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Review article

MMP-9 and/or TIMP as predictors of ischaemic stroke in patients with symptomatic and asymptomatic atherosclerotic stenosis of carotid artery treated by stenting or endarterectomy – A review

Justyna Zielinska-Turek [a,*], *Małgorzata Dorobek* [a], *Grzegorz Turek* [b], *Maria Barcikowska-Kotowicz* [c]

[a] *Department of Neurology, Central Clinical Hospital of Ministry of the Interior and Administration, Warsaw, Poland*
[b] *Department of Neurosurgery, Bródno Mazovia Hospital, Warsaw, Poland*
[c] *Laboratory of Neurogenetics, Department of Neurodegenerative Disorders, Mossakowski Medical Research Center, Polish Academy of Sciences, Warsaw, Poland*

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ABSTRACT

We still lack an optimal tool to predict ischaemic stroke in patients with symptomatic and asymptomatic carotid stenosis (CS). It has already been shown that patients at increased risk of ischaemic stroke can be identified based on the elevated plasma levels of metalloproteinases (MMPs) and reduced activity tissue inhibitor of metalloproteinase (TIMP). There are few studies presenting the role of MMP-9 and TIMP in ischaemic stroke both in patients with symptomatic and asymptomatic CS treated with stenting or endarterectomy, however we have not found any published review summarizing the role of abovementioned markers. MEDLINE was accessed via Pub Med, and searched for published studies that analyzed MMP-9 and TIMP levels in patients with asymptomatic and symptomatic internal carotid stenosis and/or examined these parameters as potential risk markers for ischaemic stroke. A total of 13 articles documenting the outcomes of patients with symptomatic or asymptomatic carotid stenosis treated by carotid stenting or endarterectomy, were analyzed. Statistically significant differences in the levels of MMP-9 and/or TIMP in patients with symptomatic and asymptomatic CS have been reported. Also the concentrations of MMP-9 and TIMP in CS patients subjected to stenting or endarterectomy were higher than in baseline group. Moreover higher levels of MMP-9 and decreased TIMP was reported to be associated with the risk of restenosis. This systematic review shows that available evidence regarding the dynamics of MMP-9 and TIMP levels may be a predictor of cerebrovascular events in both symptomatic and asymptomatic carotid stenosis in patients treated with stenting or endarterectomy.

* *Corresponding author at*: Department of Neurology, Central Clinical Hospital of Ministry of the Interior and Administration, 137 Wołoska Str., 02-507 Warsaw, Poland.
E-mail address: jzturek@gmail.com (J. Zielinska-Turek).

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1. Introduction

Stroke is a leading cause of mortality and the main reason for permanent disability in adults [1,2]. Atherosclerotic disease of the internal carotid artery results in carotid stenosis (CS), an established cause of ischaemic stroke. The prevalence of hemodynamically relevant CS (≥50%) in subjects >65 years of age is quite high (5–10%) [3,4]. According to literature, asymptomatic CS (50–99%) contributes substantially to 1–3.4% annual stroke rate [5]. Since both CS and modifiable risk factors for ischaemic stroke have been studied quite extensively, an obvious direction of further research was to identify the subjects at increased risk of stroke to provide them with adequate preventive measures. Interestingly, however, both the U.S. Preventive Service Task Force (USPSTF) and the AHA Primary Prevention of Stroke guidelines do not recommend screening for CS in general adult population [6]. This policy has been explained by difficulties in the identification of patients who may benefit from endarterectomy/stenting or pharmacotherapy alone. The validity of this assumption has been also confirmed by the results of the largest two trials that had been conducted thus far: Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Artery Trial (ACAT). None of these studies demonstrated a link between the severity of CS and the risk of stroke in asymptomatic patients. Moreover, published evidence suggests that currently available diagnostic procedures: duplex ultrasound and computed tomography could not adequately assess the risk of stroke in asymptomatic CS.

