EARLY RESETNOSIS AFTER CAROTID ENDARTERECTOMY: THE ROLE OF GROWTH FACTORS AND THE GENOTYPE OF MANNOSE-BINDING LECTIN

Theses

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Introduction

35-36 thousand new stroke events are diagnosed in Hungary every year, 80-85 % of which are of ischaemic origin. Surgery or stenting of the supraaortic arteries became important methods of stroke prevention in both symptomatic and asymptomatic cases. Since its introduction in 1989, eversion carotid endarterectomy became the gold standard in the treatment of the stenosos of the internal carotid artery. The number of operations is continuously increasing. Mid-term and long-term results are modified by restenosis formation, which can be myointimal hyperplasia or progression of the atherosclerosis on the operation field. Restenosis rate following eversion carotid endarterectomy is described as 2 to 34 % in the literature.

The denudation of the arterial endothelium during carotid endarterectomy and ischaemia reperfusion injury following crossclamping together initiate the inflammation process of the arterial wall. In consequence, growth factor production is upregulated and myointimal hyperplasia may initiate early restenosis. Experimental and cilical datas suggest that the inflammatory process may triggered by mannose binding lectin and the lectin pathway of the complement system. In a former study Rugonfalvi Kiss and his co-workers proved, that restenosis following eversion carotid endarterectomy is partially genetically determinated, and that genetic polymorphism of mannose-binding lectin (MBL) has a key role in the pathophysiology of this process. We couldn't find a study in the literature, that desribes a correlation between the frequency of carotid restenosis and the preoperative serum level or postoperative serum level changes of various circulating growth factors (Table 1).

Table 1
Distribution of carriers of normal and variant MBL genotypes in 17 and 29 patients, respectively, who had or had not at least 50% restenosis after carotid eversion endarterectomy operations.

Variable: MBL Genotypes	Patients With Restenosis, n=17 (%)	Patients With No Restenosis, n=29 (%)	P, χ^2 for Trend
A/A carriers	10 (59)	7 (24)	0.007
A/0 carriers	7 (41)	16 (55)	
0/0 carriers	0 (0)	6 (21)	

A/A vs *A/0+0/0*, χ^2, P=0.024.

Aims of the studies

We performed two studies with the following aims:

- In the first study we aimed *to define the restenosis rate of eversios carotid endarterectomy in a prospective study at our Department*. We supposed, that if our results are similar to those found in the literature, further investigations on the same population are suitible for widely acceptable conclusions.
- It is known, that PDGF has an important role in the development of atherosclerosis and cardiovascular diseases. *We studied if there is a significant correlation between the preoperative PDGF concentrations and their changes in the early postoperative period and the development of early restenosis after carotid endarterectomy.*
- VEGF has a key role in angiogenesis. In the second study *we searched for the correlation between the preoperative VEGF concentrations and their changes in the early postoperative period and the development of early restenosis after carotid endarterectomy.*
- EGF-receptors are present in the intimal smooth muscle cells of the atherosclerotic plaque. *We studied if there is a significant correlation between the preoperative EGF concentrations and their changes in the early postoperative period and the development of early restenosis after carotid endarterectomy.*
- Recently in a prospective study we found that the degree of early restenosis was significantly higher in patients homozygous for the normal genotype of mannose-binding lectin (MBL) as compared to patients who carried MBL2 variant genotypes. In the second study *the influence of the MBL2 genotype on the association between early postoperative changes in the levels of growth factors tested and the degree of restenosis was also investigated.*

Cosidering, that the work involves two independent studies, these are discussed separately.

Study I.
Long-term restenosis rate of eversion endarterectomy on the internal carotid artery

Since the first endarterectomy on the internal carotid artery was performed by deBakey in 1953, hundreds of thousands of patients have undergone carotid reconstruction worldwide. Eversion carotid endarterectomy described by Kasprzak and Raithel has become widely used since 1991 in our institution. Almost 9000 such operations have been performed in our department since then. The aim of this study was to define the long-term restenosis rate of eversion carotid endarterectomy.

