VIA MEDICA

ORIGINAL ARTICLE

Acta Angiol
DOI: 10.5603/aa.101334

ISSN 1234–950X

e-ISSN 1644–3276

Effect of carotid endarterectomy on the serum level of neurogranin

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Abstract

Introduction: *Stroke remains the leading cause of disability and death worldwide. Carotid endarterectomy (CEA) reduces the incidence of ischemic stroke or death in patients with symptomatic carotid artery stenosis more effective than pharmacological therapy alone. Neurogranin is a potential marker of brain injury previously investigated mainly in neurodegenerative diseases (Alzheimer disease), but also in ischemic stroke and traumatic brain injury.*

Material and methods: *The aim of the research was to investigate the changes in serum level concentrations of neurogranin in patients undergoing CEA. 22 patients with severe carotid artery stenosis underwent CEA. Serum levels of Neurogranin were measured by an enzyme-linked immunosorbent assay (ELISA) test at 24 h before CEA, 12 and 48 h after the surgery.*

Results: *Serum neurogranin levels show a tendency to decrease after an uncomplicated CEA, however the difference is not statistically significant ($p > 0.05$).*

Conclusions: *Serum neurogranin level does not significantly change after the CEA, therefore it may not be an useful marker of brain damage after the procedure. There is still need for further studies on bigger group of patients and patients with neurological complications to confirm these findings.*

Keywords: Neurogranin, carotid endarterectomy, biomarkers

Acta Angiol 2024

Introduction

Stroke still remains an important problem for public health, being the common cause of morbidity and mortality globally [1]. Four main types of ischemic stroke (IS) are distinguished, based on its etiology: atherothrombotic stroke, embolic stroke, venous thrombosis, and cerebral hypoperfusion. From the listed above, the most common cause is atherothrombotic occlusion of carotid artery [2].

Carotid endarterectomy (CEA) is a gold standard for invasive treatment of carotid artery stenosis, which allows to better reduce the rate of IS or death in patients with symptomatic (IS, TIA or retinal TIA), severe (≥ 70–99% stenosis) carotid artery stenosis than the optimal medical therapy (OMT) alone [3–6]. Nevertheless, like every invasive procedure, it is not entirely free of complications during the perioperative phase, which may consist of: cerebral ischemia or ischemia-reperfusion damage due to micro and macro

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Recieved: 26.06.2024; Accepted: 13.08.2024; Early publication date: 18.10.2024

embolisms, and cerebral oedema induced by the clamping and declamping of the internal carotid artery (ICA) during the CEA [7–10].

Neurogranin (Ng) is the low molecular weight protein discovered in 1990, that consists of 78 amino acids, that typically appears in granule-like structures in pyramidal neurons of the hippocampus and cortex [11]. At the beginning, Ng was identified as a neuronal, postsynaptic protein in the telencephalon of the adult rat, mainly in the dendrites and cell bodies of neurons in the hippocampus, cerebral cortex, and striatum [11, 12]. It provides a crucial function in synaptic plasticity by strengthening synaptic connections via its interactions with calmodulin [13, 14]. These mechanisms play a crucial role in long-term potentiation (LTP), a mechanism considered fundamental in memory formation [15]. Neurogranin knock-out mice despite phenotypical normality, have a significant functional impairment in spatial and emotional learning, as well as a reduction in long-term potentiation (LTP) induction [11, 15, 16]. Ng has also been found with a low expression level in the spleen, lung, and bone marrow [17], with moderate level in B-lymphocytes [18] and with a high level in platelets [19].

Human Neurogranin cerebrospinal fluid (CSF) level may serve as a synaptic dysfunction marker, which is associated with memory performance [20]. Loss of synapses has been shown to be an early stage of neurodegeneration, having place before neuronal death and cognitive decline [21–23]. Therefore, Ng has been studied in various neurocognitive disorders. In last years, number of clinical studies have shown that CSF level of Neurogranin is significantly higher in patients with Alzheimer Disease (AD), or Mild cognitive impairment (MCI) than in healthy controls [24–27]. Moreover there has been found a connection between neurogranin level in cerebrospinal fluid and the extent of dementia and decrease in brain volume in the initial phases of the AD [15, 27, 28].

