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Failure of Intraoperative Jugular Bulb S-100B and Neuron-Specific Enolase Sampling to Predict Cognitive Injury after Carotid Endarterectomy

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Abstract

OBJECTIVE—Cognitive decline occurs in 25% of patients after carotid endarterectomy (CEA). Elevated serum concentrations of S-100B and neuron-specific enolase (NSE) occur after stroke, and serum S-100B levels at 24 hours are associated with clinical outcome after both stroke and CEA. We hypothesized that we could detect acute elevations in serum levels of these markers obtained intraoperatively from the jugular bulb (JB) and that these elevations would predict cognitive dysfunction postoperatively as measured by neuropsychometric test performance.

METHODS—Forty-three patients scheduled for elective CEA were assessed with a battery of neuropsychometric tests before and 1 day after surgery. Before the carotid artery was clamped, a 6-French Fogarty catheter was inserted into the facial vein and threaded 6 cm rostrally into the JB. Serum samples were withdrawn from this catheter and simultaneously from a radial arterial catheter (A-line) at three time points: before clamping, 15 minutes into clamping, and after unclamping the carotid artery. Concentrations between groups were compared by analysis of variance and paired *t* tests.

RESULTS—Total deficit scores were significantly worse in 13 (30%) of the 43 patients 1 day after surgery. There was a trend toward elevations in JB concentrations of S-100B relative to A-line levels 15 minutes after cross-clamping (11% elevation, *P* = 0.079, paired *t* test). In addition, 15 minutes

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The authors tested the hypothesis that changes in serum S-100B and NSE during endarterectomy may predict post-operative cognitive dysfunction. This hypothesis is based on literature linking these two proteins (which are normally found in the brain extracellular space) to brain injury after surgery. After clamping of the carotid artery, levels of S-100B from the jugular bulb were significantly elevated. The fact that S-100B (but not NSE) is also elevated after a variety of conditions not associated with any "brain damage" (e.g., running a marathon, mild depression) led our laboratory to formulate the hypothesis that S-100B is a marker of BBB leakage, even in the absence of neuronal damage. This was confirmed in patients with primary central nervous system lymphoma who were undergoing iatrogenic BBB disruption with mannitol. After administration of mannitol, there was an immediate increase in S-100B serum levels, which remained elevated during the period of BBB opening (1). Subsequent work has shown a high correlation between serum S-100B levels and contrast enhancement in primary and metastatic brain tumors (2, 3). The present study confirms that S-100B extravasation from brain to blood can occur under conditions in which obvious neuronal damage has not occurred. Perhaps, as the authors suggest, there is a mild BBB disruption associated with carotid cross-clamping. Interestingly, the results provided show that S-100B extravasation across the BBB reached plateau levels that are, according to most studies, within the normal range. The importance of slight but statistically significant S-100B elevation needs to be investigated.

Damir Janigro Marc R. Mayberg

Cleveland, Ohio

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The authors evaluated the serum concentrations of S-100B and NSE from the carotid bulb and from a peripheral arterial line to determine whether changes in levels of these proteins would correlate with the neuropsychological testing decline noted to occur after carotid endarterectomy. They noted that S-100B but not NSE was elevated 15 minutes after cross-clamping in all patients and that this effect reached significance only in samples obtained from the jugular bulb. Because the elevation in S-100B occurred in the absence of a concomitant increase in NSE and was not correlated with cognitive injury, the investigators suggest that the S-100B release occurred by a mechanism that was not associated with neuronal death. They suggest that the S-100B release was related to loss of integrity of the BBB and that this could result in a complex interaction involving neuronal exposure to neurotoxic substances circulating in the blood. Although a large part of the data is very preliminary and the statistical strength of the findings is limited by the small sample size, the hypothesis is intriguing and warrants further investigation.

