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The -94Ins/DelATTG Promoter Polymorphism in the Transcription Factor NF-Kb in Patients with Popliteal Aneurysm

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Abstract

Background: Popliteal aneurysms, with a frequency of 85% of all peripheral aneurysms, have a poor prognosis with a high amputation frequency. Up to now, the -94Ins/DelATTG promoter polymorphism in the transcription factor NF-κB has been assumed to be involved in its pathophysiology. The aim of this study was to investigate the role of this genetic variant in patients with popliteal aneurysm.

Patients and methods: In total, 48 patients with popliteal aneurysm (44 males, mean age 74.5 years) and 49 healthy controls (19 males, 51.5 years) were enrolled in the study. The duplex sonographic diagnosis of popliteal aneurysm was verified in each patient by CT angiography. Popliteal aneurysms were diagnosed when the diameter of the affected vessel was at least 15 mm. In subjects of the control group, duplex examination excluded the diagnosis of popliteal aneurysm. Smoking history, arterial hypertension, diabetes mellitus, hyperlipoproteinemia (HLP), hyperuricemia, coronary heart disease (CHD) and carcinoma were recorded as comorbidities. For the NF-κB polymorphism, the -94Ins/DelATTG polymorphism (rs28362491) in the NF-κB gene was investigated.

Results: With 50.5%, the id genotype of -94Ins/DelATTG polymorphism was the most frequently encountered genotype (46.9% in the control group versus 54.2% in patients with popliteal aneurysm). At second position, the genotype ii followed with 35.1% (36.7% in the control group versus 33.3% in patients with popliteal aneurysm) and genotype dd with 14.4% (16.3% in the control group versus 12.5% in patients with a popliteal aneurysm). However, there was no significant difference in the distribution of genotypes. In the case of allele distribution, with 60.2% for allele i in the control group and 60.4% for allele i in patients with a popliteal aneurysm, and for allele d in 39.8% of the control group and 39.6% in patients with a popliteal aneurysm no significant differences could be found. Binary logistic regression analysis showed a clear association only between male gender and smoking with popliteal aneurysm but not for the -94Ins/DelATTG genotypes.

Conclusion: In contrast to male gender and smoking habits, no significant differences in the geno distributions of -94Ins/DelATTG polymorphism were detected with respect to the diagnosis of popliteal aneurysms.

Keywords: NF-kB Promoter Polymorphism; Popliteal Aneurysm

Introduction

Popliteal artery aneurysms are the most common peripheral artery aneurysms and account for 85% of all cases. They are often associated with abdominal aortic aneurysms (40 to 50%) and are frequently bilateral (25% to 70%) [1-3]. Well-established risk factors include smoking, atherosclerosis, and connective tissue disorders such as Marfan and Ehler-Danlos syndromes. Non-modifiable risk factors are advanced age, male gender, Caucasian race, and family history of an aneurysmal disease [2,4]. Heart disease and stroke have also been reported to be more commonly found in this patient group [5-7]. Vascular inflammation is a crucial pathological event in aneurysm formation [8-10]. Furthermore, chronic inflammation in the media and adventitia also plays a key role in the pathogenesis of aortic aneurysm [9].

In angiotensin II-infunded mice, aneurysmal tissues are characterized by the recruitment and infiltration of monocytes/macrophages, proliferation of smooth muscle cells (SMCs), degradation of extra-cellular matrix components including elastin and collagen, and increments in expressions and activities of matrix metalloproteinases (MMPs) [11,12]. Transgenic mice overexpressing the dominant-negative form of IκBα under the Tie2 promoter/enhancer (E-DNIκB mice) exhibited functional inhibition of NF-κB signalling specifically in the endothelium which prevented obesity- and age-related insulin resistance and enhanced longevity [13]. Osteopontin up-regulates the expression of MMP and urokinase-type plasminogen activator (uPA) via the NF-κB signaling pathway, thereby accelerating the degradation of extracellular matrix and playing an important role in the pathogenesis and development of aortic aneurysms [14]. On other site, treatment with pyrrolidine dithiocarbamate, an antioxidant inhibitor of NF-κB, inhibited elastase-induced experimental aneurysms in the mouse, along with suppression of aortic wall NF-κB and activator protein 1 (AP1) transcription factor activities, reduced expression of proinflammatory cytokines, and suppressed MMP-9 activity [15]. MicroRNAs (miRNAs) miR-195 suppressed abdominal aortic aneurysm through the TNF-α/NF-κB and VEGF/PI3K/Akt pathway [16]. It has been postulated that the NFKB1 -94ins/del ATTG polymorphism may contribute to the risk of developing intracerebral aneurysms [17]. The aim of this study was to investigate the association of NF-κB polymorphisms in the development of popliteal aneurysms.