Synaptic degeneration plays role in development of all neurodegenerative disorders. However, surprisingly, the cerebrospinal fluid (CSF) neurogranin level was not elevated in other neurodegenerative disorders including Parkinson's disease (PD), frontotemporal dementia, Lewy body dementia, progressive supranuclear palsy, or multiple system atrophy [15, 29, 30]. This phenomenon can be elucidated by the fact that the areas of the brain impacted by Alzheimer's disease (AD) exhibit the greatest level of Ng [15, 29, 30]. The correlation between PD and Ng concentration remains unclear, because most of the studies, including these mentioned above [29, 30], showed lower Ng level in patients with PD [31, 32], while Bereczki et al. [33] showed that CSF Ng levels are elevated in Parkinson's disease (PD) patients in a manner unique to the condition and linked to the extent of motor disorder and cognitive deterioration.

CSF neurogranin concentrations were also increased in prion-induced Creutzfeldt-Jakob disease (CJD), which showed it may be an useful marker with diagnostic and prognostic abilities [34]. Yeşilyurt et al. [35] investigated Ng as a potential marker of neurological damage in carbon monoxide poisoning, showing it may detect a neuronal injury, even if imaging methods couldn't detect it. Increased Neurogranin levels were also found in patients after epileptic seizure, which shows, that Ng can be considered as a biomarker in the differential diagnosis of epileptic seizure and Psychogenic non-epileptic seizures (PNES) [36].

Several studies showed increased Neurogranin concentrations in blood samples of patients after acute traumatic brain injury (TBI), or mild traumatic brain injury (mTBI), suggesting that Ng may serve as a valuable biomarker for traumatic brain damage [37–39].

In the recent study, Kusdogan et al. [40] found that serum level of Neurogranin was significantly higher in patients with acute ischemic stroke than in control group. Similar results were obtained by De Vos et al. [41] who concluded, that CSF Neurogranin level was significantly elevated, and correlated with infarct volume.

Objectives

The objective of our study was to examine alterations in the concentration of Neurogranin in the serum of patients with severe carotid artery stenosis undergoing CEA.

Material and methods

The study cohort consisted of 22 individuals (57 to 82 years old, with a mean age of 71.36 years). The degree of internal carotid artery stenosis varied between 70 to 90%. Patients were admitted to the Department of Vascular Surgery and Angiology of Medical University in Lublin, Poland, and were scheduled to undergo carotid endarterectomy. Every patient had a clinical evaluation by a neurologist both before and after CEA. No abnormalities from normal status were identified in this neurological evaluation. The study's inclusion criteria were: carotid artery stenosis > 50% in symptomatic patients (symptoms of stroke/TIA < 6 months before), or > 60% in asymptomatic patients with at least 1 feature suggesting higher stroke risk on best medical therapy (BMT). The exclusion criteria were: inability to provide informed consent, complete occlusion of the internal carotid artery, intracranial artery lesion more significant than the proximal carotid lesion, brain dama-

Table 1. Characteristics of patients

Patient ID	Sex	Age	Location	%	Stroke/TIA	Symptoms	Other diseases
1	M	74	R	90	No	Tinnitus, hypoacusis	None
2	F	68	L	90	No	Tinnitus, dizziness	Diabetes, arterial hypertension, ischaemic heart disease
3	M	57	R	70	No	None	Ischaemic heart disease
4	M	78	R	80	No	Visual disturbances	Diabetes, arterial hypertension
5	M	74	L	90	No	Tinnitus, dizziness	Diabetes, arterial hypertension, ischaemic heart disease
6	F	67	R	90	Stroke	Dizziness	Diabetes, arterial hypertension
7	M	67	L	90	Stroke	Hemiparesis	Diabetes, arterial hypertension
8	F	79	L	80	No	None	Arterial hypertension
9	M	78	R	90	Stroke	Hemiparesis	Arterial hypertension
10	F	63	L	90	No	Tremor	Diabetes, arterial hypertension
11	M	63	L	80	No	None	Arterial hypertension, ischaemic heart disease
12	M	74	R	90	Stroke	None	Arterial hypertension
13	M	63	L	90	Stroke	Hemiparesis	Arterial hypertension
14	F	82	L	80	No	Dizziness	Arterial hypertension
15	M	74	L	90	No	None	Diabetes, arterial hypertension, ischaemic heart disease
16	M	76	L	80	Stroke	None	Arterial hypertension
17	M	76	L	85	TIA	None	Diabetes, arterial hypertension, ischaemic heart disease
18	F	64	L	90	TIA	None	Diabetes, arterial hypertension
19	F	72	L	70	No	None	Arterial hypertension
20	M	77	L	90	Stroke	Hemiparesis	Arterial hypertension
21	M	67	R	90	Stroke	Hemiparesis	Diabetes, arterial hypertension
22	M	77	L	80	No	Dizziness, visual disturbances	Arterial hypertension

