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The neurological status and the increased perioperative risk among the patients undergoing the procedure of carotid endarterectomy

Aktualny stan neurologiczny a ryzyko okołooperacyjne związane z leczeniem miażdżycowego zwężenia tętnic szyjnych

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Keywords

carotid plaque, ultrasonography, virtual histology

Słowa kluczowe

blaszka szyjna, ultrasonografia, wirtualna histologia

S u m m a r y

Introduction. The background of this study was a suggestion that carotid plaques may differ in their pathology, and, being related to the increase of the microembolism phenomenon, have an impact on the neurological status following carotid endarterectomy, thus resulting in perioperative risk.

Aim. The aim of the study was to assess whether patients operated for carotid stenosis may vary in respect of perioperative risk, carotid plaque morphology, perioperative microembolism and neurological status following carotid endarterectomy.

Material and methods. 126 patients were included in the analysis, and divided into 3 subgroups: asymptomatic, past symptomatic (having neurological symptoms in the past) and recently symptomatic (symptoms present within the last 14 days prior to the operation). The following parameters were analysed: microembolism, presence of perioperative neurological complications, and the character of carotid plaque (as assessed by detailed computer analysis). The statistical analysis was performed with Kruskal-Wallis and Fischer's exact tests.

Results. The effect of microembolism was definitely the highest among the recently symptomatic group ($p = 0.0001$ against both other groups). Carotid plaques, as assessed by detailed computer analysis, also showed a significantly higher presence of determinants of unstable carotid plaque ($p = 0.0001$, and $p = 0.0012$ against respective groups). The same relationships were shown in direct morphological analysis of carotid plaques ($p < 0.05$).

Conclusions. The incidence of microembolism differs in patients with carotid disease in to the timing and duration of the neurological symptoms. The unstable carotid plaque is much more closely associated with recent neurological symptoms. This may indicate the need for a precise definition of a "symptomatic patient".

S t r e s z c z e n i e

Wstęp. Skala mikrozatorowości zależna jest w znacznej mierze od charakteru zmian miażdżycowych i w związku tym może ona przyczyniać się do zwiększenia ryzyka okołooperacyjnego.

Cel pracy. Ocena czy chorzy operowani z powodu miażdżycowego zwężenia tętnic szyjnych mogą różnić się pod względem stopnia powikłań okołooperacyjnych obrazu morfologicznego zmian miażdżycowych oraz zjawiska mikrozatorowości.

Materiał i metody. Ocenie poddano 126 chorych. Spośród badanych wyodrębniono 3 grupy chorych: bezobjawowych, objawowych, ale bez aktualnie obecnych objawów oraz chorych z objawami neurologicznymi utrzymującymi się bezpośrednio przed operacją. Badanych oceniano pod względem: zjawiska mikrozatorowości, obecności powikłań okołooperacyjnych oraz analizowano komputerowo ultrasonograficzny obraz szyjnych zmian miażdżycowych (metoda szczegółowej analizy rozkładu pikseli – tzw. wirtualna histologia). Zależności statystyczne oceniano za pomocą testów Kruskala-Wallisa oraz testu zgodności Fischera.

Wyniki. Stwierdzono, że zjawisko mikrozatorowości było zdecydowanie najwyższe wśród chorych, u których objawy utrzymywały się bezpośrednio przed operacją ($p = 0{,}0001$ względem pozostałych grup). Pozostałe grupy nie różniły się pod względem natężenia mikrozatorowości pomiędzy sobą ($p = NS$). Wykazano też, że w grupie chorych o objawach utrzymujących się bezpośrednio przed operacją zmiany miażdżyco-

Conflict of interest
Konflikt interesów

None
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we cechuje zdecydowanie większa zawartość tkanek o obniżonej echogeniczności (cecha zmian niestabilnych) niż w pozostałych grupach ($p = 0{,}0001$ do $p = 0{,}0012$). Podobne różnice wykazano w obrazie morfologicznym szyjnych zmian miażdżycowych pomiędzy badanymi grupami ($p < 0{,}05$).

