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Association Between Inflammatory Markers and Cognitive Impairment in Patients with Asymptomatic Carotid Stenosis

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Abstract

BACKGROUND: Certain inflammatory mechanisms are involved in the carotid atherosclerotic process, and determining the inflammatory activation can be useful in the assessment of cognitive impairment in patients with asymptomatic carotid stenosis (ACS).

AIM: This study aimed to correlate these markers of inflammation with the degree of asymptomatic carotid stenosis (ACS) and the degree of cognitive impairment.

MATERIALS AND METHODS: One hundred and twenty patients with carotid stenosis and 60 patients without carotid stenosis were enrolled in the study. Clinical, neurological, and laboratory evaluations (C-reactive protein [CRP], fibrinogen, tumor necrosis factor alpha [TNF-α]) were performed, as well as evaluation of intima-media thickness (IMT) and carotid stenosis degree. Cognitive functions were assessed with the Addenbrooke's Cognitive Examination test. Neuroimaging tests were included.

RESULTS: There was no significant correlation in the asymptomatic group between TNFα and IMT and between fibrinogen, CRP, and IMT both on the left and the right side. In the same group, there was a statistically significant association between the degree of carotid stenosis and low-to-moderate degree of cognitive impairment on the right side ($p < 0.05$) and left side ($p < 0.05$). A moderately weak negative statistically significant correlation between the severity of cognitive impairment and the degree of stenosis in the asymptomatic group was reported. A high degree of carotid stenosis (≥70%) on the right increased the chance of a moderate degree of cognitive impairment by 6 times compared to the low degree of carotid stenosis in the asymptomatic group. The high degree of carotid stenosis (≥70%) on the left increased the chance of a severe degree of cognitive impairment by 20 times compared to the low degree of stenosis in the asymptomatic group.

CONCLUSIONS: ACS increases the risk of cognitive impairment.

Introduction

The presence of carotid atherosclerosis is a potential risk factor for cognitive function impairment [1], [2], [3], [4]. Carotid artery stenosis and increased intima-media thickness (IMT) are associated with cognitive impairment including the individuals who have not experienced stroke. The major mechanisms associated with cognitive impairment in carotid stenosis are embolization and hypoperfusion which cause lacunar or silent brain infarcts.

Certain inflammatory mechanisms are involved in the atherosclerotic process, so determining the inflammatory activation can also be useful in the risk assessment in patients with carotid artery disease. Atherosclerotic lesions in the carotid arteries have been associated with increased serum levels of different inflammatory markers, i.e., tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and fibrinogen [5], [6], [7], [8], [9]. This study aimed to correlate these markers of inflammation with the degree of asymptomatic carotid stenosis (ACS) and the degree of cognitive impairment.

Materials and Methods

The study included 180 patients aged 50–70 years divided into 3 groups:

- ACS – Patients with ACS (without transient ischemic attack or stroke)
- Symptomatic carotid stenosis (SCS) – Patients with SCS (with transient ischemic attack or stroke)
- Control group (CG) – CG of patients with headache or vertigo, with normal findings of the carotid arteries.

All patients and/or their closest relatives were informed of the aim and course of the study and signed the informed consent to it.

Other inclusion criteria were the presence of risk factors for cerebrovascular diseases, carotid artery stenosis (unilateral and/or bilateral), a neuroimaging examination (computed tomography [CT] or magnetic resonance imaging [MRI]) excluding the non-vascular brain damage, and the presence of headache or vertigo.

The exclusion criteria were the presence of aphasia, intracerebral hemorrhage or other diseases, vascular malformations, tumors, abscesses, multiple sclerosis, and stroke with the National Institute of Health Stroke Scale (NIHSS) score higher than 15.

Laboratory tests

Blood for TNF-α was collected in patients in a fasting state from the cubital vein and the level was determined with a standard immunoassay technique. Standard inflammation parameters were also determined (CRP and fibrinogen), through a blood sample from the cubital vein.

