% of CEA patients exhibit cognitive dysfunction, a subtle form of neurologic injury, within 1 day of CEA (5,6). Glial markers of neuronal injury (S100B) are elevated in patients who exhibit cognitive dysfunction within 1 day of CEA (7) and reflect opening of the blood–brain barrier (8). Additionally, we have data that demonstrate cognitive dysfunction exhibited within 1 day of CEA is associated with earlier mortality after CEA (9); patients who exhibit cognitive dysfunction within 1 day of CEA experience mortality 4 years earlier than those who do not exhibit cognitive dysfunction within 1 day of CEA. We have also demonstrated that type 2 diabetes is an independent risk factor for cognitive dysfunction (10). In this study, we will investigate factors that might contribute to the increased risk of type 2 diabetic patients undergoing CEA to exhibit the subtle, but significant, cognitive dysfunction.

Type 2 diabetes has been associated with accelerated atherosclerosis (11) and elevated systemic inflammation (12–14). Inflammation may play a significant role in accounting for the increased risk of cognitive dysfunction in type 2 diabetic patients. Studies have shown that monocyte activation and infiltration are specifically implicated in the initiation of chronic inflammation and atherosclerosis (12). C-reactive protein (CRP) is a nonspecific marker of systemic inflammation that has been strongly associated with adverse cardiovascular outcomes in both healthy patients and those with coronary artery disease (15–18). Intercellular adhesion molecule-1 (ICAM-1) is a glycoprotein expressed on endothelial cells and cells of the immune system (19). Matrix metalloproteinase-9 (MMP-9) is secreted from macrophages (20), is involved in the breakdown of vasculature extracellular matrices, and has also been investigated for its various roles in inflammation (21–24). Many previous studies have demonstrated that CRP, ICAM-1, monocytes, and MMP-9 activity are all elevated in type 2 diabetic patients compared with nondiabetic patients. In our previous work, we have demonstrated that type 2 diabetes is a risk factor for cognitive dysfunction (10). We have also previously shown that elevated levels of ICAM-1 (25), monocyte counts (26), and MMP-9 activity (27) are associated with higher incidences of cognitive dysfunction in nondiabetic patients following CEA. We have yet to demonstrate a relationship between CRP and cognitive dysfunction. However, given the previous work done on CRP, we are inspired to do so in this study.

Considering previous findings that *1*) type 2 diabetes is a risk factor for cognitive dysfunction following CEA; *2*) elevated ICAM-1, MMP-9, and monocyte counts are associated with more cognitive dysfunction in CEA patients; and *3*) type 2 diabetic patients have elevated levels of CRP, ICAM-1, MMP-9 activity, and monocytes, we hypothesize that type 2 diabetic patients with elevated preoperative systemic inflammation are more likely to exhibit cognitive dysfunction following CEA than those with lower preoperative systemic inflammation. To date,

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there are no studies that investigate this relationship.

We will evaluate preoperative systemic inflammation by measuring CRP, ICAM-1, MMP-9 activity, and monocytes and compare these levels between type 2 diabetic patients with and without cognitive dysfunction 1 day after CEA.

RESEARCH DESIGN AND METHODS

Patients, anesthesia, and surgery

We obtained written informed consent from 115 type 2 diabetic patients undergoing CEA. Patients were enrolled in this Institutional Review Board–approved observational study (http://www.clinicaltrials.gov, NCT00597883). Eligible patients were scheduled for elective CEA for high-grade carotid artery stenosis and clinically diagnosed as having type 2 diabetes, whether therapeutically treated or not. Although the name of each patient's medication was available, information regarding complications of type 2 diabetes, duration of disease, duration of treatment, or fasting and postprandial glucose control was not available. All patients received general anesthesia with standard hemodynamic and temperature monitoring, as previously described (5). None received blood transfusions. The surgical technique, anesthetic management, and indications for CEA are previously described (5,28).

Cognitive measures

All patients were examined with a battery of neuropsychometric tests that interrogate four cognitive domains—verbal memory, visuospatial organization, motor function, and executive function—as previously described (5,6,28,29). The four domains and their respective tests are: verbal memory—Controlled Oral Word Association, Buschke Selective Reminding, Boston Naming, and Hopkins Verbal Learning Test; visuospatial organization—Rey Complex Figure Copy and Recall; motor function—Grooved Pegboard Dominant/Non-Dominant and Fine Finger Tapping Dominant/Non-Dominant; and executive function—Halstead-Reitan Trails Parts A and B.

A reference group composed of 156 elderly patients undergoing spine surgery was used to account for trauma of surgery ≤4-h duration, residual effects of general anesthesia, and practice effect associated with repeated neuropsychometric testing. The reference patients are ≥60 years undergoing lumbar level laminectomy or microdiscectomy on ≤2 levels without fusion, tumor/cyst, or blood loss necessitating transfusion. These patients experience similar surgical and anesthetic times as well as a similar general anesthetic.