Wnioski. Stopień mikrozatorowości może różnić się pomiędzy chorymi z miażdżycowym zwężeniem tętnic szyjnych w zależności od okresu występowania objawów neurologicznych. Morfologiczny obraz szyjnych zmian miażdżycowych u chorych z trwającymi objawami neurologicznymi bezpośrednio przed zabiegiem operacyjnym ściślej koreluje z cechami niestabilnych zmian miażdżycowych. Wskazuje to na zasadność zwrócenia uwagi na problem precyzyjnej definicji „chorego objawowego".

INTRODUCTION

The decision on the length of the interval between endarterectomy and a recently suffered ischaemic stroke remains a controversial issue.

The risk for an early repeat brain stroke within one month in such patients receiving conservative therapy and waiting for an operation remains high and may amount to as much as 34-36% (1, 2). It is recommended to keep the interval between the stroke and endarterectomy of internal carotid artery below 1 month to potentially reduce the risk for a repeat brain stroke (2, 3).

The European Carotid Surgery Trial (ECST) also demonstrated that in the case of a long-delayed surgery or application of conservative treatment, the risk for brain stroke in patients operated for carotid artery stenosis gradually matches the similar risk in patients receiving conservative therapy. Thus, if transient ischemic attack (TIA) or stroke occurred over 2 years ago, the risk in the above groups of patients becomes comparable (4).

The combination of these two seemingly opposite factors, and reports indicating that the degree of carotid stenosis in many cases does not have to correlate with the presence or lack of neurological symptoms (5, 6) suggest the pathophysiological changes in the carotid plaque as an important catalyst of neurological symptoms.

Evaluation of echogenicity of carotid lesions, based on the analysis of the grey-scale median (GSM) score is an acknowledged method of diagnosing unstable carotid plaque, yet a number of limitations seem to exist. Recently, the method of detailed pixel distribution analysis (PDA), dubbed as "virtual histology", has been proposed, also based on computer-aided GSM analysis (7-11). Since it is possible to assign the echogenicity of given tissues to relevant grey-scale partitions as required, the technique allows to identify focal lesions in carotid plaque, as has been evidenced by studies comparing the method with histopathological evaluation (8, 10).

Degenerative morphological changes occurring in carotid plaque may not only contribute to its rupture, but also to microembolism, considered one of the main causes of neurological symptoms (12, 13).

The hypothesis underlying this study was that carotid plaques of various morphology may be responsible for microembolism to a different degree. We have also assumed that symptomatic patients may be affected by microembolism to various degrees, depending on the timing of neurological symptoms preceding the surgical intervention.

AIM

The aim of the study was to assess whether patients operated for carotid artery stenosis (asymptomatic, recently symptomatic, and currently asymptomatic but with a history of neurological symptoms) may differ in relation to the following:

- perioperative complications,
- microembolism,
- carotid plaque morphology.

MATERIAL AND METHODS

A total of 126 patients treated with carotid endarterectomy were evaluated, comprising 85 men and 41 women (mean age 65 ± 5.3 years old). All the patients were considered eligible for the procedure based on valid indications (14, 15). 46 patients were asymptomatic, whereas 80 were symptomatic.

The symptomatic patients were divided into two subgroups differing by the their symptom timing prior to the surgery: 55 patients were found to have a history of TIA within the previous 2 years, with symptoms having resolved completely more than 3 months preceding the surgery, while 25 patients had suffered neurological symptoms in the 3-month period directly preceding the operation. The cut-off period was assumed as 3 months (16, 17).

Consequently, 3 subgroups of patients were analysed:

- subgroup I – asymptomatic patients (46 patients),
- subgroup IIa – patients symptomatic in the past, yet without active neurological symptoms within the 3 months preceding the operation (55 patients),
- subgroup IIb – symptomatic patients with active neurological symptoms within the 3-month period directly preceding the surgery (25 patients).

Prior to the surgery, all the patients underwent ultrasound evaluation of the morphological picture of their carotid plaque applying PDA method according to Lal et al. (7).

Microembolism was intraoperatively evaluated with TCD registering the flow in the middle cerebral artery (Pionier/EME Nicolet device, USA). Selected flow parameters were registered, along with the presence

of microemboli at three stages of the operation: stage I – vessel preparation, stage II – vessel clamping, and stage III – following clamp release. In our Department, microembolic signals (MES) are identified as high-intensity transient signals (HITS) < 0.3 s, with intensity increase of more than 4dB above background intensity, unidirectional within the Doppler velocity spectrum (18).