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This study investigates the correlation of serum levels of S-100B and NSE to performance on neuropsychological tests in 43 patients undergoing carotid endarterectomy. The authors report a significantly higher S-100B concentration in the jugular bulb 15 minutes after cross-clamping compared with baseline measurements. In addition, higher A-line S-100B concentrations 15 minutes after cross-clamping in patients with postoperative neuropsychological deficits trend toward significance compared with those without deficits. They conclude that the rapid elevation of jugular bulb S-100B levels represents an alteration of the BBB that occurs independently of neuronal injury and cognitive deficits.

Increased serum S-100B and NSE levels have been associated with neuropsychological deficits starting 24 hours after a stroke or intraoperative ischemia. The question of whether intraoperative measurements of these serum markers would indicate clinically significant ischemia is an important one that could improve the safety of carotid artery surgery. In the present study, the clear increase of S-100B levels 15 minutes after carotid cross-clamping compared with baseline values and its lack of association with deficits in neuropsychological testing indicate that either the early release is not related to neuronal injury or the testing is not sensitive enough. Given the study methodology, the authors' suggestion of two different biochemical mechanisms for serum S-100B level elevation is reasonable: one related to a possible BBB disruption without evidence of neuronal injury, the other caused by the release of intracellular proteins after neuronal death. The trend toward significance for higher A-line S-100B levels noted 15 minutes after carotid artery cross-clamping in patients with neuropsychological deficits should be studied further with more patients and possibly different measurement intervals to determine their predictive value. The originality and potential clinical relevance of the present study make it an important addition to the existing literature.

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This study attempted to prove the hypothesis that intraoperative jugular bulb serum levels of S-100B and NSE during carotid endarterectomy would be higher than peripheral serum levels and would predict cognitive dysfunction postoperatively, as measured by neuropsychometric testing. Forty-three patients undergoing elective carotid endarterectomy were included in this study, which measured jugular bulb and peripheral arterial enzyme levels before carotid artery clamping, 15 minutes after clamping, and after unclamping. Neuropsychometric testing was performed preoperatively and 1 day postoperatively.

The authors' hypotheses were not confirmed by this study. No statistically significant differences in jugular bulb enzyme levels compared with peripheral levels were found, and cognitive decline after carotid endarterectomy was not correlated with intraoperative levels of either S-100B or NSE. However, a positive finding of this study was that, among all patients, levels of jugular bulb S-100B 15 minutes after clamping were significantly elevated compared with levels at baseline ($P=0.04$). There was also a trend toward higher concentrations of arterial line S-100B at 15 minutes in injured versus uninjured patients ($P=0.075$).

Although intraoperative jugular bulb serum concentrations of S-100B or NSE are not predictive of cognitive injury in carotid endarterectomy patients, it is intriguing that elevations in jugular bulb S-100B levels occur early after carotid clamping, independent of NSE concentrations. The authors speculate that mild hypoperfusion associated with carotid cross-clamping may cause BBB dysfunction and a secondary leak of interstitial cerebral parenchymal S-100B into the periphery. It will be interesting to determine through further investigations whether this notion is correct.

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compared with levels at baseline ($P = 0.040$, one-way analysis of variance). No significant changes were found between any time point in levels of S-100B from the A-line blood or of NSE from either the JB or the A-line. Subtle cognitive decline after CEA was not correlated with intraoperative levels of S-100B or NSE, but there was a weak, statistically nonsignificant, association between a rise in 15-minute S-100B levels and cognitive injury that was not seen with JB samples.

CONCLUSION—Although intraoperative levels of S-100B and NSE from the JB failed to predict cognitive injury, carotid cross-clamping, independent of injury, seems to be associated with early elevations in S-100B.