ID — identification, M — male, F — female, TIA — transient ischemic attack, L — left, R — right

ge in the course of other nervous system diseases, prior ipsilateral CEA, history of disabling stroke (modified Rankin score ≥ 3), active inflammation and expected survival time < 5 years. Carotid endarterectomy was conducted under local anesthesia without the use of a shunt. CEA was performed through a longitudinal arteriotomy, running from the carotid bifurcation to the anterolateral surface of the internal carotid artery (ICA). The carotid artery was clamped, and the arteriotomy was closed with primary sutures. There were no complications after the procedure. Table I presents a summary of the demographic information and relevant medical history of the patients.

The extent of internal carotid artery stenosis was assessed using a high-resolution ultrasonography Doppler scan, using a Toshiba Aplio 500 device equipped with a high frequency (11 MHz) linear probe. The sonographer, a specialist in vascular medicine, was uninformed of the subject's clinical condition.

Based on Doppler studies, patients were qualified for the CEA procedure as determined by the guidelines set forth by the European Society of Vascular Surgery. Patients with severe carotid artery stenosis were identified using criteria established by NASCET (North American Symptomatic Carotid Endarterectomy Trial) according the following formula: % ICA stenosis = (1-[narrowest ICA diameter/diameter normal sistal cervcal ICA])×100 [5].

Serum samples were collected from the antecubital vein of patients 24 hours before CEA, 12 hours after the surgery, and 48 hours after the surgery.

Serum for specific protein analysis was obtained by centrifugation of whole blood at 3000 rpm (603 × g) for 15 min in a laboratory centrifuge at a tem-

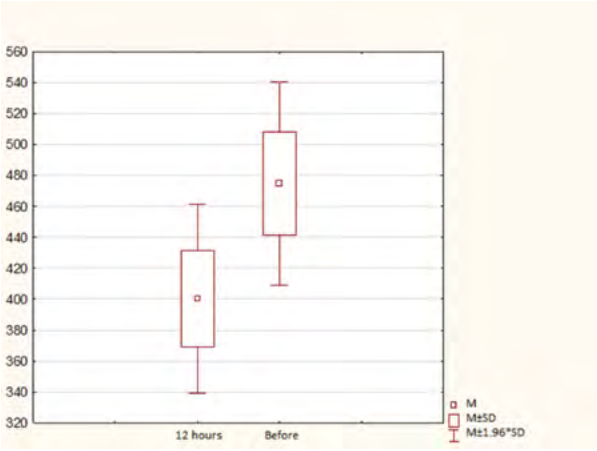

Figure 1. Neurogranin levels in patients 12 hours after and before the procedure, p=0.167511
M – mean; SD – standard deviation

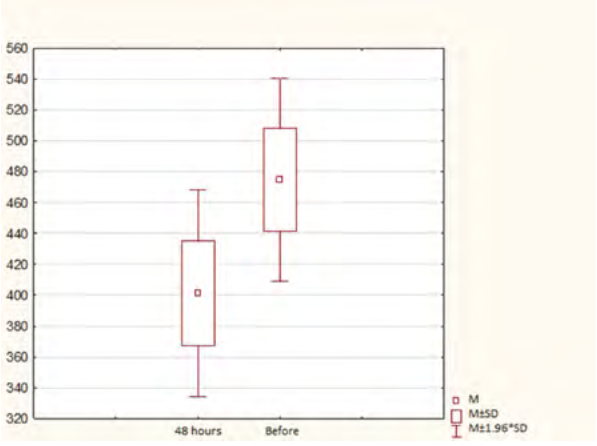

Figure 2. Neurogranin levels in patients 48 hours after, and before the procedure, p=0.070216
M – mean; SD – standard deviation