Ultrasound examination of carotid arteries

The presence of carotid atherosclerosis was determined with B-mode ultrasonography with a 7.5 MHz probe according to the Atherosclerosis Risk in Communities protocol and complemented by color Doppler imaging [10]. Ultrasound examination evaluated the common carotid arteries, carotid bifurcation, and the first 2 cm of the internal carotid artery. IMT was measured in mm. Criteria for categorization of the arterial stenosis were defined as increased IMT, low degree (<50%), moderate degree (50–70%), and high degree (>70%) of stenosis, uni or bilateral.

Neuropsychological evaluation

Cognitive functions were evaluated with Addenbrooke's Cognitive Examination (ACE) and the ACE-Revised (ACE-R) test, which is an expanded version of the Mini-mental test [11]. Orientation in time and space, attention, calculation, speech, memory, and visuospatial abilities were determined. The test was carried out 6 months after hospitalization in patients with symptomatic stenosis, 3 months after the confirmation of the diagnosis in patients with asymptomatic stenosis, and 3 months in the CG of patients with headache and vertigo. Orientation with attentiveness, memory, fluency, language, and visuospatial abilities were assessed. The test has a maximum score of 100 and cognitive impairment is classified as:

- Dementia-free ACE-R> 90/100
- Mild cognitive impairment ACE-R: 80–90/100
- Initial dementia ACE-R: 65–76/100
- Moderate dementia ACE-R: 35–64/100
- Severe dementia ACE-R <35/100.

CT of the brain

CT of the brain was performed with Siemens's device, on admission and 24–72 h afterward, and the location and dimensions of the eventual acute ischemic lesions were calculated.

Nuclear MRI

Nuclear MRI of the brain was performed in 6 months after the examination in all patients.

Stroke severity

Stroke severity was determined according to the NIHSS score (range 0–30). Stroke was classified as mild (≤8), moderate (9–15), and severe (≥16) according to the NIHSS score [12].

Statistical analysis

Statistical analysis was performed in statistical programs: STATISTICA 7.1 and SPSS 17.0. The collected data were processed using the following statistical methods:

- Databases were created using specific computer programs for that purpose. Their processing was performed using standard descriptive and analytical methods
- Attributive statistical series were analyzed by determining coefficients of relationships, proportions, and rates, and by determining statistical significance between the detected differences – difference test
- Numerical series were analyzed with central tendency measures and data dispersion measures (mean and standard deviation)
- In the numerical series where there was no deviation from the normal distribution, the significance of the difference was tested with a difference test and a *t*-test, and where there was a deviation from the normal distribution, the significance of the difference was tested with the Mann–Whitney U-test
- The statistical significance of differences was analyzed by analysis of variance (ANOVA). There is a large selection of so-called *post hoc* tests performed after the ANOVA test when it yields statistically significant results. These tests are also called multiple comparison tests. The purpose is to find out which difference (among most variables) is due to the overall statistically significant result. *Post hoc* Tukey HSD test was used in the study
- Multiple regression analysis was used to determine the relationship between the dependent-criterion variable and the system of predictor variables of interest.

Correlational relations were computed using Pearson's correlation coefficient (*r*) and x^2 test

- The Shapiro–Wilk's test examined the normal distribution of the variables
- For confidence interval (CI) (95% CI) statistical significance was defined for error level <0.05 (*P*)
- Results were presented in tabular and graphical form.

The obtained results were compared between ASC and SCS groups with the CG.

RESULTS

The average values of TNF-α pg/m are displayed in Table 1, with the highest values recorded in the SCS group and the lowest in the CG. The difference between the mean values of TNF-α pg/m in the three groups was statistically significant for $p < 0.05$ ($p = 0.000000$), owing to the statistically significant difference between ACS versus SCS group, ACS versus CG, and ACS versus CG ($p = 0.000022$, $p = 0.000513$).