The review of the abovementioned recommendations shows clearly that we lack an optimal strategy to predict ischaemic stroke in patients with asymptomatic CS. However, some previous studies demonstrated that matrix metalloproteinases may play a role in vascular remodelling and destabilization of atherosclerotic plaques in the internal carotid arteries [7]. Furthermore, it has already been shown that patients at increased risk of ischaemic stroke can be identified based on the elevated plasma level of MMPs and reduced activity tissue inhibitor of metalloproteinase (TIMP), i.e. characteristic features of atherosclerotic plaque instability. This is a relatively recent finding; therefore the issue was the subject of only few published studies. Nevertheless, analysis of plasma MMP and TIMP levels seems to be highly promising in the context of stroke prediction in asymptomatic patients with CS.

However, we did not find any published review paper summarizing recent studies examining the role of MMP-9 and TIMP levels in patients subjected to carotid stenting or endarterectomy due to asymptomatic or symptomatic CS. Therefore, the aim of this systematic review was to present available evidence regarding the dynamics of MMP-9 and TIMP levels as a predictor of cerebrovascular events in CS.

2. Clinical implications

2.1. Search strategy

MEDLINE was accessed via Pub Med, and searched for published studies that analyzed MMP-9 and TIMP levels in patients with asymptomatic and symptomatic internal carotid stenosis and/or examined these parameters as potential risk markers for ischaemic stroke. The search was based on various combinations of the following keywords and phrases: 'ischaemic stroke', 'internal carotid artery stenosis', 'MMP-9', 'TIMP', 'atherosclerosis', 'cardiovascular disease' and 'metalloproteinase'. Also PubMed's 'related articles' functionality was used to identify publications that have not been found by means of the keyword search.

2.2. Inclusion/exclusion criteria

The review included MEDLINE-indexed papers published between 1989 and 2017, and non-indexed articles of Polish authors. The studies of patients under 18 years of age, animal models, cadaveric experiments, letters to the editors were not eligible for the review. Also the papers that did not provide any information about MMP-9 and TIMP levels, and those presenting concentrations of these markers solely in atherosclerotic plaques were excluded from the analysis.

2.3. Data extraction

Two independent authors (J.Z.-T. and M.D.) extracted the following data from the eligible publications: (1) type of the study, (2) characteristics of the study group, (3) MMP-9 and TIMP levels in the study subjects, and (4) relationship between concentrations of these markers and the study outcome, if any. Characteristics of the study type included information whether the results were collected prospectively or retrospectively, also about follow-up duration, inclusion/exclusion criteria and outcome measures. Characteristics of the study group included the number of patients, their mean age, clinical status at hospital admission and CS severity. MMP-9 and TIMP levels were recorded for patients with asymptomatic and symptomatic internal carotid artery stenosis, as well as for individuals who underwent carotid stenting (CAS) and carotid endarterectomy (CEA).

A total of 13 articles, all written in English, documenting the outcomes of 1097 patients with symptomatic (SCS) or asymptomatic carotid stenosis (ACS) treated by either carotid stenting or endarterectomy, were analyzed. The largest group consisted of 300 patients, the smallest of 11 patients.

Clinical characteristics of SCS and ACS patients included in these studies are summarized in Table 1, separately for individuals subjected to carotid stenting (CAS) and for those treated by carotid endarterectomy (CEA). MMP-9 and TIMP levels in those groups are shown in Table 2.

2.4. MMP-9 and TIMP levels in patients with symptomatic and asymptomatic carotid stenosis

Statistically significant differences in MMP-9 and/or TIMP levels in patients with symptomatic (e.g. ischaemic stroke, transient ischaemic attack – TIA, amaurosis fugax – AF) were demonstrated in two papers and asymptomatic CS in only one (Table 2). The authors of a Polish study found no significant differences in baseline plasma levels of MMP-9 of patients with symptomatic and asymptomatic CS (0.14 ng/L, range 0.1–

Table 1 – Description of studies.