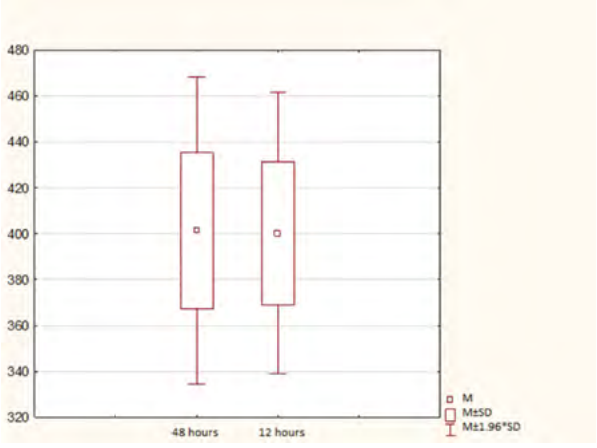

Figure 3. Neurogranin levels in patients 48 and 12 hours after the procedure, p=0,980852
M – mean; SD – standard deviation

perature of 4°C and stored in –80°C prior analyses. Plasma without signs of hemolysis was analyzed using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) technique. The protocols were adapted from a commercially developed assay manufactured by Bioassay Technology Laboratory (BT Lab, Zhejiang, China). The concentrations of Neurogranin (NRGN; Cat. No: E3883Hu) were quantified based on the optical density (OD) at 450 nm using the BioTek ELx808™ Absorbance Microplate Reader (BioTek, Winooski, VT, USA). Samples for each participant were diluted to fit the range of the standard curve and run in duplicate on the same plate. Briefly, the plates have been pre-coated with a human antibody, specific for each analyzed protein. A specific biotinylated antibody was added to sample each well. Then, streptavidin-HRP was added to the sample and standard wells. After incubation, the plates were washed with washing buffer 5 × with an automatic plate washer. Substrate solutions were added and once again the plates were incubated. The reaction was terminated by the addition of a stop solution. The concentration of protein levels in samples was calculated based on the standard curves using the average of the duplicate values.

Distribution of the collected data was evaluated using the Shapiro-Wilk's test, showing normal distribution. Furthermore, data on the neurogranin level was analyzed using one-way repeated measures ANOVA test with post hoc student's t-test. Correlation analysis was performed using the Spearman rank correlation.

The neurogranin values were expressed in mg/ml. The values of $p < 0.05$ were considered significant.

Results

The study revealed, that there was a tendency for neurogranin serum concentration to decrease 12 hours after CEA when compared to level before surgery (Fig. 1), and then neurogranin level remained at the same level 48 hours after CEA (Fig. 3), however the results were not statistically significant ($p = 0.1858$).

The repeated measures ANOVA test showed that there is no significant difference ($p > 0.05$) in the neurogranin levels before the procedure (474.6859 mg/ml), 12 (400.1833 mg/ml) and 48 hours (401.2827 mg/ml) after the procedure.

Serum Neurogranin concentrations in patients and a comparative analysis are presented in Table 2.

There was also no difference in serum neurogranin concentrations in three measurements between males and females ($p > 0.05$). The difference in serum neurogranin concentrations between younger (< 69 years) and older (> 69 years) patients in three measurements was not significant ($p > 0.05$).

Table 2. Serum levels of neurogranin and a comparative analysis

		Neurogranin level [mg/ml]				
	N	Mean	Median	SD	SE	p
Before	22	474.686	467.218	157.522	33.5837	p = 0.185892
12 h after	22	400.183	416.171	146.502	31.2344	
48 h after	22	401.283	407.228	159.944	34.1002	
Difference					**Significance**	
Before – 12h after					p = 0.167511	
Before – 48h after					p = 0.070216	
12h after – 48h after					p = 0.980852	

SE — standard error; SD — standard deviation, N — number of patients

Discussion

Up to now, neurogranin was mainly investigated as the biomarker of neurocognitive disorders in Alzheimer disease. Several studies have shown that CSF Ng level were significantly higher in patients with AD, than in healthy controls [24–28, 42–44]. However, contrary to CSF, plasma levels of Neurogranin were not significantly different in patients with AD, compared to controls [45, 46]. That may suggest, that Neurogranin level in blood may be increased only in case of sudden neurological damage, when the Neurogranin level rises more rapidly, and the blood-brain barrier is disrupted. Increased serum level of neurogranin in patients with TBI seems to support this hypothesis [37–39].