Table 1: Average TNF-α values pg/m in the three groups

Group	Average	n	SD	min.	max.
I	5.9	60	3.480995	0.36	16.4
II	10.8	60	6.983847	0.428	40.657
III	2.78	60	1.567037	0.36	7.729

TNF-α: Tumor necrosis factor alpha, n: number, SD: Standard deviation, Min.: Minimum, Max.: Maximum.

Average fibrinogen values are displayed in Figure 1; average values in the ACS and SCS groups are higher than the reference value, whereas the average value in the CG is within the normal range. The difference between the mean fibrinogen values in the three groups was statistically significant at $p < 0.05$ ($p = 0.000000$) due to the statistically significant difference between ACS versus CG and SCS group versus CG ($p = 0.000022$), the remaining differences being non-significant.

The average CRP values are displayed in Table 2. The average values are higher in the ACS and SCS groups, whereas the values in the CG are normal. The difference between the mean CRP values in the three groups was statistically significant for $p < 0.05$ ($p = 0.000000$) due to the statistically significant difference between ACS versus SCS group and SCS versus CG ($p = 0.000084$, $p = 0.000022$), the remaining differences being non-significant.

Table 2: Average CRP values in the three groups

CRP/group	Average	n	SD	Min.	Max.
I	6.0	60	2.53708	1.0	12.0
II	16.3	60	22.88299	0.0	112.0
III	2.23	60	1.41576	0.0	6.12

CRP: C reactive protein, n: Number, SD: Standard deviation, Min.: Minimum, Max.: Maximum.

The average values of IMT are shown in Table 3. The average IMT values are increased in the ACS and SCS groups, whereas they are normal in the CG. The difference between the mean values of IMT on both sides in the three groups is statistically significant for $p < 0.05$ ($p = 0.000000$) due to the statistically significant difference between ACS versus CG and SCS versus CG ($p = 0.000022$), the remaining differences are not significant.

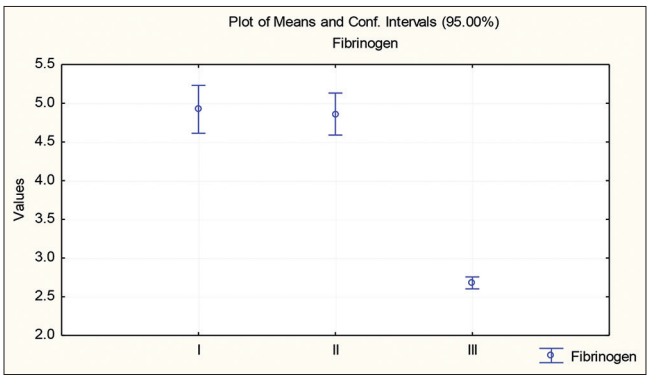

Figure 1: Average fibrinogen values in the three groups

Increased IMT and degree of stenosis in the ACS and SCS group, on the left and right side are shown in Figure 2. The percentage difference between the registration of low-grade stenosis versus moderate and high-grade carotid stenosis on both sides in the ACS and SCS groups was statistically significant for $p < 0.05$ (difference test, $p = 0.0000$). The percentage difference registered between the two groups regarding the degree of carotid stenosis on the right and the left side is not statistically significant for $p > 0.05$.

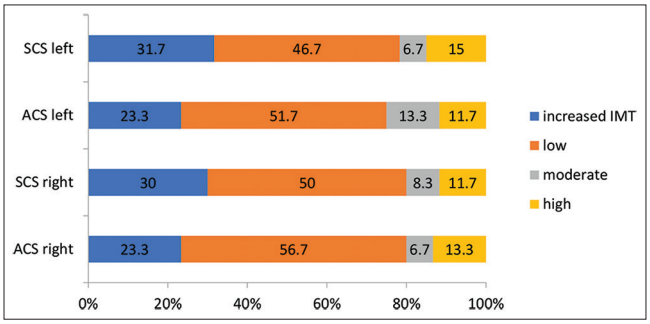

Figure 2: Increased intima-media thickness and degree of stenosis in the asymptomatic carotid stenosis and symptomatic carotid stenosis group, left and right

In the ACS group, we did not find a statistically significant correlation between TNFα and IMT on the right and left side ($r = -0.09$ and $r = -0.07$, respectively); between the fibrinogen and IMT on the right and left side ($r = 0.08$ and $r = 0.04$, respectively) and between CRP and IMT on the right and left side ($r = 0.12$ and $r = 0.16$, respectively).