Patients and methods

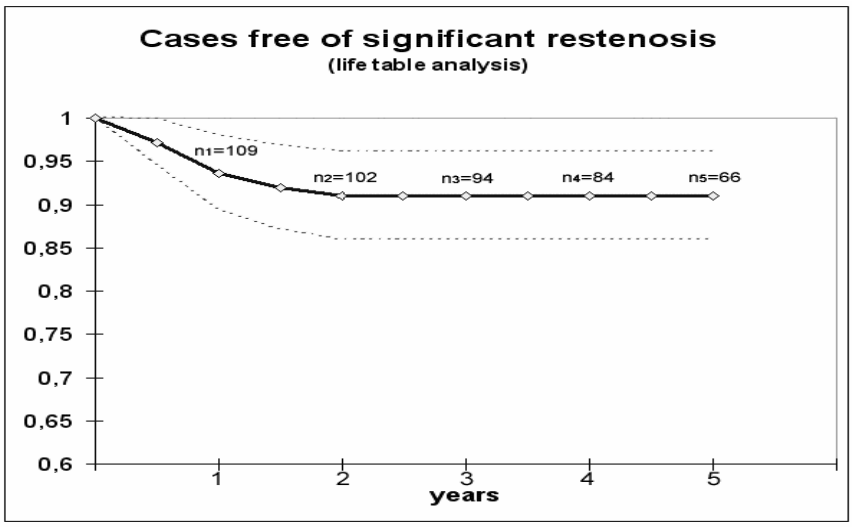
Between 1991 and 1993, 171 operations were performed on 151 patients by the same surgeon. Male-female ratio was 2:1, the average age of the patients was 63.4 (42-84) years. Cumulative perioperative stroke morbidity and mortality was 0.8 %. Patients underwent regular checkup in every 6 months. The percentage rate of restenosis calculated from velocity measurement was determined. Restenosis above 70 %, according to NASCET criteria, was considered as significant. The mean follow-up time was 56 months. Data were analized by life-table method. Survival data were compared to the age and sex matched Hungarian population. Patency rates were compared to data of patients in the literature, who underwent eversion and standard carotid endarterectomy. In cases of redo surgery patch plasty or PTFE interposition were performed. The rate of reoperations has decreased in the last 4-5 years, since percutaneous transluminal angioplasty has become the preferred choice of redo procedures.

Results

The perioperative combined stroke morbidity and mortality rate was 0.8 %. The 5-year patient survival rate was 85 %, the recurrent stenosis free rate and the recurrent significant stenosis rate were 88 % and 91 % at 5 years, respectively (Figure 1). The survival rate compared to the average population is similar in the endarterectomy group

than in the age and sex matched Hungarian population (85 % versus 82 % at 5 years). In the group of 11 patients having significant restenosis (9 %) only 2 had redo surgical procedures in 3 cases. Restenosis was detected in 4 patients at 6 month's control, in 4, 2 and 1 patients 12, 18, 24 months following endarterectomy, respectively. Indication for surgery was ipsilateral transient ischaemic attack (TIA) in one patient and bilateral high grade (>90 %) stenosis in the other. Ultrasound examinations indicated restenosis of greater than 50 % in 12 % of all cases (13 of 109 cases). Ultrasound plaque morphology showed intimal thickening typical of myointimal hyperplasia without significant calcification except in one case where the echodensity suggested calcification. Histological examination in the redo surgical cases showed myointimal hyperplasia.

Figure 1. Survival free from significant restenosis following eversion endarterectomy of the internal carotid artery (the number of sudied cases in postoperative year 1-5 were 109, 102, 94, 84 and 66, respectively, the interrupted lines show 95 % confidence intervals).



Discussion

Early restenosis following carotid endarterectomy is due to either myointimal hyperplasia or residual stenosis. In cases of early restenosis, clinical symptoms are found only in 1-2 % of the patients, because the neointimal layer is smooth, not thrombogenic, or embologenic. Symptoms in patients with neointimal hyperplasia are usually due to absence of proper collateral circulation, or are results of haemodynamic

changes. According to the literature, the occurence of restenosis following carotid reconstructions is related to the closing method of the arteriotomy. Our early data published previously show a 3.9 % significant restenosis rate after a 27 months follow-up in the 80 first cases after introducing the eversion technique. The results of some multicentric trials indicate restenosis rates of 0,3 % to 3,6 % after 15-23 months of follow-up time.

The 9 % restenosis rate after five years in our study is acceptable, considering the effects of the learning curve. We could not find a single study with longer follow-up period, than ours (56 months average). Our study lacks a comparison performed by conventional methods, because the eversion technique has become dominant in the last ten years.