Reference	Year		Participants	Assay	Outcomes/aim	Conclusion
Loftus et al. [11]	2000	Patient with asymptomatic and symptomatic CS admitted for carotid endarterectomy (CEA)	UK: 75 patients	ELISA (24 h preoperatively)	Profile of MMPs (1, 2, 3 and 9), TIMPs (1, 2)	• Expression of MMP-9 is significantly higher in symptomatic patients only 1 month before CEA, moreover in unstable carotid plaques. • MMP-9 may be a strong candidate for pharmacotherapy aimed at stabilizing plaques and preventing stroke
Alvarez et al. [10]	2004	Patients with symptomatic (stroke, TIA, ASX) and symptomatic CS classified for TEA	Spain: 40 patients (27 S, 13 AS)	ELISA (24 h before surgery)	Profile of MMPs (2, 9)	• MMP-9 was significantly higher in the symptomatic group and in patients with unstable plaques • MMP-2 was significantly higher in patients with symptoms
Eldrup et al. [9]	2006	Patient referred for carotid ultrasound examination, symptomatic or asymptomatic	Denmark: 207 patients (88 AS, 119 S)	ELISA (after the ultrasound examination)	Profile of MMP-9	• MMP-9 level associated with 2 fold risk of stroke or CVD
Gondalia et al. [18]	2007	Patients with symptomatic (stroke, TIA, ASX) CS classified for CEA	Sweden: 13 (all symptomatic)	ELISA (1, 5, 9 min before clamping, just before clamping and 15 min after start of reperfusion)	Profile of MMP-9, MCP-1, ICAM-1 and oxLDL	• No statistically significant change was observed concerning MMP-9 during surgery
Suzue et al. [13]	2007	Patients with symptomatic (stroke) and asymptomatic CS classified for CEA	Japan: 112 patients (72 S, 40 AS)	• ELISA (during surgery) Zymography (carotid plaques)	Profile of MMPs (2, 9)	• There was no significant difference with respect to the activity MMP-9, although it was greater in the vulnerable than stable plaques
Taurino et al. [20]	2008	Patients with symptomatic and asymptomatic CS admitted for TEA	Italy: 15 patients	ELISA (before surgical procedure, 1 week and 1 month thereafter)	Profile of MMPs (2, 9) and TIMP-2	• MMP-9 before surgery was significantly higher in patients with CS than in healthy control • MMP-9 at week after surgery was decreased, and 1 month drastically decreased • MMP-2 was higher in patients with CS than controls • TIMP-2 no significant changes in baseline, 1 week and 1 month after surgery, and in control group
Setacci et al. [17]	2008	Patients with symptomatic (stroke, TIA, ASX) and asymptomatic CS classified for CAS	Italy: 57 patients	ELISA (before stenting, immediately afterwards and at the 30 day follow-up)	Profile of MMPs (2, 9), PAPP-A, hs-CR, IL-6	• No statistically significant change was observed in levels MMP-9 and MMP-2
Ishigaki et al. [19]	2008	Patients with symptomatic (stroke, TIA) and asymptomatic CS undergoing CEA for ipsilateral internal ICA	Japan: 41 patients (21 S, 20 AS)	ELISA (5 min after intravenous administration of heparin and immediately before clamping of the ICA, 1, 5 and 20 min after declamping ICA)	Profile of MMP-9	• The concentrations of MMP-9 at 20 min after ICA declamping were significantly higher than those before ICA clamping or at 1 min after ICA declamping
Sapienza et al. [21]	2009	Patient with symptomatic and asymptomatic, severe, recurrent carotid artery stenosis	Italy: 52 patients	ELISA	Profile of MMPs (2, 9) and TIMPs (1, 2)	• Patients with symptomatic restenosis had significantly higher active MMP-2 and 9, lower TIMP-1 and 2
Musialek et al. [8]	2013	Patient with CS ≥50% symptomatic or asymptomatic	Poland: 300 patients (110 AS, 190 S)	ELISA (morning between 7 and 9 a.m. at admission)	Profile of MMPs (8,9,10), TIMP, IL (1β, 6, 8,18), leptin	• Plasma levels of the MMPs did not differ between the study group • TIMP was significantly lower in the CS-symptomatic patients

Table 1 (*Continued*)