The criteria for cognitive dysfunction 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 (9,30), a Z-score was generated based on the reference group's performance; the mean difference score of the reference group was subtracted from the difference score for the CEA patient and then divided by the SD of the reference group: $([\text{Difference}_{CEA} - \text{Mean Difference}_{Reference}]/SD_{Reference})$. Therefore, each test is evaluated in units of SD of the 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 reference group in two or more cognitive domains or *2*) ≥1.5 SD worse performance than the reference group in all four cognitive domains. The neuropsychometric tests, their scoring, and performance calculations are described in greater detail in previous work (5,9,28,31).

A variety of factors can affect the neuropsychometric performance of patients after CEA, but only age >75 years and type 2 diabetes have been previously shown to independently affect performance (10). Statin use has been previously associated with less cognitive dysfunction in asymptomatic patients having CEA (9). The apolipoprotein E (apoE)-ε4 polymorphism has been previously shown to be a risk factor for impaired cognitive performance after CEA (32). Other factors that *might* also affect performance, but have not been shown to independently affect performance, were evaluated as well. These included years of education, BMI, a history of smoking, extensive peripheral vascular disease, hypertension requiring medication, symptomatic status, and duration of cross-clamping of the carotid artery. We have included these factors in our uni- and multivariate analyses.

Laboratory tests

Blood samples were obtained from radial arterial lines into untreated blood collection tubes prior to the start of surgery. The samples were centrifuged, the supernatants extracted, and the plasma was stored at −80°C. As previously described (27), MMP-9 activity was determined by calculating the ratio of MMP-9 to its inhibitor, tissue inhibitor of metalloproteinase-1 (TIMP-1). Therefore, to calculate the level of MMP-9 activity, we measured both MMP-9 and TIMP-1 concentrations in the plasma. The concentrations of MMP-9, TIMP-1, ICAM-1, and CRP were measured using commercially available ELISA kits (R&D Systems, Minneapolis, MN).

Preoperative monocyte counts, glucose levels, HbA_{1c}, and lipid profiles were obtained from hospital laboratory tests drawn during standard routine preadmission testing ≤72 h before surgery. All 115 type 2 diabetic patients had these laboratory values and plasma available. Insulin has been implicated in some studies as an anti-inflammatory and antiatherogenic agent (33). To account for any interacting inflammatory effects of insulin, other type 2 diabetes medications, or HbA_{1c}, we have included these variables in our analysis.

Statistical analyses

Statistical analysis was performed using R environment for statistical computing (R Development Core Team, Vienna, Austria). For univariate analyses, Student *t* test, Wilcoxon rank sum test, Fisher exact test, Pearson χ^2 test, and simple logistic regression were used where appropriate. A multiple logistic regression model was constructed to identify independent predictors of cognitive dysfunction in the type 2 diabetic CEA patients only; no reference patients were analyzed in the regression model. All variables with $P < 0.20$ in a simple univariate logistic regression with cognitive dysfunction were entered into the final model. Model fit and calibration were confirmed with the likelihood ratio test, Hosmer-Lemeshow goodness-of-fit test, and receiver operating characteristic analysis. $P \leq 0.05$ was considered significant.

RESULTS—In our cohort, 21.7% of type 2 diabetic patients exhibited cognitive dysfunction 1 day after CEA. Eleven patients were taking insulin. Eighty-eight of the remaining patients were taking other type 2 diabetes treatments: metformin (N = 70), glyburide (N = 9), sitagliptin (N = 6), and glimepiride (N = 3). Sixteen were not taking any medication for their type 2 diabetes. There were no significant differences in the incidence of cognitive dysfunction among the type 2 diabetes treatments (insulin 18.2%,

metformin 22.9%, glyburide 22.2%, sitagliptin 16.7%, glimepiride 0%, and no medication 25.0%). All variables were comparable between the reference group and CEA patients, including age >75 years (31.0 vs. 29.6%; $P = 0.74$), except for statin use; significantly more CEA patients were taking statins than reference patients (60.8 vs. 29.7%; $P < 0.001$). Of the reference patients, 10.3% had type 2 diabetes.

In univariate analyses, type 2 diabetic patients with cognitive dysfunction 1 day after CEA had significantly higher preoperative levels of monocyte counts ($9.1 \pm 2.0 \times 10^9$/L vs. 7.2 ± 2.0; $P < 0.001$), CRP (32.5 ± 12.9 vs. 10.8 ± 9.9 mg/L; $P < 0.001$), ICAM-1 (392.7 ± 63.0 vs. 345.4 ± 60.6 ng/mL; $P < 0.001$), and MMP-9 activity (0.75 ± 0.30 vs. 0.46 ± 0.30; $P < 0.001$) than those without cognitive dysfunction. HbA_{1c} significantly correlated with ICAM-1 ($P = 0.001$; $R^2 = 0.09$). There were no significant differences in inflammatory levels among the type 2 diabetes treatments.

By univariate analyses with cognitive dysfunction, statin use, symptomatic status, apoE-ε4 status, preoperative monocyte counts, CRP, ICAM-1, and MMP-9 activity were indicated for inclusion in the final multivariate logistic regression model predicting cognitive dysfunction in type 2 diabetic CEA patients. Each unit of preoperative monocyte counts (odds ratio [OR] 1.76 [95% CI 1.17–2.93]; $P = 0.005$) and CRP (OR 1.17 [1.10–1.29]; $P < 0.001$) was significantly associated with higher odds of cognitive dysfunction at 1 day in type 2 diabetic patients undergoing CEA (Table 1).