Our reoperation rate (2.7 %) is comparable to that of some centers (1.2 to 3.6 %). The survival rate of the average Hungarian population of the same age group is similar than the survival rate found in our operated group (82 % versus 85 % at 5 years).

Significant restenosis after carotid surgery is not a clear indication for redo surgery, because it is rarely symptomatic. In our experience reintervention is indicated in symptomatic cases only, or when an explicit progression is found in cases of 90 % restenosis or higher. Our previous results show higher complication rates in redo surgery than in primary cases. In cases of redo procedures patch plasty or PTFE interposition is performed.

Conclusions

The perioperative morbidity data and the late results in our institution are comparable to those of multicentric studies. Our five year restenosis rate (9%) seems acceptable and encouraging for the future. The ultrasound and the histological findings suggest the atherosclerosis does not play a significant role in the development of restenosis after the eversion method. Corresponding to the results of prospective clinical studies our data indicate that eversion endarterectomy on the internal carotid artery is safe, effective and durable, thus may become the standard procedure for the treatment of significant carotid artery stenosis.

Study II.

Early raise in serum VEGF and PDGF predisposes for restenosis after eversion endarterectomy in patients with a normal MBL2 genotype

Growth factors could have a direct pathophysiological role in the formation of early restenosis. Platelet derived growth factor (PDGF) was found to be the main factor responsible for proliferation of vascular smooth muscle cells. Vascular endothelial growth factor (VEGF) is able to promote growth of vascular endothelial cells derived from arteries and veins and an angiogenic response in different in vivo models. Epidermal growth factor (EGF) is a very potent proliferation stimulator of various epithelial cell types and, in a lesser extent, of smooth muscle cells.

Recently in a prospective study by Rugonfalvi Kiss and his co-workers, performed in patients with severe carotid atherosclerosis was found that the degree of early restenosis was significantly higher in patients homozygous for the normal (A/A) genotype of mannose-binding lectin (MBL) as compared to patients who carried MBL2 variant genotypes. They found significant difference in restenosis rate among men and women only in presence of normal MBL2 genotype.

No data on the relationship between the incidence of restenosis and the preoperative levels or early postoperative changes of the circulating levels of different growth factors have been reported. Therefore we studied if there is a significant correlation between the preoperative PDGF, EGF and VEGF concentrations and their changes in the early postoperative period on one hand and the development of marked (>50%) restenosis over the follow-up period of 14 months duration on the other hand. The influence of the MBL2 genotype on the association between early postoperative changes in the levels of growth factors tested and the degree of restenosis was also investigated.

Patients and methods

In this prospective study a total of 82 consecutive patients (55 men, 27 women, 66.2 ± 8.9 (mean ± S.D.) years old) with severe (mean: 83.1 ± 9 %) stenosis of carotid artery undergoing elective eversion carotid endarterectomy between October 2000 and March 2003 were included and followed-up. The study protocol was approved by the Institutional Review Committee at Semmelweis University in Budapest and the subjects gave informed consent.

Indication for carotid eversion endarterectomy was in accordance with American Heart Association guidelines. Out of the 82 patients 26 (31.7%) were asymptomatics, 43 (52.4%) had TIA,11 (13.4%) had minor stroke and only 2 (2.4%) had major stroke. The patients with TIA were operated within one months of the onset of the symptoms. The patients with stroke were operated on after 4-8 weeks of the last insult, with CT without fresh ischemic signs . The operation and the clinical and radiological follow-up were performed as described earliel. Carotid duplex scan (CDS) sonography was undertaken at 5.7 (4.6-8.0) weeks (in the following: 6 weeks), 6.8 (6.2-7.9) months (7 months), and 13.8 (12.3-19.0) months (14 months), respectively. Two patients died during the observation period, one before the 7-month and one before the 14-month visit, respectively. All carotid duplex scans were performed by an experienced radiologist. The common carotid, internal carotid and external carotid arteries on both sides were examined in the standard fashion. We recorded the peak systolic velocity (PSV) and the end diastolic velocity (EDV) in the common carotid artery (CCA), in the internal (ICA) and the external carotid arteries (ECA). The spectral measurements were taken with a doppler angle of 55 to 65°. The diagnostic criteria for internal carotid artery stenosis and restenosis were based on peak systolic velocities and end diastolic velocities as well as internal carotid artery:common carotid artery ratios. The velocity spectra of the ICA were further categorized as mild (<50%), moderate (50-69%) and severe (≥70%).