Reference	Year		Participants	Assay	Outcomes/aim	Conclusion
Zhang et al. [16]	2015	Patients with symptomatic (stroke) and asymptomatic CS classified for CAS	China: 74 patients (43 S, 31 AS)	ELISA (before stenting, at 24 h, 3 and 6 months after CAS procedure)	Profile of MMP-9, IL-1β, IL-6, TGF-β, MCP-1 and sVCAM-1	• MMP-9 increased 24 h after stenting • MMP-9 – high expression continued for at last 3 months after stent implantation
Gabrile et al. [12]	2016	Patients with symptomatic (stroke, TIA, AF) and asymptomatic CS classified for CEA	Brazil: 11 patients (6 S, 5 AS)	ELISA (preoperative period and 1, 6 and 24 h after CEA)	Profile of MMPs (8, 9), IL (1β, 4, 6, 8, 10), TNF-α, hs-CRP, VEGF	• Peak serum values for MMP-8, MMP-9, IL-6 and IL-10 were observed 6 h after CEA • Symptomatic patients exhibited higher serum concentrations of MMP-8, MMP-9, IL-1β, IL-4, IL-8, hs-CRP, TNF-α
Lekic et al. [14]	2017	Patients with symptomatic and asymptomatic CS	Croatia: 100 patients (40 with mild	artherosclerosis of carotid artery disease, 40 with artherosclerosis of carotid artery disease, 20 healthy volunteers	ELISA	Profile of MMPs (2, 9) in urine, and CD4, CD25 and Foxp3 in blood
•		Significant increase MMP-2 in patients with large stenosis of the carotid artery • Statistically significant difference in the MMP-9 enzyme concentration in patients with artherosclerosis, stenosis and the controlled group				

S, symptomatic; AS, asymptomatic; CEA, carotid endarterectomy; CVD, cardiovascular death; TEA, thromboendarterectomy; TIA, transient ischaemic attack; AF, amaurosis fugax; MMP, matrix metalloproteinase; MMPs, matrix metalloproteinases; TIMP, tissue inhibitor of metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases; CAS, carotid artery stenting; ICA, internal carotid artery.

Table 2 – MMP-9 and TIMP levels in patients with symptomatic and asymptomatic carotid stenosis (CS).

References	Symptomatic CS (SCS)		Asymptomatic CS (ACS)		MMP-9 SCS vs ACS	TIMP SCS vs ACS
	MMP-9	TIMP	MMP-9	TIMP		
Musialek et al. [1]	0.14 ng/L	130.7 ng/ml	0.13 ng/L	146.2 ng/L	Not significant	Significant
Alvarez et al. [3]	1026.1 ng/ml	N/A	377.84 ng/ml	N/A	Significant	N/A
Eldrup et al. [2]	47	N/A	40	N/A	Significant	N/A

N/A, not applicable.

0.2 ng/L vs. 0.13 ng/L, range 0.1–0.2 ng/L) [8]. Symptomatic patients showed no statistically significant differences in MMP-9 levels determined prior to and 6 months after the manifestation of the last symptoms. However, symptomatic and asymptomatic patients participating in this study differed significantly in terms of their TIMP levels (130.7 ng/ml vs. 146.2 ng/ml). Eldrup et al. analyzed MMP-9 levels in CS patients with ipsilateral stroke/cardiovascular death and in subjects with asymptomatic CS contrary to Musialek found statistically significant intergroup differences in MMP-9 levels (47 ng/ml vs. 40 ng/ml) [9]. They also demonstrated that the probability of ipsilateral stroke or cardiovascular death in patients in whom plasma concentration of MMP-9 exceeded the median value for the study group (41.9 ng/mL) was significantly higher than in those with lower (what was the cut off) blood levels of this metalloproteinase. Also Alvarez et al. found a statistically significant association between an increase in serum concentration of MMP-9 and presence of symptomatic CS [10]. In the study conducted by these authors, mean concentrations of MMP-9 in symptomatic and asymptomatic CS patients amounted to 1026.10 ± 412.9 ng/mL and 377.84 ± 164.08 ng/mL, respectively. Loftus et al. presented significantly higher concentration of MMP-9 in symptomatic patients with CS, but only within one month before CEA. There was no differences in asymptomatic patients, symptomatic >6 months and 1–6 months before surgery [11]. Also Gabrile et al. showed similar findings, however not only MMP-9 serum concentration in his group was higher in symptomatic patients, but also of MMP-8, IL-1β, IL-4, IL-8, hs-CRP, TNF-α [12]. Interestingly, both Loftus et al. and Suzue et al. showed that the concentration, production, and expression of MMP-9 was significantly higher in unstable carotid plaques [11,13]. Other papers were