The average scores of ACE-R test are shown in Figure 3. Mild cognitive impairment was registered in the ACS group, moderate cognitive impairment was seen in the SCS group, and CG, the cognitive functions were normal. The difference between the mean scores of the three groups was statistically significant for

Table 3: Average IMT values in the three groups, left and right side

Group	Right average	Right SD	Right minimum	Right maximum	Left average	Left SD	Left minimum	Left maximum
I	0.9	0.113931	0.8	1.5	0.97	0.146706	0.7	1.7
II	0.96	0.139521	0.0	1.0	0.9	0.159661	0.0	1.0
III	0.7	0.190420	0.4	1.0	0.7	0.227359	0.0	1.0

SD: Standard deviation. IMT: Intima-media thickness.

$p < 0.05$ ($p = 0.00$) due to the statistically significant difference between ACS versus SCS group, ACS versus CG, and SCS versus CG ($p = 0.000022$).

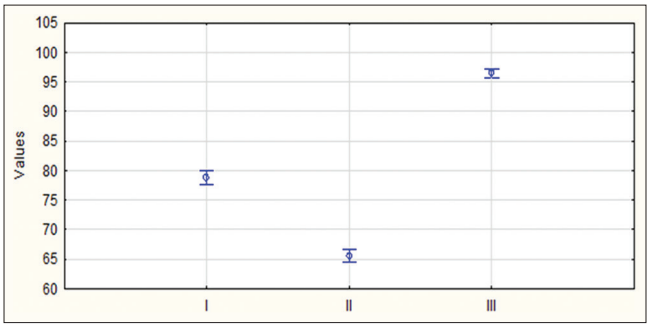

Figure 3: Average values of the Addenbrooke's cognitive examination-revised scores in the three groups' plot of means and confidence intervals (95.00%). I: Asymptomatic carotid stenosis group, II: Symptomatic carotid stenosis group, III: Control group, : Score

According to the degree of cognitive impairment according to ACE-R score in the three groups, we found mild and moderate cognitive impairment in the ACS group, the difference is statistically significant for $p < 0.05$ (difference test, $p = 0.0001$) (Table 4). In the SCS group moderate and severe cognitive impairment was registered, the difference is statistically significant for $p < 0.05$ (difference test, $p = 0.0285$).

Table 4: Degree of cognitive impairment according to ACE-R score in the ACS and SCS groups

Degree/group	ACS group		SCS group	
	Number	%	Number	%
Mild	41	68.3	/	/
Moderate	19	31.7	36	60.0
Severe	/	/	24	40.0
Total	60	100.0	60	100.0

ACE-R: Addenbrooke's cognitive examination-revised, ACS: Asymptomatic carotid stenosis, SCS: Symptomatic carotid stenosis.

In the ACS group, we found a moderately weak statistically significant correlation between the degree of cognitive impairment and the degree of carotid stenosis on the right side ($r = -0.2923$, $p = 0.023$) and a moderately negative statistically significant correlation between the degree of cognitive impairment and the degree of carotid stenosis on the left side ($r = -0.4109$, $p = 0.001$) (Figure 4a and b).

In the SCS group, there was no statistically significant correlation between the degree of cognitive impairment and the degree of carotid stenosis on the right side ($r = -0.1516$, $p = 0.248$), but we found a moderately negative significant correlation between the degree of cognitive impairment and the degree of stenosis on the left side ($r = -0.4921$, $p = 0.000$) (Figure 4a and b).

In the ACS group, there was no statistically significant association between the degrees of carotid stenosis on the right side and degrees of cognitive impairment for $p > 0.05$ (Pearson Chi-square: 6.17048, $p = 0.103604$) (Table 5).