Table 1—*Univariate and multivariate logistic regression model*

	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Age >75 years	1.80 (0.62–4.92)	0.26		
Education (years)	1.06 (0.94–1.22)	0.36		
BMI (kg/m^2)	1.03 (0.94–1.13)	0.58		
History of smoking	1.31 (0.50–3.30)	0.57		
Hypertension	1.29 (0.52–3.17)	0.58		
Statin use	0.34 (0.13–0.83)	0.02	0.64 (0.13–3.24)	0.58
Type 2 diabetes medication	0.98 (0.99–1.01)	0.89		
PVD	1.82 (0.69–5.42)	0.24		
Symptomatic status	3.04 (1.22–8.15)	0.02	2.92 (0.58–17.63)	0.20
Cross-clamp duration (min)	1.00 (0.98–1.04)	0.62		
apoE-ε4 carrier	2.52 (0.84–7.25)	0.10	1.37 (0.16–13.12)	0.77
Glucose (mg/dL)	0.99 (0.98–1.01)	0.36		
HbA_{1c} (%)	0.78 (0.43–1.48)	0.42		
LDL (mg/dL)	1.00 (0.99–1.01)	0.79		
HDL (mg/dL)	1.03 (1.00–1.07)	0.59		
Total cholesterol (mg/dL)	1.00 (0.99–1.01)	0.72		
Triglycerides (mg/dL)	1.00 (0.99–1.01)	0.78		
Monocyte counts (×10^9/L)	1.55 (1.23–2.00)	<0.001	1.76 (1.17–2.93)	0.005
CRP concentration (mg/L)	1.15 (1.10–1.22)	<0.001	1.17 (1.10–1.29)	<0.001
ICAM-1 concentration (ng/mL)	1.01 (1.01–1.02)	0.001	1.01 (1.00–1.03)	0.07
MMP-9 activity	1.05 (1.01–1.23)	<0.001	1.05 (0.81–1.08)	0.07

PVD, peripheral vascular disease.

CONCLUSIONS—Patients with type 2 diabetes are at higher risk of exhibiting cognitive dysfunction, a subtler form of neurologic injury than stroke, after CEA. Additionally, type 2 diabetic patients are known to have elevated systemic inflammatory markers compared with nondiabetic patients (12–14). This study is the first of its kind to link an elevated preoperative systemic inflammatory state with cognitive dysfunction 1 day after CEA in a cohort of type 2 diabetic patients. Our data demonstrate that for each unit of monocyte count (× 10^9/L) and CRP concentration (mg/L), type 2 diabetic patients are 76 and 17% more likely to exhibit cognitive dysfunction 1 day after CEA, respectively. Although ICAM-1 and MMP-9 activity did not maintain predictive significance in the multivariate logistic regression model, they are significantly elevated in those with cognitive dysfunction in univariate analyses.

These findings are novel to the literature in that they link cognitive dysfunction after CEA to preoperative inflammatory values in type 2 diabetic patients. The findings also support previous studies that have demonstrated deleterious effects of inflammation on cognition (34). The mechanism of this effect remains unclear, but we speculate that elevated systemic inflammation preoperatively may exacerbate the inflammatory response and stress of undergoing CEA. It is reasonable to consider that systemic inflammatory markers, like monocytes, cross the blood–brain barrier and cause cytokine release in the central nervous system. These cytokines then potentially cause local inflammation in the brain and contribute to cognitive dysfunction. Whether the elevated inflammation remains in the periphery or infiltrates the central nervous system to act directly on the brain is unclear, but should be studied further in animal models.

Cognitive dysfunction at 1 day can have a significant impact on quality of life such as earlier retirement, disability, and mortality (35) and has been associated with actual brain injury via elevations in glial markers of neuronal injury (S100B) (7); cognitive dysfunction is a pertinent consideration of surgical risk. Our observations suggest that type 2 diabetic patients with an elevated preoperative systemic inflammatory state are more likely to exhibit significant cognitive dysfunction 1 day after CEA. This finding has important implications for the preoperative medical management of high-risk type 2 diabetic patients undergoing CEA to treat high-grade carotid artery stenosis and requires further investigation.

In conclusion, we find that type 2 diabetic patients with elevated levels of preoperative systemic inflammatory markers, like CRP and monocyte counts, are more likely to exhibit cognitive dysfunction 1 day after CEA. These observations have implications for the preoperative medical management of this high-risk group of surgical patients undergoing carotid revascularization with CEA.

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E.J.H. obtained study funding; was responsible for the concept, design, and supervision of the study; acquired the data; interpreted the data; and handled critical revision of the manuscript. J.L.M. acquired the data, interpreted the data, and handled critical revision of the manuscript. S.S.B. carried out all statistical analysis, interpreted the data, and handled critical revision of the manuscript. E.S.C. obtained study funding; was responsible for the concept, design, and supervision of the study; interpreted the data; and handled critical revision of the manuscript. E.J.H. and E.S.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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