Blood samples were drawn preoperatively and 4 (3-5) days (median (interquartile range)) after the operation. Serum was separated and stored immediately at -80°C. EDTA-anticoagulated blood samples were obtained for DNA preparation preoperatively.

Serum concentrations of total cholesterol and triglycerides (Roche/Hitachi), HDL-

cholesterol and LDL-cholesterol (Human, Wiesbaden, Germany) were measured in a Cobas Mira Plus clinical chemistry analyzer. Serum concentrations of VEGF, EGF and PDGF-AB were determined by commercial ELISA methods using the Quantikine human VEGF, EGF and PDGF-AB kits (R&D Systems, Minneapolis, MN).
Total genomic DNA was extracted from white blood cells using the method of Miller. Determination of the alleles of the *MBL2* gene and the regulatory promoter variants were performed by PCR using sequence specific priming (PCR-SSP) as described.
Statistical analyses were made using GraphPad Prism V 3.0 for Windows software package (GraphPad Software, San Diego California USA). Non parametric tests were used for group comparison. Comparison of categorical variables was done with Fisher`s exact test. Multiple regression analysis was done with the SPSS 10.0 (SPSS Inc., Chicago , IL) software. Values are presented as median (25th-75th percentile), unless otherwise stated.

Results

Relationship between the preoperative growth factor levels and the extent of carotid stenosis

We had a perioperative duplex control after 6 weeks of the operations and we could not find any residual stenosis. At 6 months marked restenosis as defined as >50% was observed in 9 patients, and at 14 months in 12 patients. Out of these patients clinically significant (>70%) restenosis was observed in the same four patients (4/82=4.9%) at both 6 and 14 months. There was no correlation between the preoperative or postoperative levels of any growth factor and the degree of carotid stenosis measured on the side of operation or on the contralateral side by CDS.

Changes of PDGF, VEGF and EGF concentration in early postoperative period

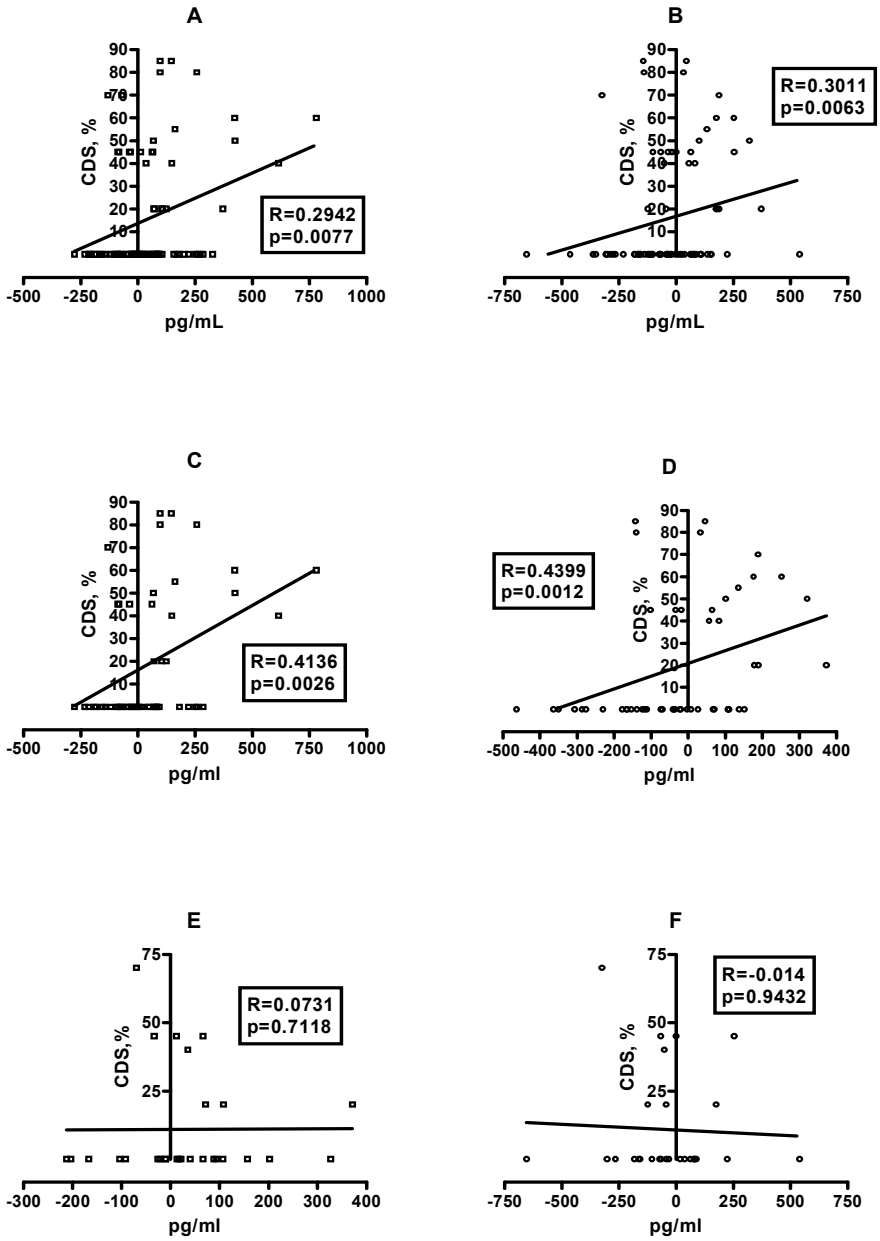
Serum PDGF, VEGF and EGF levels were measured in the samples obtained from the patients before operation and 4 days post surgery. Direction of the changes in growth factor concentrations varied patient-by-patient. When we divided the group of patients