Keywords

Carotid endarterectomy; Neuron-specific enolase; Neuropsychological tests; S-100B; Serum markers of cerebral ischemia

Carotid endarterectomy (CEA) is an effective means of preventing stroke in appropriately selected patients (5,9,19,20). However, cognitive decline revealed by neuropsychometric (NP) testing occurs in approximately 25% of patients after CEA (6,7). Elevations in serum concentrations of two biochemical markers, S-100B and neuron-specific enolase (NSE), indicate cerebral injury (1,2,15,18,24), and elevations in S-100B 24 hours after CEA are associated with new neuropsychometric deficit (3). We hypothesized that increased serum levels of S-100B and NSE obtained from the jugular bulb (JB) would be higher than levels obtained from peripheral samples and that these JB levels would correlate better with cognitive dysfunction because they reflect changes specifically in the brain.

PATIENTS AND METHODS

Patients

Forty-three patients undergoing elective CEA were recruited to participate in this Institutional Review Board-approved study. We included all patients who were able to perform the NP evaluation in English and excluded from NP assessment all patients who either sustained a postoperative stroke or had pain scores greater than 4 at their first follow-up examination because pain is a confounder that interferes with cognitive performance (8). Patients were assessed with a battery of NP tests at two time points: before surgery and 1 day after surgery. All examinations were performed at least 3 hours after any analgesic or sedative medication was administered. One patient had a postoperative transient ischemic attack 24 hours postoperatively but after NP testing had been completed.

Anesthesia

No patients were premedicated. All patients received general anesthesia, with routine hemodynamic and temperature monitoring recorded continually every minute. Sedation before induction consisted of fentanyl and midazolam. Anesthetic agents for induction included one or more of the following: propofol or etomidate and succinylcholine, cisatracurium, or rocuronium; for maintenance: isoflurane or sevoflurane with nitrous oxide in oxygen (2:1) and cisatracurium or rocuronium; and for emergence: neostigmine and glycopyrrolate and labetalol or esmolol for hemodynamic control. For CEA patients, a radial arterial catheter for measuring blood pressure continuously and an eight-channel electroencephalographic monitor (Neurotrac II; Telefactor Corp., West Conshohocken, PA) monitor were used. Significant electroencephalographic change upon clamping of the carotid artery was defined as a 50% or greater decrease in amplitude in the α or β frequencies and a similar increase in the δ or θ frequencies or complete loss of all cerebral electrical activity.

Surgery

All CEAs were performed by members of either the neurovascular service (DOQ, RAS, ESC) or the vascular service (AIB). For CEA surgery, the patient was positioned supine with the head in an extended midline position. An incision was made along a skin crease from just below the angle of the mandible to near the midline through skin, subcutaneous tissue, and platysma. The common, internal, and external carotid arteries were exposed and controlled. All CEA patients received a 5000- to 6000-U bolus of heparin. Three patients received shunts. In patients operated on by AIB, a proximal saphenous vein patch was used.

During surgery, the facial vein was cannulated with a 6-French Fogarty irrigating catheter on the same side on which the CEA was being performed. It was passed 6 cm rostral to the level of the JB and remained there until surgical closing (Fig. 1).

All patients were extubated in the operating room and recovered for 1 to 3 hours in a postoperative care unit. CEA patients were transferred to the intensive care unit, where they stayed overnight. All patients remained in the hospital for at least 1 day for postoperative pain scoring and NP testing.

Blood Draws

Five to 10 ml of blood was drawn into untreated tubes for all CEA patients from an arterial line and from the JB before carotid cross-clamping (preclamp), 15 minutes into cross-clamping, and after unclamping (postclamp). Blood samples were centrifuged, and the supernatants were extracted and stored at -80°C until analysis for NSE and S-100B.