published recently by Lekic et al. and Eilenberg et al. In the first paper, the authors showed statistically significant increase in levels of MMP-9 in urine of patients with higher degree of stenosis and symptomatic plaque – average values for stenosis <60% vs 79–99% amounted to 3679.5 pg/ml vs. 859.7 pg/ml, respectively [14]. In the second paper the authors showed that circulating MMP-9/NGAL complex is associated with atherosclerotic plaque vulnerability in patients with carotid artery stenosis [15].

2.5. *Concentrations of MMP-9 and/or TIMP in CS patients subjected to stenting (CAS) or endarterectomy (CEA)*

Zhang et al. conducted an extensive study to verify an association between serum level of MMP-9 and the stenting procedure. In this study, concentrations of MMP-9 were assessed prior to the procedure, 24 h, 3- and 6-month thereafter [16]. Elevated levels of MMP-9 were observed for at least 3 months post-procedure, which suggested that this metalloproteinase may be involved in the process of in-stent stenosis. Aside from a tendency to intra-procedural bleeding, carotid stenting was not associated with any other complications. Analyse of MMP-9 level in patients with symptomatic CS treated by stenting ($n = 57$) showed elevated levels of MMP-9 not only 24 h post-stenting but also up to 30 days thereafter; concentrations of MMP-9 determined prior to the stenting, 24 h and 30 days post-procedure amounted to 100 pg/ml, 125 pg/ml and 118 pg/ml, respectively (Setacci et al. similar to Zhang et al.). Carotid stenting was associated with two TIA episodes directly after the procedure, two TIA episode and death within a month after the discharge from the hospital [16,17].

Contrary to the mentioned above reports, which focused on a link between carotid stenting and MMP-9 levels in CS patients, Gondalia et al. analyzed an association between serum concentration of this metalloproteinase and endarterectomy [18]. Serum levels of MMP-9 were analyzed prior to and during clamping of the artery, and 15 min after its release. Although mean levels of MMP-9 during and after the clamping were higher than at the baseline, the difference in the whole study group was not statistically significant. However, a significant increase in MMP-9 level was found in patients with diabetes mellitus, high concentrations of haemoglobin, high leucocyte and platelet counts, as well as in individuals with contralateral stenosis, whereas older persons, subjects with elevated blood pressure and those operated on for the left-side stenosis presented with significantly lower concentrations of this metalloproteinase. Similar results were reported by Ishigaki et al. [19]. In this study serum concentrations of MMP-9 at 1, 5 and 20 min after the ICA declamping were significantly higher than at the baseline ($p < 0.05$). Interestingly, 3 out of 41 participants of this study, who recovered from anaesthesia with new neurologic deficits, presented with the highest concentrations of MMP-9 at 1, 5 and 20 min post-declamping. In another study, Taurino et al. analyzed concentrations of MMP-9 and TIMP prior to CEA, as well as 1 week and 1 month after the procedure; moreover, this study included a control group [20]. Baseline concentration of MMP-9 in patients qualified for CEA (23.8 ng/mL) turned out to be significantly higher than in healthy controls (11.4 ng/mL). Although patients with symptomatic CS presented with higher baseline plasma levels of MMP-9 than individuals with the asymptomatic stenosis, the difference was not statistically significant. However, baseline plasma concentrations of MMP-9 in persons with an evidence of cerebral lesions on preoperative neuroimaging were significantly higher than in the controls. One week and one month after the CEA, a decrease in MMP-9 level was observed in nearly 50% and in more than 90% of the study subjects, respectively. Contrary to MMP-9, no statistically significant changes were observed in plasma levels of TIMP in CS patients and controls, either at the baseline or after a 1-week/1-month follow-up.