Table 5: Contingency table between the degree of cognitive impairment and degree of carotid stenosis on the right in the ACS group

Degree of stenosis/right	Mild degree/cognition	Moderate degree/cognition	Total/rows
Increased IMT	9	5	14
Low **	27**	7	34
Moderate	2	2	4
High **	3	5**	8
Total/Columns	41	19	60

**(p<0.05). IMT: Intima-media thickness, ACS: Asymptomatic carotid stenosis.

There was a statistically significant association between the degree (low and high) of carotid stenosis on the right and the degree (mild and moderate) of cognitive impairment for $p < 0.05$ (Pearson Chi-square: 7.3087, $p = 0.006862$) in the ACS group (Table 5).

According to the cross-ratio, a high degree of carotid stenosis (≥70%) on the right increases the chance of a moderate degree of cognitive impairment by 6 times compared to the low degree of carotid stenosis OR = 6.4286 (1.2281–33.6505) in the ACS group.

In the SCS group, we found a statistically significant association between the degrees of carotid stenosis on the right and the degrees of cognitive impairment for $p < 0.05$ (Pearson Chi-square: 8.32672, $p = 0.039721$) (Table 6).

Table 6: Contingency table between the degree of cognitive impairment and degree of carotid stenosis on the right in the SCS group

Degree of stenosis/right	Moderate degree/cognition	Severe degree/cognition	Total/rows
Increased IMT	10	8	18
Low**	21**	9	30
Moderate	4	1	5
High**	1	6**	7
Total/columns	36	24	60

** (p<0.05), IMT: Intima-media thickness, SCS: Symptomatic carotid stenosis.

There was a statistically significant association between the degree (low and high) of carotid stenosis on the right and the degree (moderate and severe) of cognitive impairment for $p < 0.05$ (Pearson Chi-square: 7.3087, $p = 0.006862$) in the SCS group (Table 6).

According to the cross-ratio, a low degree of stenosis (<50%) on the right is not a risk factor, on the contrary, it reduces the chance of a severe degree of cognitive impairment compared to the high degree of stenosis OR = 0.0714 (0.0435–0.8670) in the SCS group.

According to the cross-ratio, a high degree of stenosis (≥70%) on the right increases the chance of a severe degree of cognitive impairment by 14 times compared to the low degree of stenosis OR = 14,000 (1.4661–133.6901) in the SCS group.

In the ACS group, there was a statistically significant association between the degrees of carotid stenosis on the left and the degrees of cognitive

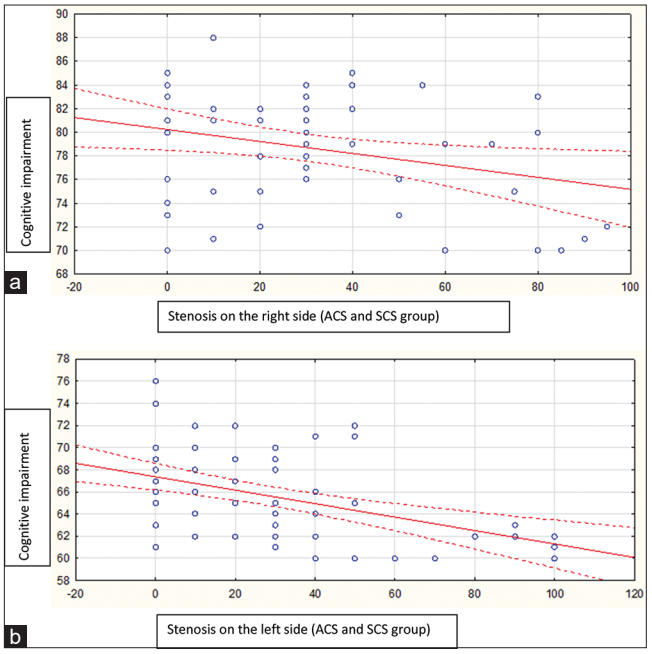

Figure 4: (a) Correlation between the degree of cognitive impairment according to Addenbrookes and degree of carotid stenosis on the right side (asymptomatic carotid stenosis [ACS] and Symptomatic carotid stenosis [SCS] group). (b) Correlation between the degree of cognitive impairment according to Addenbrookes and degree of carotid stenosis on the left side (ACS and SCS group)

impairment for p < 0.05 (Pearson Chi-square: 11.4363, p = 0.009586) (Table 7).