NP Evaluation

Patients were assessed with a battery of NP tests. All examinations were administered by the same research assistant (AR), who was trained to administer and score these NP tests under the supervision of a neuropsychologist (Yaakov Stern). Four raw scores were generated from this battery of three NP tests, which were chosen to represent a limited range of cognitive domains. Halstead-Reitan Trails Parts A and B evaluated “visual conceptual and visuomotor tracking” by timing how long it took a subject to connect consecutively numbered circles with a single line (Part A) and then connect the same number of consecutively numbered and lettered circles by alternating between the two sequences (Part B). The Controlled Oral Word Association test evaluated verbal fluency and provided information on the function of the dominant hemisphere (e.g., left). Patients were asked to generate as many words beginning with three target letters (C, F, and L) as they could in 1 minute. Their raw score was the sum of the words produced for all three letters. The copy portion of the Rey Complex Figure test was administered to assess perceptual and visual spatial organization and provided information on the function of the nondominant hemisphere (e.g., right). Patients were asked to copy the Rey complex figure to the best of their ability (12). A standardized scoring system (16) was used to evaluate both the presence of specific design features and the accuracy of their location. Although we would have preferred a more extensive battery, our elderly population of patients tolerated the one described above because of its short administration time.

The degree of pain was assessed at the same time as NP testing was performed by use of an 11-point Numeric Pain Intensity Scale adapted from a previous study (4). No patients had to be eliminated from the analysis on the basis of pain score (8).

NSE and S-100B Analysis

NSE and S-100B were analyzed by immunoluminometric technique (Sangtec Medical AB, Bromma, Sweden, and the Department of Medical Neurochemistry, University Hospital of Lund, Lund, Sweden).

Statistical Measures

For each NP test, the change in performance was calculated by subtracting the baseline score from the postoperative score. A normative data set for these changes was derived from a control population for each NP test. The mean change and standard deviation for the control population were then used to calculate a *z* score for each test, called a *test deficit score*, which was a measure of how far each CEA patient's performance deviated from the mean performance of the control group. To illustrate cognitive decline, a point system was used to transform negative *z* scores into points for each NP test (6). For each patient, the total number of test deficit scores was summed to produce the total deficit score. This total deficit score represents overall performance on the NP battery. Total deficit scores greater than 5 represented a change worse than 2 standard deviations from those of control patients (6).

Mean concentrations of NSE and S-100B were compared across time points between injured and uninjured patients by one-way analysis of variance (ANOVA). Jugular concentrations were compared with peripheral concentrations by paired *t* test. All statistical tests were calculated by use of SPSS software (version 11.5; SPSS, Chicago, IL).

RESULTS

Perioperative and intraoperative parameters are shown in Table 1 for all patients. These parameters are comparable to those observed in larger cohorts seen previously in our institution (3). Serum levels of S-100B were 11% higher in samples obtained from the JB 15 minutes into cross-clamping than in those from the A-line ($P = 0.079$, paired *t* test) (Fig. 2A). Elevations in JB samples were not, however, associated with injury, as measured by NP test (Fig. 3, A and B). There was a trend toward significance for higher concentrations of S-100B from the A-line at 15 minutes for injured versus uninjured patients (Fig. 4A) ($P = 0.075$, one-way ANOVA). There were no significant changes in NSE concentrations (Fig. 4, B and D).

Proportionate elevations in S-100B from baseline were no greater in injured than uninjured patients at either 15 minutes into cross-clamping or postclamp (Fig. 4A). Whereas the injured group showed nonsignificant proportionate elevations in S-100B relative to the uninjured group from the A-line 15 minutes into cross-clamping, the uninjured group paradoxically had a higher proportionate elevation than the injured group in samples from the JB (Fig. 4C).

Among all patients, the 15-minute JB S-100B sample was significantly elevated compared with the jugular baseline sample (0.11 ± 0.037 versus 0.085 ± 0.033 $\mu\text{g/L}$, respectively, $P = 0.040$ by one-way ANOVA) (Fig. 4C). This pattern was not observed for NSE (9.27 ± 3.14 $\mu\text{g/L}$ [baseline] versus 8.70 ± 3.14 $\mu\text{g/L}$ [15 min]) (Fig. 4D). For both proteins, serum concentrations after the carotid was unclamped were not different from baseline (8.43 ± 3.04 $\mu\text{g/L}$ for NSE and 0.10 ± 0.036 $\mu\text{g/L}$ for S-100B, $P = 0.82$ and $P = 0.80$, respectively, by one-way ANOVA).