The incidence of microembolism and the ultrasound image of carotid plaque evaluated with PDA were analysed for each of the patient subgroups distinguished by the presence of neurological symptoms or a lack thereof.

The neurological status of each of the operated patients was assessed by an experienced neurologist collaborating on a permanent basis with our Department. Perioperative complications were diagnosed based on the neurological evaluation supplemented with a CT scan.

The following exclusion criteria were applied: neurological deficits caused by vertebrobasilar lesions, presence of other potential foci of microembolization (atrial fibrillation, heart valve disease, circulatory insufficiency, or history of cardiac infarction), and no possibility of TCD monitoring (lack of an acoustic window).

Statistical methods

The results were analysed with Stata 7.0 software. The distribution of components with different echogenicity characteristic for given tissues (blood, fatty tissue, muscle tissue, fibrous tissue and calcified tissue) in the three groups varying by the nature of their symptoms (or lack thereof) was examined with Kruskal-Wallis test. The relationships between the incidence of microembolism at all three stages of the surgery were also examined with Kruskal-Wallis test. Fischer's exact test was used to examine the relationships between the occurrence of perioperative complications in the three groups. $p < 0.05$ was set as statistically significant.

RESULTS

Analysis of the primary data for the analysed patient subgroups showed the prevalence of risk factors typical for atherosclerosis and endarterectomy, such as hypertension, diabetes, significant (> 60%) flow decrease in the middle cerebral artery, and shunting in the examined subgroups to be similar and statistically non-significant (p = NS).

The relationship between the presence of microemboli and the patient subgroups

The risk of microembolism was found to be the highest in the first stage of the surgery (vessel preparation) for all the three subgroups.

The incidence of microembolism at this stage of the surgery varied across the subgroups. Thus, the median number of microemboli for subgroup IIa (recent symptoms) was the highest, equaling 23 microemboli at this stage of surgery, whereas for the two remaining subgroups of patients it equaled 4 microemboli. This difference was exceptionally strong statistically ($p = 0.0001$). The differences between the numbers of microemboli in the two remaining subgroups (I and IIb) were statistically non-significant, with $p = 0.74$.

The differences in the number of microemboli released into the arterial circulation at the remaining two stages of the procedure (clamping and clamp release) were for all the three subgroups small and statistically non-significant (p = NS). The results have been presented quantitatively in table 1, and graphically in the form of a box-and-whisker plot in figure 1.

The relationship between the echogenicity of carotid lesions and the patient subgroups

The analysed patient subgroups, differing by the presence and the timing of neurological symptoms, i.e. subgroup I, IIa, and IIb showed different echogenicity of carotid lesions. PDA demonstrated components with echogenicity consistent with blood, fatty tissue,

Tab. 1. The relationship between the occurrence of microemboli in given patient subgroups (in relation to the presence of neurological symptoms)

TCD – measured as microemboli	Subgroup I (asymptomatic) N = 46	Subgroup IIa (symptomatic: symptoms present < 12 weeks prior to surgery) N = 25	Subgroup IIb (symptomatic: no symptoms directly preceding surgery; symptoms present > 12 weeks) N = 55
Hits prior to clamping (min, max) median (25%, 75%)	(0, 26) 4 (2, 9)	(1, 80) 23 (18, 32)	(0, 44) 4 (2, 12)
Subgroup I vs subgroup IIa vs subgroup IIb: p = 0.0001		**Subgroup I vs subgroup IIa p = 0.0001**	**Subgroup I vs subgroup IIb p = 0.74** **Subgroup IIa vs subgroup IIb p = 0.0001**
Hits during clamping (min, max) median (25%, 75%)	(0, 128) 1 (0, 3)	(0, 12) 1 (1, 4)	(0, 89) 2 (0, 7)
Subgroup I vs subgroup IIa vs subgroup IIb: p = 0.28			
Hits following clamp release (min, max) median (25%, 75%)	(0, 85) 2 (1, 14)	(0, 123) 4 (1, 12)	(0, 144) 6 (2, 15)
Subgroup I vs subgroup IIa vs subgroup IIb: p = 0.40			