by the presence of marked (>50%) restenosis at 7 months, increase in VEGF levels occurred significantly (p=0.0044) more frequently in patients with than in those without subsequent marked early restenosis, in the case of PDGF a similar tendency (p=0.0653) was found while no such difference occurred with EGF. There were no differences between symptomatic and asymptomatic patients between the early postoperative changes of VEGF (p=0.209) or PDGF (p=0.248) levels.
Since these findings suggested an association between early VEGF and PDGF increment and restenosis, we evaluated further our data in this direction, considering MBL2 genotypes carried by the patients as well.

Correlation between the changes of VEGF and PDGF serum concentrations and the CDS values measured 7 months and 14 months post surgery is restricted to the patients carrying the normal MBL2 (A/A) genotype

The extent of the early postoperative increase in both VEGF and PDGF levels (in the following: ΔVEGF and ΔPDGF) significantly correlated to the 7 months CDS values (Figure 2, panels A and B), while its correlation to the CDS values measured at the end of the follow- up period (14 months) was not found to be significant.
The patients were divided into two groups according to their MBL2 genotype. Group 1: (MBL2 genotype: *A/A*) 53 patients homozygous for the normal MBL2 allele Group 2 (MBL2 genotypes: *A/O* or *O/O*) .29 patients who carried the variant allele as heterozygotes or homozygotes. When the relationship between the extent ΔVEGF and ΔPDGF values and the 7 months CDS values (Figure 2, panel C and D) or 14 months CDS values were analyzed highly significant Spearman correlation coefficients were found at both time points of follow up in Group 1 (Figure 2, panels C and D). By contrast, no correlation was found in the patients of Group 2. (Figure 2, panels E and F).

Figure 2. Correlation of the early (4 days – before surgery) changes in the serum VEGF (left panel) and PDGF (right panel) levels and to the carotid Doppler scan values measured 7 months postsurgery in all patients (A,B), patients carrying only the normal *A/A* (C,D) or only the variant *O/O* or both the variant and normal alleles (*A/O*) (E,F) of MBL2.



Clinically significant (>50%) restenosis is predicted by the pronounced increase in VEGF and PDGF levels only in patients with A/A MBL2 genotype

The patients were divided into two subgroups according to the degree of ΔVEGF or ΔPDGF values (Table 2). The odds ratio of the patients with high versus low (≤90 pg/ml vs >90 pg/ml) ΔVEGF (Table 2) values to develop marked restenosis (CDS>50%) was calculated by logistic regression analysis adjusted to age, gender and preoperative BMI values.