The described hypothesis might also explain the results obtained in our study. Higher baseline levels of neurogranin in patients with carotid artery stenosis might represent brain damage, caused by chronic ischemia. Chronic cerebral hypoperfusion (CCH) triggers a series of molecular and cellular mechanisms that result in the deterioration of the blood-brain barrier (BBB) and the degeneration of neurons [47]. Consequently, disruption of the blood-brain barrier (BBB) can lead to increased levels of brain injury indicators, such as neurogranin, in the peripheral blood. Successful, uncomplicated CEA reduces brain ischemia, which is represented by the lower neurogranin serum level. However, this changes are not statistically significant. In the future, there is a need for further studies, that will include patients with neurological complications after the CEA, to see if in case of sudden neurological damage, neurogranin levels will be significantly affected.

The first study, that investigated changes in neurogranin level in patients with acute ischemic stroke was held by De Vos et al. in 2017 [41]. The study group included 50 patients: 40 with an acute ischemic stroke, and 10 with TIA. The authors measured CSF and blood neurogranin levels at admission, and after 24h, 72h, 7 days, 1 month and/or 3 months post stroke. Elevated levels of plasma neurogranin were associated with larger infarct volume. However, neither the severity of the stroke nor the long-term prognosis were indicated by neurogranin in plasma or cerebrospinal fluid [41].

Similar results were obtained by Kusdogan et al. [40], who held a prospective case-control study on a group of 86 patients with acute ischemic stroke, and 55 healthy volunteers. Serum Neurogranin level was measured at the single time point, within the first 24 h after the admission. Serum levels of Neurogranin was significantly higher in patients with stroke, compared with the healthy controls, however, there was no significant correlation between neurogranin levels and lesion volume, National Institutes of Health Stroke Scale (NIHSS), nor modified Rankin Scale scores (mRS) score at admission, 6-month mortality or 6-month mRS.

Best to our knowledge, neurogranin has not been previously investigated in the perioperative period of CEA; however some other biomarkers of brain injury were previously studied before and after this procedure.

In a cohort of 22 patients undergoing CEA, Rasmussen et al. [48] examined alterations in blood concentrations of neuron-specific enolase (NSE) and S100B before and after the surgery (12, 24, 36, and 48 hours post-CEA). Prior to CEA, the authors observed a notably elevated NSE level, which subsequently declined after the surgery. However, the S100B level did not vary significantly. Study revealed no association between changes in cognitive performance and changes in blood levels of NSE or S100B protein [48].

Connolly ES Jr et al. [49] held a study on a cohort of 25 individuals that comprised both patients with neurological complications, who showed notable

changes in their performance on neuropsychometric tests, and uninjured patients, who underwent CEA. Authors assessed the serum concentrations of the same biomarkers: S100B and NSE. The samples were obtained before (24 hours and before clamping) and 24, 48, 72 hours after the operation. S100B serum levels observed in a group of patients with neurological complications in the post-operative phase were statistically significantly ($p < 0.05$) elevated in comparison to the group of uninjured individuals. S100B serum levels were increased not only after the surgery but also through the preclamp period. No significant difference was observed in NSE levels between patients with or without neurological complications at any time point [49].

The study conducted by Brightwell et al. [50] examined a cohort of 52 individuals diagnosed with carotid artery stenosis. A total of 28 patients had CEA and 24 underwent stenting of the carotid artery. The baseline values of S100B and neuron-specific enolase were elevated in comparison to control group of healthy individuals. The stenting group showed a temporary increase in S100B levels, however it was not statistically significant. In the endarterectomy group there wasn't any change. NSE levels also showed a non-significant tendency to rise 48 hours after surgery in the CEA group and to decrease in the CAS group. Again, these changes did not reach statistical significance. Statistically significant ($p = 0.015$) changes in S100B levels were observed at 24 hours in individuals with neurological impairment after the procedure, as well as in those with emboli identified by the perioperative transcranial Doppler scan.