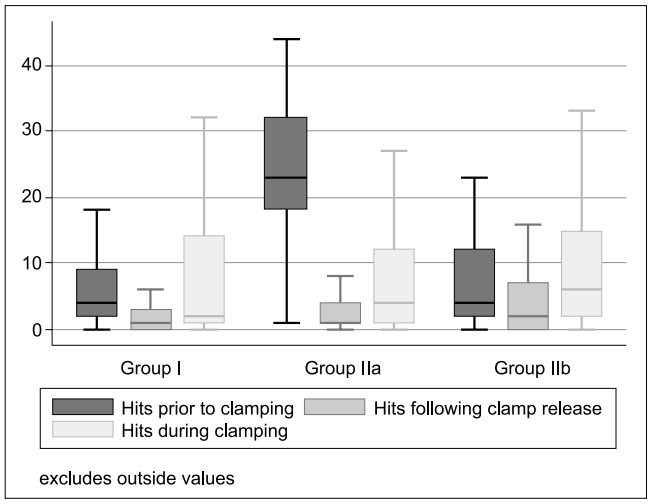

Fig. 1. The differences in microembolism incidence between the subgroup (box-and-whisker plot)

muscle tissue and fibrous tissue (partitions 1-4: tab. 2) to be most common in subgroup IIa (recent neurological symptoms). The lesions in subgroup I (asymptomatic) showed similar distribution of echogenicity as the lesions found in subgroup IIb (once symptomatic but no recent symptoms). The content of tissue with echogenicity similar to calcified lesions is similar in all 3 subgroups. See table 3 and figure 2 for detailed data and differences.

Tab. 3. Complication rate in the subgroups

	Complications	
Subgroup I, N = 46	0	
Subgroup IIa, N = 25	5 (23.8%)	p < 0.01
Subgroup IIb, N = 55	2 (3.7%)	

The relationship between the occurrence of perioperative complications and the analysed patient groups

A direct relationship has been found between the studied patient subgroups and the prevalence of perioperative complications. In subgroup IIa (recent symptoms), i.e. the subgroup with a naturally higher perioperative risk, perioperative complications were found in 5 out of 25 patients, amounting to as much as 20.0 % of the patients in this subgroup. The number of complications in subgroup IIb (1 complication

Tab. 2. The relationship between the percentage of tissue with given echogenicity (pixel distribution analysis – partition 1 = tissues with echogenicity consistent with blood, partition 2 = tissues with echogenicity consistent with adipose tissue, partition 3 = tissues with echogenicity consistent with muscle tissue, partition 4 = consistent with fibrous tissue, and partition 5 = consistent with calcified tissue) in the patient subgroups

Pixel distribution analysis	**Subgroup I (asyptomatic) N = 46**	**Subgroup IIa (symptomatic: symptoms present < 12 weeks prior to surgery) N = 25**	**Subgroup IIb (symptomatic: no symptoms directly preceding surgery; symptoms present > 12 weeks) N = 55**
Partition 1 (min, max) median (25%, 75%)	(0, 27) 0.24 (0, 4.8)	(0, 77.7) 21.6 (5.5, 36.8)	(0, 38.2) 0.48 (0, 2.3)
Subgroup I vs subgroup IIa vs subgroup IIb: p = 0.0001		**Subgroup I vs subgroup IIa p = 0.0001**	**SubgroupI vs subgroup IIb p = 0.60** **Subgroup IIa vs subgroup IIb p = 0.0001**
Partition 2 (min, max) median (25%, 75%)	(0, 31.9) 2.5 (0.4, 11.5)	(0, 74.0) 39.9 (25.6, 53.1)	(0, 65.5) 6.6 (0.6, 21.2)
Subgroup I vs subgroup IIa vs subgroup IIb: p = 0.0001		**Subgroup I vs subgroup IIa p = 0.0001**	**Subgroup I vs subgroup IIb p = 0.13** **Subgroup IIa vs subgroup IIb p = 0.0001**
Partition 3 (min, max) median (25%, 75%)	(4.5, 93.7) 51.1 (33.6, 63.7)	(0, 57.4) 24.7 (9.0, 43.1)	(0.8, 88.6) 52.5 (39.8, 66.6)
Subgroup I vs subgroup IIa vs subgroup IIb: p = 0.0001		**Subgroup I vs subgroup IIa p = 0.0001**	**Subgroup I vs subgroup IIb p = 0.64** **Subgroup IIa vs subgroup IIb p = 0.0001**
Partition 4 (min, max) median (25%, 75%)	(0, 69.6) 31.5 (14.5, 47.7)	(0, 50.8) 7.6 (3.0, 11.1)	(0.26, 98.4) 22.3 (8.1, 44.7)
Subgroup I vs subgroup IIa vs subgroup IIb: p = 0.0002		**Subgroup I vs subgroup IIa p = 0.0001**	**Subgroup I vs subgroup IIb p = 0.22** **Subgroup IIa vs subgroup IIb p = 0.0001**
Partition 5 (min, max) median (25%, 75%)	(0, 43.1) 1.2 (0, 10.1)	(0, 15.9) 0.34 (0, 1.6)	(0, 30.6) 0.56 (0, 5.1)
Subgroup I vs subgroup IIa vs subgroup IIb: p = 0.37			