The odds ratio of the MBL2 *A/A* genotype carrying patients with high versus low early ΔVEGF was 16.69 (1.86-149.61, p=0.012) and 20.00 (2.25-177.63, p=0.007) for the 7 months and 14 month CDS values, respectively. By contrast,marked (>50%) restenosis occurred rarely in patients with MBL2 *A/O* or *O/O* genotypes, and no significant difference between patients with low and high ΔVEGF was found in this group (Table 2).

We found less marked but significant risk of marked restenosis in patients who exhibited pronounced (>30 pg/ml) ΔPDGF values, with adjusted odds ratios of 7.21 (1.04-49.63) (p=0.045) and 9.23 (1.45-58.70) (p=0.019), respectively.

Discussion

We found that early marked restenosis as defined as >50% in carotid arteries after eversion endarterectomy occurs with high probability in patients who are homozygous for the normal MBL2 *A* allele and exhibit a marked elevation (in the upper tertile of whole group) in serum VEGF and/or PDGF levels on day 4 postsurgery. In contrast, restenosis occurred much less frequently in patients who carried variant MBL2 *O* alleles or showed a low early VEGF and/or PDGF increase. According to our unpublished study high VEGF and PDGF levels observed at 4 days postsurgery remained elevated in most patients at least till the next (6 weeks) follow-up visit. Odds ratio for restenosis adjusted for possible confounding variables at 7 months and 14 months was more than 16 and 20, respectively for the high vs. low early increase in serum concentration of VEGF, and a similar albeit lower odds ratios were found for the early PDGF increase.

By contrast we did not find significant correlation between the early changes of EGF and restenosis.

We found no significant differences between the patient groups with or without restenosis according to their clinical parameters, risk factors and 14-months carotid duplex scan values.

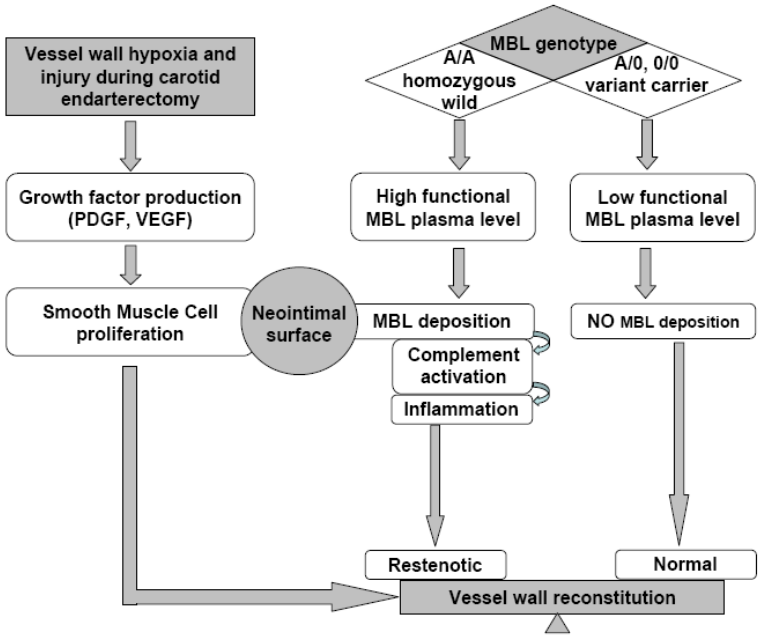
Table 2. Prediction of clinically significant (>50%) restenosis on the basis of high (in the highest tertile) early increment (4 days post surgery) of serum VEGF concentration in patients with normal (*A*) and variant (*O*) alleles of mannose-binding lectin (MBL2).

	Patients with *A/A* MBL2 genotype		Patients with *A/O* or *O/O* MBL2 genotypes++		All patients	
Restenosis	≤50%	>50%	≤50 %	Restenosis	≤50%	>50%
7 MONTHS POSTSURGERY						
ΔVEGF LOW*	31	1	21	ΔVEGF LOW*	31	1
ΔVEGF HIGH**	13	7	7	ΔVEGF HIGH**	13	7
Unadjusted OR (95% CI) (P value)	16.69 (1.86-149.61) (0.012)		0.956 (0.035-26.11) (1.000)		9.10 (1.74-47.57) (0.009)	
Adjusted+ OR (95% CI) (P value)	19.09 (1.77-211.35) (0,010)		Cannot be calculated		8.06 (1.45-44.75) (0.017)	
14 MONTHS POSTSURGERY						
ΔVEGF LOW*	30	1	19	ΔVEGF LOW*	30	1
ΔVEGF HIGH**	12	8	7	ΔVEGF HIGH**	12	8
Unadjusted OR (95% CI) (P value)	20.00 (2.25-177.63) (0.007)		0.371 (0.017-8.09) (0.558)		5.16 (1.39-19.15) (0.014)	
Adjusted+ OR (95% CI) (P value)	27.73 (2.42-317.26) (0.008)		Cannot be calculated		5.50 (1.41-22.45) (0.014)	