A statistically significant association was observed between the degree (low and high) of carotid stenosis on the left and the degree (moderate and severe) of cognitive impairment for p < 0.05 (Pearson Chi-square: 10.1130, p = 0.001472) in the ACS group (Table 7).

Table 7: Contingency table between the degree of cognitive impairment and degree of carotid stenosis on the left side in the ACS group

Degree of stenosis/left	Moderate degree/cognition	Severe degree/cognition	Total/rows
Increased IMT	11	3	14
Low**	24**	7	31
Moderate	5	3	8
High**	1	6**	7
Total/columns	41	19	60

**(p<0.05). IMT: Intima-media thickness, ACS: Asymptomatic carotid stenosis.

According to the cross-ratio, a high degree of carotid stenosis (≥70%) on the left increases the chance of severe degree of cognitive impairment by 20 times compared to the low degree of stenosis OR = 20.5714 (2.1077–200.7823) in the ACS group.

In the SCS group, there was a statistically significant association between the degree of carotid stenosis on the left side and the degree of cognitive impairment for p > 0.05 (Pearson Chi-square: 13.7759, p = 0.003227) (Table 8).

Table 8: Contingency table showing the degree of cognitive impairment and the degree of carotid stenosis on the left side in the SCS group

Degree of stenosis/left	Moderate degree/cognition	Severe degree/cognition	Total/rows
Increased IMT	16	3	19
Low**	17**	11	28
Moderate	2	2	4
High**	1	8**	9
Total/columns	36	24	60

**(p<0.05), SCS: Symptomatic carotid stenosis.

A statistically significant association was observed between the degree (low and high) of the carotid stenosis on the left and the degree (moderate and severe) of cognitive impairment for p <0.05 (Pearson Chi-square: 6.7080, p = 0.009597) in the SCS group (Table 8).

According to the cross-ratio, a high degree of stenosis (≥70%) on the left increases the chance of a severe degree of cognitive impairment compared to a low degree of stenosis by 11 and a half times (OR = 11.693 [1.3016–105.0321]) in the SCS group.

According to the cross-ratio, the low degree of carotid stenosis (<50%) on the left side is not a risk factor, on the contrary, it reduces the chance of a severe degree of cognitive impairment (OR = 0.1941 [0.0435–0.8670]) in the SCS group.

Discussion

At present, there has been an increased interest in studying the role of carotid stenosis related to the impairment of cognitive functions among patients with ACS. Besides the traditional vascular risk factors, many studies have focused on the relationship between the activity of certain markers of inflammation and the development and progression of atherosclerotic lesions, [5], [7], [8], [13], [14], especially in the carotid arteries [9], [15], [16], [17], [18], [19]. In this study, we found a significant association between the elevated average values of the inflammatory markers in patients with asymptomatic and SCS compared to the values of the CG. The average values of TNFα in both groups of patients with carotid stenosis (asymptomatic and symptomatic) were increased, and this difference was statistically significant compared to the CG. Our results are similar to the results presented in the study of Elkind *et al*. [20] where the levels of TNF-α and TNF tumor receptor, measured by immunoassay technique, were related to IMT of the carotid arteries (measured on B-mode) in patients without prior history of stroke. According to the results, any increase in the level of TNF receptors increased the percentage of the participants with an increased IMT of the carotid arteries by 1.5 mm or more. The study of Kyriakidis *et al*. has also observed carotid plaque involvement and elevated levels of metalloproteinases and cytokines, such as TNF α and IL 6 [21]. We also found increased average values of fibrinogen and CRP in the asymptomatic and SCS group, compared to the CG. Our results are similar to the results of the epidemiological studies, that also found increased levels of CRP and fibrinogen in patients with carotid stenosis [22], [23], [24]. In the asymptomatic group, there was a non-significant correlation between the TNF-α and IMT, and non-significant correlation between fibrinogen and IMT, and

a weak positive non-significant correlation between CRP and IMT on both sides.