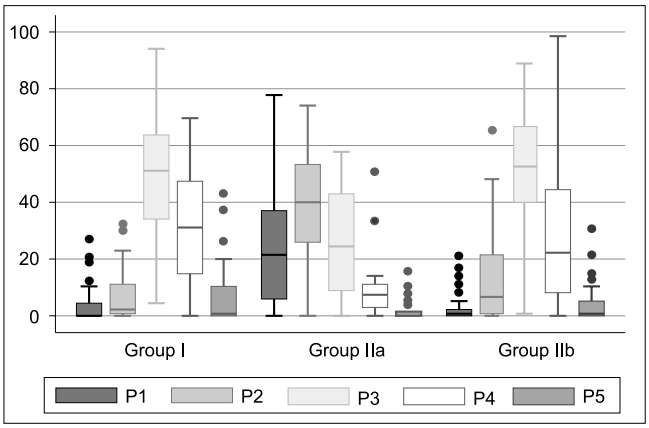

Fig. 2. Relationship shown in table 3 (box-and-whisker plot)

event in 55 patients, i.e. 1.75%), in turn, and in subgroup I (0 complications in 41 patients) was comparable and statistically non-significant (tab. 2).

The overall number of complications was then comparatively high (a total of 5 complications per 126 patients). It is, however, important to note that the total number of 5 complications was comprised by 1 stroke (IIb subgroup), and 4 TIAs that resolved within 24 hours following the surgery.

DISCUSSION

Carotid endarterectomy is considered a safe procedure successfully reducing the risk for ischaemic brain stroke (14, 15). Despite this and intervention therapy being widely-acknowledged, its efficiency cost-wise (the proportion of the number of procedures necessary to prevent 1 brain stroke) remains unclear (19, 20). Studies such as VA-CSP and ACAS have shown that to prevent one brain stroke, it is necessary to remove stenosis in 40-80 carotid arteries in asymptomatic patients (16, 21).

It is, at this point, important to note the considerable confusion related to the "symptomatic patient" term. The question arises whether these are patients with neurological symptoms directly preceding the surgical intervention, or patients with a history of neurological symptoms in the past, and if so, for how long the symptoms have not been present.

The question seems crucial, as NASCET and ECST coordinators did not raise the issue at all. Currently, some researchers acknowledge the importance, yet apply varying, random criteria. Most commonly, a period of 3 months (12 weeks) preceding the intervention is considered the cut-off value separating symptomatic and asymptomatic patients (17, 22, 23). Others tend to arbitrarily assume this period to be 6 months (24-26). Molloy and Markus have suggested a 12-month period as relevant (27). Recently, O'Brien et al. have assumed a 4-week period as adequate based on histopathological results (26).

Such discrepancies in arbitrary and randomly assumed definitions of symptomatic vs. asymptomatic patients are bound to raise controversies. At the same time, paradoxically, it is a proof of an *a priori* assumption made as regards the cyclic frequency of the processes taking place within the plaque, ranging from degenerative, leading to its break-down and rupture, to reparatory ones, i.e. periods when patients in fact do not require surgical intervention (28-33).