*≤90 pg/ml, **>90 pg/ml, +adjusted to age, gender and BMI of the patients, ++Odds ratios

These novel findings extend our previous results obtained in the same patients' population where Rugonfalvi Kiss and his co-workers reported a dramatically decreased risk of developing restenosis after carotid eversion endarterectomy in patients carrying variant MBL O alleles. A possible conceptual mechanism of the events, which lead to restenosis is suggested in Figure 3. The intimal injury caused by eversion carotid endarterectomy, and the ischaemia/reperfusion injury caused by crossclamping of the carotid artery together initiate the release of PDGF and VEGF. Both growth factors are essential for smooth muscle proliferation, migration and matrix formation and for triggering neointimal hyperplasia giving rise to a vicious circle resulting in restenosis. In addition, activation of the lectin route of complement initiated by MBL binding to intracellular components from endothelial cells, has been shown to occur during ischaemia/reperfusion injury. As a result of subsequent complement activation highly potent activation products are generated which may also release PDGF and activate smooth muscle cells and macrophages. Our findings indicate that both growth factor release and complement activation are necessary for restenosis development (Figure 3).

Figure 3. Putative relationship between MBL2 polymorphisms, serum level of growth factors and myointimal proliferation leading to restenosis after carotid endarterectomy.



Conclusions

In conclusion, our present findings definitely indicate that – at least after eversion type carotid endarterectomy – restenosis occurs primarily in patients who are homozygous for the wild MBL2 allele (A/A), a genotype associated with high MBL levels, and marked complement activating capacity in conjunction with an upregulation of PDGF and VEGF production in the early postoperative period. Our findings support the results of Rugonfalvi Kiss and his co-workers published earlier in a prospective study. They found that in patients with severe carotid atherosclerosis the degree of early restenosis was significantly higher in patients homozygous for the normal genotype of MBL2 as compared to patients who carried MBL2 variant genotypes. No data on the relationship between the incidence of restenosis and the preoperative levels or early postoperative changes of the circulating levels of different growth factors have been reported. No significant differences between the presence of risk factors and restenosis formation was found in the patient groups.

During eversion endarterectomy the intima is denudated, and crossclamping of the artery leads to ischaemia/reperfusion injury. These impacts result in a pathological process initiating the release of growth factors, finally resulting in neointimal hyperplasia and early restenosis formation. In addition, activation of the lectin route of complement initiated by MBL binding to intracellular components from endothelial cells, has been shown to occur during ischaemia/reperfusion injury. Patients carrying variant MBL2 alleles have a markedly decreased MBL serum level, which has a protective role against the development of restenosis according to our findings.

This is a clearly hypothesis generating study, conclusions of which should be supported in different cohorts. A such study is underway in our departments.

Novel findings

- We could not find a single study, regarding to the development of restenosis following eversion carotid endarterectomy, with longer follow-up period, than ours.
- Corresponding to the results of prospective clinical studies our data indicate that eversion endarterectomy on the internal carotid artery is safe, effective and durable, thus may become the standard procedure for the treatment of significant carotid artery stenosis.
- The perioperative morbidity data and the late results in our institution are comparable to those of multicentric studies, therefore further investigations on the same population are suitible for widely acceptable conclusions.
- No data on the relationship between the incidence of restenosis and the preoperative levels or early postoperative changes of the circulating levels of different growth factors have been reported.
- Restenosis occurs primarily in patients who are homozygous for the wild MBL2 allele (A/A) according to our findings.
- Patients carrying variant MBL2 alleles (A/O or O/O) have a markedly decreased MBL serum level, which has a protective role against the development of restenosis.
- Our findings indicate that both growth factor release (VEGF and/or PDGF) and complement activation are necessary for restenosis development.
- We did not find significant correlation between the early changes of EGF and restenosis.

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