The results from the neuropsychological testing found mild cognitive impairment in the ACS group, moderate cognitive impairment in the SCS group, and no cognitive impairment in the CG. ACE and the ACE-R test were selected as a sensitive tool for discovering cognitive changes in patients with or without stroke, helping to identify them even in the early stages of the disease, allowing early intervention and eventual delay in the development of cognitive impairment with appropriate cognitive rehabilitation [25], [26], [27]. For example, the study of Lees RA and colleagues has explored the benefits of ACE in detecting cognitive impairment in patients with stroke [28]. Still, there are limitations of this test owing to the fact that many stroke brain patients usually have motor difficulties that adversely affect the performance of the test (for example: Drawing) and often have difficulty with the speech [27], [29].

It was shown that carotid artery stenosis increases the risk of early cognitive impairment. Potential mechanisms that may lead to cognitive decline include microembolic ischemic lesions of the brain tissue from unstable carotid plaques and cerebrovascular hemodynamic insufficiency, detected in 15–19% of the patients with ACS [30], [31].

The study by Johnston *et al*. showed that a high degree (≥70%) of carotid artery stenosis on the left side was associated with cognitive impairment, whereas such a significant correlation was not observed with right-side carotid stenosis [2]. This correlation was recorded in patients without evidence of stroke on MRI. These observations support the idea that ACS may be an independent risk factor for cognitive impairment and decline. In our study, we also found a moderately negative statistically significant correlation between the degree of cognitive impairment and the degree of carotid artery stenosis on the left side in the asymptomatic group, i.e., a high degree of carotid stenosis (≥70%) on the left increased the chance of severe degree of cognitive impairment by 20 times compared to the low degree of stenosis in the asymptomatic group. Similar results were found in the Tromsø study, where subjects without a history of stroke and with carotid stenosis were evaluated, showing that subjects with carotid stenosis had significantly lower levels of performance on several subsets of cognitive tests [32]. In the Framingham Offspring Study, stenosis of the internal carotid artery ≥50% was associated with a higher prevalence of poorer performance on executive function [33]. Another study evaluating ACS and cognitive function found that ACS was associated with overall cognitive impairment independent of known vascular risk factors and patients with stenosis had worse domain-specific scores in both learning/memory and motor/processing speed. Almost half of the patients were impaired in at least two cognitive domains [30]. The study of Martinić-Popović *et al*. recommended that if asymptomatic advanced carotid stenosis indeed causes cognitive impairment, the decision on surgical treatment might consider cognitive evaluation using a neuropsychological test as a clinical definition of symptomatic carotid disease and may be considered important as the effective treatment of vascular risk factors in stroke/TIA free patients with carotid stenosis [34].

Conclusions

ACS increases the risk of cognitive impairment. Targeting the inflammatory markers would lead to a slowing down of the atherosclerotic process and the development of carotid stenosis. Neuropsychological tests should also be used as a standard evaluation method to choose the most appropriate therapeutical approach in patients with a high degree of ACS.

Reccomendation for Experts

ACS may be an independent risk factor for cognitive impairment. A high degree of carotid stenosis (≥70%) in asymptomatic patients may increase the chance of a moderate-to-severe degree of cognitive impairment, so physicians should always keep that in mind, to promptly use the appropriate neurophysiological tests. All this would lead to proper and timely treatment of these patients.

Ethical Consideration

Experiments were performed with the understanding and consent of each subject, with the approval of the local ethics committee.

Author Contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Elena Joveva, Marija Karakolevska Ilova, and Marija Dimitrovska. The first draft of the manuscript was written by Marijan Jovev and Aleksandar Serafimov and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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