The results of numerous studies on unstable carotid plaque indicate that in our present state of knowledge it is possible to pre-operatively identify some determinants of vulnerable lesions. US evaluation of the lesions, applying GSM method seems to play an essential role here (5, 24, 25, 34, 35). There seems to exist a direct relationship between GSM values, the histopathological picture (23, 36), and microembolism (22). Also, a direct relationship between microembolism and the presence of neurological symptoms or lack thereof (12, 13, 27, 37, 38) has been determined. Study results suggest symptomatic lesions to be characterized by an increased risk of microemboli forming (22, 39-45), and microembolism as such to be a strong predictor of the occurrence of neurological symptoms (12, 13, 22, 27, 37, 46).

The objective of this study was to determine the relationship between the presence of recent neurological symptoms and two important predictors of unstable carotid plaques, i.e. their morphology and microembolism.

The obtained results seem interesting, as we have found statistically significant differences between the number of microemboli released into the central nervous system between the subgroup IIa (recent neurological symptoms) and subgroup I (asymptomatic patients), with $p < 0.0001$. At the same time, we have not determined differences in the number of released microemboli between subgroups I and IIb (history of neurological symptoms > 3 months prior to the surgery), with $p = 0.74$. The following interpretation seems plausible: patients with no symptoms directly preceding the surgery may to a large extent have carotid lesions similar in character to those present in asymptomatic patients. This can serve as an indirect proof for the hypothesis of cyclic frequency of reparative and degenerative processes occurring within the plaque. This could mean that the processes of lesion break-down in patients whose neurological symptoms are resolving are gradually replaced with plaque stabilization processes.

The assumed classification of the patients into the 3 subgroups has shown them to vary by the morphology of the carotid lesions. The percentage of tissue components with echogenicity considered as "protective" (7), i.e. displaying characteristics of calcified tissue or fibrous and muscle tissue was considerably higher in subgroups I and IIb ($p = 0.0001$ and $p = 0.0012$ respectively). In subgroup IIa (patients with recent neurological symptoms) the percentage of components displaying echogenicity consistent with tissues considered as "risk factors", such as fatty tissue and blood, prevailed ($p < 0.0001$ against subgroup I and IIb).

The generalized rate of perioperative complications was relatively high, i.e. 4.31%. Importantly, however, 4 out of 5 complications were TIAs, and they resolved in an early perioperative period. Across all three subgroups, a total of 1 stroke occurred. It is probable that the relatively high incidence of TIA was in fact due to the contribution of an experienced neurologist assessing all the patients in the perioperative period. It is common knowledge that in centres where postoperative neurological status of the patients is evaluated by the surgeon, the lower TIA diagnosis rate is largely due to the lack of a neurologist in charge. The comparison of the complication rate in the studied subgroups may constitute another proof, indirect this time, for the fact that the presence of symptoms directly preceding the surgical intervention is a separate, independent risk factor.

The above can obviously be distorted by the fact that some of the patients suffered a significant permanent neurological deficit in recent past, or by the small sample size (5 complications in total, yielding wide confidence intervals, and precluding a complex multifactor analysis). Still, it is significant that in the asymptomatic patient subgroup the complication rate was minimal (0%) and comparable with subgroup IIb (symptomatic, but over 3 months prior to the surgery) – 1.85%. These results compared with the large complication rate (19.05%) in patients with recent neurological symptoms (subgroup IIa) seem surprising.

The authors of this study are aware of its limitations. Drawing far-fetched conclusions based on the small sample size (5 complications) would be premature. Another limitation of this study is the arbitrary classification of the enrolled patients into the subgroups according to the cut-off period of 12 weeks prior to the surgical intervention, adopted after Blaser et al. (16) and other authors (17, 22, 47, 48)".

Nonetheless, the existing relationships between the given subgroups and the number of released microemboli, the morphology of carotid lesions, and the presence of perioperative complications seem to suggest the need for a precise definition of a "symptomatic patient".

CONCLUSIONS

1. The timing of neurological symptoms may have significant impact on the incidence of microembolism.
2. The morphologic picture of carotid plaques in patients with neurological symptoms directly preceding the surgical intervention correlates more closely with the determinants of unstable carotid lesions.
3. This seems to suggest the need for a precise definition of a "symptomatic patient".

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