2.6. *Association between MMP-9 and TIMP levels and the risk of restenosis*

One published study analyzed an association between elevated levels of MMP-9 and TIMP and the risk of restenosis after CEA. The study conducted by Sapienza et al. included 621 patients subjected to CEA, among them 52 patients with symptomatic and asymptomatic internal carotid artery restenosis [21]. The restenosis was classified as early, intermediate and late. Individuals with restenosis, either active or latent one, presented with elevated levels of MMP-9 and decreased concentrations of TIMP. Detailed analysis demonstrated lower levels of TIMP in symptomatic patients as well as individuals with late restenosis.

3. Future directions

We have reviewed 13 recent publications documenting applicability of MMP-9 and TIMP as predictors of cerebrovascular event in patients with asymptomatic or symptomatic CS treated by stenting or endarterectomy. Available evidence is limited to formulate any unequivocal conclusions in this matter. Most previous studies demonstrated that after stenting or endarterectomy, patients with symptomatic CS showed an increase in MMP-9 concentration and a decrease in TIMP level. Therefore, most researchers concluded that both MMP-9 and TIMP may serve as markers of brain ischaemia in CS patients [9,10].

The study conducted by Eldrup et al. adds to this evidence, showing that patients with MMP-9 concentrations exceeding median value for the whole study group (41.9 ng/ml) had twice as high the risk of ipsilateral stroke than the remaining subjects. The study demonstrated that patients with symptomatic CS presented with elevated levels of MMP-9, which the authors speculated to result from an increase in the number of cells releasing this enzyme, i.e. macrophages and leukocytes. This hypothesis was also confirmed by Loftus et al. [11] who found that the level of MMP-9 within the atherosclerotic plaques of patients with a recent history of CS symptoms was significantly higher than in individuals who did not experience any symptoms for more than one month. According to Alvarez et el., metalloproteinases may be responsible for destabilization of atherosclerotic plaques, and may play an important role in the etiopathogenesis of cerebral ischaemic events. These authors found elevated levels of MMP-9 both in patients with a history of ischaemic events and in patients with unstable atherosclerotic plaques, and observed a positive correlation between concen-

tration of gelatinase B (MMP-9) and presence of macrophages within the plaques. These findings were confirmed by other authors who demonstrated a link between an increase in MMP-9 level, plaque instability and resultant greater likelihood of a cerebral ischaemic event [22–25]. According to Alvarez et al., these findings may have diagnostic and therapeutic implications, since elevated plasma level of MMP-9 may be useful in identification of patients at increased risk of stroke. However, Musialek et al. concluded that circulating biomarkers, such as MMP-9 and TIMP, are not accurate predictors of symptomatic CS [8]. In the study conducted by these authors, patients with symptomatic CS showed a decrease in TIMP levels, which suggested a disruption in MMP-9/TIMP balance, but without a concomitant change in MMP-9 level.