The other study conducted by Terlecki et al. [52] examined the plasma concentration of kyneuric acid (KYNA) in a cohort of 40 individuals with stable or unstable carotid artery plaque, who had undergone carotid artery stenting or carotid endarterectomy. The investigation included samples taken before the surgery, as well as at 1, 6, 24, and 48 hours post--surgical. KYNA plasma concentrations before surgery were greater in patients with unstable carotid plaque receiving carotid endarterectomy (CEA) compared to individuals with stable carotid plaque undergoing CEA and patients undergoing carotid artery stenting. Patients with postoperative neurological complications exhibited elevated plasma KYNA levels. Furthermore, the level of KYNA increased during the postoperative period in all groups. The KYNA value demonstrated a positive correlation with the level of inflammation as assessed by the neutrophil-lymphocyte ratio (NLR) [52].

Several brain damage markers were previously investigated by Ilzecki et al. [53,54] in a series of studies on a group of patients treated with uncomplicated carotid endarterectomy. Glial fibrillary acidic protein (GFAP), neurofilament light polypeptide (NEFL) and brain lipid-binding protein (FABP7) did not show any significant change after the procedure ($p > 0.05$) [53, 54]. However, serum levels of carnosine dipeptidase 1 (CNDP1) and terminal hydrolase L1 (UCHL1) Ubiquitin C, Microtubule associated protein tau (MAPt) and myelin basic protein (MBP) were significantly reduced ($p < 0.05$) 12 hours after endarterectomy compared to the pre-surgery levels. These levels thereafter returned to normal 48 hours after CEA [55, 56].

In a separate study conducted by Ilzecki et al. [57] in 2016, the blood concentration of NSE showed a statistically significant rise 48 hours after CEA, compared to the observed values 12 hours after surgery and before surgery ($p <0.05$).

The mechanisms by which different proteins identified as markers of brain injury exhibit distinct effects after CEA surgery remain unknown. One of the options is that some of them may exhibit greater sensitivity in identifying brain damage, and only these are capable of detecting minor brain injuries such as silent ischemia following carotid endarterectomy, microemboli, ischemia-reperfusion, and so on. The others, less sensitive, may be decreased after CEA, when the chronic brain ischemia is reduced after this procedure. Third group - biomarkers that don't significantly change after the CEA procedure, may not be sensitive enough to detect reduction in brain damage, caused by decrease of brain ischemia after CEA. The authors acknowledge the limitations of the study: a limited sample size of 22 patients, the absence of a control group consisting of healthy individuals, the lack of neurological complications in patients following the CEA. Hence, in order to comprehensively grasp the function of these biomarkers, further rigorous study is required on a larger cohort of patients, including those with neurological complications, as well as a control group of healthy volunteers with a diverse range of biomarkers. Thus, our work might be regarded as an initial, pilot investigation.

Conclusions

Neurogranin level does not significantly change in the perioperative period of CEA, therefore it may not be enough sensitive biomarker of brain damage after this procedure. Due to limitations of the study, it is necessary to do further researches on a broader cohort of patients, encompassing individuals with neurological complications after the surgery.

Article information and declarations

Data availability statement: All of the data used in this study is available on request from the authors.

Ethics statement: The study was approved by the Ethics Committee of the Lublin Medical University (KE-0254 / 82 / 2021) (29.04.2021).
Author contributions: Conceptualization — MI, JT and SP; methodology — MI; software — JT; MI — check; JT and SP— formal analysis, JT — investigation; MI and JT — resources; MI, JT and SP — data curation; JT and MI — writing, rough preparation; JT — writing--review and editing; MI and SP — visualization; JT— supervision; MI and SP — project administration; JT and MI — receiving funding, MI; TZ and PT — approval.
Funding: This research received no external funding.
Acknowledgments: We would like to thank ale the coauthors of this article.
Conflict of interest: The authors declare no conflict of interest.
Supplementary material: None.

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