DISCUSSION

The concomitant use of S-100B and NSE is critical to elucidating their respective roles in cerebral monitoring. Differences in their cellular localization and pharmacodynamics are very telling. S-100B is a dimeric acidic calcium-binding protein found intracellularly in the brain. The heterodimer ($\alpha\beta$) and homodimer ($\beta\beta$, called S-100B) are present in high concentrations in astrocytes and Schwann cells (15). Small quantities of S-100B are also located in the cerebrospinal fluid at concentrations of 1.43 ± 0.49 $\mu\text{g/L}$ (17) and in the brain interstitial fluid as well (21). The S-100B protein has a half-life in the serum of 2 hours (22). Conversely, NSE is the neuronal form of the intracytoplasmic glycolytic enzyme enolase. It is a homodimer composed of $\gamma\gamma$ subunits with a molecular weight of 78,000. NSE is localized throughout the

cytoplasm of neurons, including soma, axon, and dendrites, but not the nucleus (14). It has a half-life in human serum of 24 hours (15). Serum concentrations of NSE peak between 7 hours (24) and 2 days (18) after cerebral injury. Elevations in NSE concentrations correlate with infarct volume, although less convincingly than S-100B levels (18). It is ambiguous whether NSE serum concentrations successfully predict functional outcome after stroke, with some studies finding a positive association (15,24) and others failing to show a correlation (18).

Although intraoperative levels of S-100B and NSE from the JB failed to predict cognitive injury, carotid cross-clamping, independent of injury, seems to be associated with early elevations in S-100B but not NSE. Significant intraoperative elevations in serum S-100B concentrations that are independent of both patient outcome and NSE concentrations suggest that early increases in S-100B may not indicate brain injury. Conversely, the role of late elevations (5-48 h) in serum concentrations of S-100B in predicting neurological outcome is well documented. After stroke, serum S-100B concentrations correlate with infarct volume and clinical outcome after a 2- to 3-day latency (18,24). Interestingly, serum S-100B levels also peak after this time period (2,18,24). Likewise, we have previously observed elevations in S-100B in CEA patients in the injured group relative to the uninjured group at 24, 48, and 72 hours after surgery (3). Our results, taken together, are consistent with findings in the coronary artery bypass literature in which early elevations of S-100B occur as a function of patient parameters unrelated to patient outcome (perfusion time [23] and patient age [10]), whereas late elevations (starting 5 h after surgery) are correlated with patient outcome (10).

This collective body of research suggests two distinct mechanisms of S-100B release: an early mechanism occurring within minutes of an inciting event and a late release after a 5- to 72-hour latency. The mechanism of early release is as yet undefined. One possible cause for early elevations in serum S-100B may be that low-level hypoperfusion associated with carotid cross-clamping results in mild blood-brain barrier dysfunction, which in turn allows stores of interstitial cerebral parenchymal S-100B to leak out into the periphery (11).

Although preliminary, our data also show a trend toward significance for A-line S-100B elevations at 15 minutes in injured versus uninjured patients (Fig. 4A). Although more subjects are needed to confirm this finding, our data raise the possibility that A-line concentrations offer an advantage over JB levels in predicting NP deficit. This effect might occur because elevations in S-100B that occur in all patients during cross-clamping and that are probably a result of increases in blood-brain barrier permeability are diluted by the circulating blood pool in the A-line sample. This hypothesis is supported by the trend shown in Figure 4, A and C, in which S-100B does not increase appreciably in the A-line samples from uninjured patients at 15 minutes but increases in both injured and uninjured patients in the JB sample at 15 minutes. It is possible, therefore, that the dilution of the JB blood helps to diminish the effects of changes caused by noninjury.