In all previous studies, CS patients who had been subjected to carotid stenting or endarterectomy showed an increase in MMP-9 levels [12,13]. According to Zhang et al., elevated levels of this metalloproteinase was present immediately after the CAS, and also after a longer follow-up period. This implies that metalloproteinases may also play an important role in in-stent restenosis, which has been already confirmed in a CS patient after stenting [26]. Using a new in vitro model, the authors demonstrated that the expression of MMP-9 may be regulated by suppression of ERK1/2/Elk-1 pathway (extracellular signal – regulated kinases1/2/humans encoded by theELK1gene). Moreover, they showed that administration of telmisartan, an established suppressor of ERK 1/2, may reduce morbidity after CAS. Setacci et al. confirmed that CAS is a safe procedure in patients with symptomatic CS treated shortly after the onset of symptoms. They showed that CAS does not pose a risk of neurological complications, yields high success rate and it associated with very low postoperative incidence of minor cerebrovascular events. Aside from MMP-9, the authors of this study also determined serum levels of other markers, such as PAPP-A, Hs-CRP, IL-6, etc. Although the study showed an increase in serum concentration of MMP-9 that persisted for up to 30 days after CAS, the authors concluded that in contrast to PAPP-A, Hs-CRP and IL-6, this metalloproteinase is not an accurate marker of atherosclerotic plaque destabilization in patients subjected to CAS due to symptomatic CS. All three studies analysing MMP levels in CS patients treated by endarterectomy demonstrated a post-procedure increase in this marker. Interestingly, the authors of one of those studies, Gondalia et al., found a positive correlation between the levels of free radicals and MMP-9, which implies that this metalloproteinase may play a role in the pathophysiology of brain tissue damage. Aside from the level of free radicals, concentration of MMP-9 correlated also positively with the number of leukocytes (a source of metalloproteinases), presence of concomitant diabetes mellitus or contralateral stenosis. More advanced atherosclerosis is known to be associated with elevated metalloproteinase level) [27,28]. Similar findings were also reported by Ishigaki et al. who observed elevated levels of MMP-9 in the jugular bulb not only after the artery clamping, but also for at least 20 min after declamping. Moreover, they demonstrated that patients with transient post-procedure neurological deficits presented with significantly higher MMP-9 levels than healthy controls. This implies that MMP-9 may be an accurate marker of cerebral insult resulting from hypoperfusion during CEA. Furthermore, the authors emphasized that the increase in MMP-9 level in patients after CEA may result also from scalp ischaemia during clamping of the external carotid artery, even if blood was collected just above the confluence of the common facial vein [19,20].

A few recent studies addressed the problem of in-stent restenosis in patients after CAS [21]. However, the results of this research are inconclusive and it is still unclear if MMP-9 may be considered a marker of coronary restenosis. The only study analysing the issue in relation to carotid arteries has been conducted by Sapienza et al. According to these authors, an increase in MMP-9 level was the only independent predictor of in-stent restenosis in the carotid artery [20]. Importantly, concentrations of MMP during the late phase of in-sent restenosis were significantly higher than at earlier stages of the process. In-stent restenosis was associated with a decrease in TIMP levels. The authors speculated that the changes in MMP-9 and TIMP levels were associated with the release of growth factors and cytokines within the atherosclerotic plaques. They concluded that patients who require repeated intervention due to increased risk of in-stent restenosis may be identified based on the dynamics of their plasma MMP-9/TIMP levels.

Recently the discussion concerning relation between MMPs and inflammatory/immunological process within atherosclerotic plaque has been raised in publications. Eilenberg et al. observed that patients with atherosclerotic changes have significantly lower percentage of T lymphocytes in peripheral blood compared to the healthy volunteers. The authors found correlations between regulatory immune process and the level of MMP – downregulation of the enzymes level of MMP-9 and percentage of regulatory T cells [15]. Ammirati also stated that inflammatory/immune profile of the patients may play important role in the assessment of the risk of stroke [14,29]. Cytokines such as IL-6 and THFα are useful in prediction of plaque presence, whereas metalloproteins may be useful in prediction of its instability.

One potential limitation of this study may be a publication bias resulting from preferential publishing of the studies that documented the accuracy of MMP-9/TIMP as biomarkers. Furthermore, it should be remembered that the levels of MMP-9 documented by various authors might be also influenced by centre-specific differences in CAS and CEA techniques. There is still not enough evidence to conclude unequivocally that an increase in MMP-9 concentration and a concomitant decrease in TIMP level could become accurate markers of ongoing ischaemia. The systematic review of limited published data suggests that concentration of MMP-9 may reflect changes in brain circulation, such as hypoperfusion. However, still more evidence is needed to support the notion that MMP-9/TIMP are independent predictors of cerebrovascular events in patients with CS.

Conflict of interest

None declared.

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