Also worth noting is that the elevation seen in the A-line sample in the injured group (approximately 0.03 $\mu\text{g/L}$) is significantly less than the previously published difference in the injured group between baseline and 24 hours after surgery (0.35 $\mu\text{g/L}$) (3). Such a small absolute change is likely to have a very small positive predictive value for injury, given the variability in the data. In addition, the finding that the injured group has higher preclamp concentrations of S-100B (3) is consistent with published literature. In the present study, this elevation was larger in the JB than the A-line samples. We do not yet have an explanation for this phenomenon.

CONCLUSION

Intraoperative serum concentrations of S-100B and NSE from the JB do not predict cognitive outcome in patients undergoing CEA. Elevation in JB serum sample S-100B concentrations occurs in patients during carotid cross-clamping. This elevation is independent of both NSE concentrations and patient outcome and seems to mirror the time course of early elevations seen in patients undergoing cardiac surgery. Although the mechanism of such elevations is unknown, we are currently performing research to determine whether increases in blood-brain barrier permeability caused by hypoxia during carotid cross-clamping result in S-100B leaking from the brain interstitial space into the periphery.

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FIGURE 1.

Diagram of cross-clamped carotid artery (red) with 6-French irrigating catheter inserted in the stump of the facial vein and advanced through the jugular vein (blue) to the level of the JB. The jugular vein was clamped beneath the facial vein during blood draws to ensure a venous sample from brain-perfused blood.

FIGURE 2.

A, graph showing S-100B concentrations from A-line and JB for all time points. There is a statistically significant difference between preclamp JB and 15-minute JB (*, $P = 0.040$, one-way ANOVA). There was a trend toward significance for 11% higher JB S-100B concentrations than peripheral ($P = 0.079$, *paired t test*). B, graph showing NSE concentrations from A-line and JB for all time points. There are no significant differences between any time points. Error bars, *standard error of the mean*.

FIGURE 3.

A, bar graph showing S-100B and NSE in A-line versus JB for injured and uninjured groups at 15 minutes as a proportion of baseline values. There are no significant differences in proportionate changes for either S-100B or NSE. B, bar graph showing S-100B and NSE in A-line versus JB for injured and uninjured groups at postclamp as a proportion of baseline values (uninjured, 43.0 ± 17.9 min; injured, 42.2 ± 16.9 min, means $\pm$ standard deviation). There are no significant proportionate changes seen in either marker at postclamp. Error bars, standard error of the mean.

FIGURE 4.

A, graph showing S-100B from A-line for injured versus uninjured group at each time point. There was a trend toward significance for elevated 15-minute concentrations in the injured group (**, $P = 0.075$, one-way ANOVA) but not in the uninjured group. B, graph showing NSE from A-line for injured group versus uninjured group at each time point. There are no statistically significant differences by one-way ANOVA. C, graph showing S-100B from JB for injured group versus uninjured group at each time point. There was a significant difference between uninjured baseline concentrations and uninjured 15-minute concentrations (*, $P = 0.041$, one-way ANOVA). D, graph showing NSE from JB for injured group versus uninjured group at each time point. There are no statistically significant differences by one-way ANOVA. Error bars, standard error of the mean.

TABLE 1
Perioperative and intraoperative parameters

	All patients (standard deviation)
No.	43
Age (yr)	70.2 (8.2)
Sex (male/female)	65%/35%
Handedness (right/left)	88%/12%
Height (cm)	171.8 (9.8)
Weight (kg)	77.6 (15.8)
Education (yr)	15.0 (3.3)
Hypertension	60%
Diabetes mellitus	26%
Previous stroke or transient ischemic attack	49%
Previous myocardial infarction	26%
Previous carotid endarterectomy	19%
Duration of surgery (min)	155.6 (36.3)
Duration of cross-clamp (min)	42.8 (14.7)
Fentanyl (µg/kg)	2.0 (1.0)
Midazolam (mg/kg)	0.03 (0.01)
Side of operation (right/left)	56%/44%