Materials and Methods

Patients

On the basis of a-priori power calculations with an alpha level of α=0.01 with a mean effect strength of w=0.25 and taking into account a power of 0.80, we recruited 48 patients with a popliteal aneurysm (44 male with 74.5 years, and 4 females with 78.2 years) and 49 individuals without popliteal aneurysm as a control group (19 male and 30 female). Duplex sonographic diagnosis of popliteal aneurysm was verified in each patient by CT angiography using 3 mm slices. For the diagnosis of popliteal aneurysm, the measurement specification was set according to Wright et al. (18) with a popliteal artery diameter of at least 15 mm. All patients with a popliteal aneurysm larger than 15 mm and all symptomatic aneurysms were included in this study. In subjects of the control group, aneurysm was excluded by a color- coded duplex examination of the popliteal artery. The popliteal artery was described as normal in males with a size smaller than 1.1 mm and in females smaller than 0.8 mm, following in accordance with Wolf et al. Furthermore, aneurysms in the femoropopliteal junction and suture aneurysms after peripheral revascularization were excluded from the study. Patients with popliteal aneurysm were significantly older than subjects without this disease (71.5 vs. 47.8 years, $p<0.0001$). The characterization of patients and control group is shown in Table 1.

Table 1: Characterization of the study cohort

	Popliteal aneurysm (P) (n=48)		**Control group (V) (n=49)**	
	male	female	male	female
Age	44 (74.5 years)	4 (78.25 years)	19 (51.5 years)	30 (51.6 Years)
Nicotin, active	28 (63.6 %)	2 (50.0%)	9 (47.3%)	15 (50.0%)
Ex-nicotin	16 (36.4 %)	0	0	0
Hypertension	44 (100%)	2 (50%)	3 (15.7%)	3 (10.0%)
Diabetes	11 (25%)	1 (25%)	0	0
Hyperlipo proteinaemia	23 (52.2%)	1 (25%)	0	1 (3.3%)
Hyperuricaemia	3 (6.8%)	0	0	0
CHD	20 (45.4%)	1 (25%)	0	1 (3.3%)
Carcinoma	10 (2.3%)	2 (50.0%)	1 (5.2%)	1 (3.3%)
Renal insufficiency	7 (15.9%)	0	0	0
COPD, emphysema	6 (13.6%)	0	0	0

Continous variables are presented as mean + standard deviation. Categorical variables are presented as an absolute percentage. Abbreviations: CHD: Corona Heart Disease, COPD: Chronic Obstructive Pulmonary Diasease

Genetic Analysis

The Ethics Committee of the University of Göttingen has approved the performance of genetic tests of the -94 ins/delATTG promoter polymorphism in the transcription factor NF- kB on patients in this study. For genetic investigations, fresh venous EDTA-anticoagulated blood was obtained from study participants. Preparation of genomic DNA was carried out using

a QIAamp blood extraction kit (Qiagen) in accordance with the manufacturer´s instructions. Genotyping of the -94Ins/DelATTG polymorphism in the NF-κB gene was performed using fragment length analysis (forward primer 5′-tgg acc gca tga ctc tat ca-3′; reverse primer 5′-gaa tcc caa ggg ctg ga-3′). PCR amplification was performed in an Eppendorf Mastercycler Gradient (2 min at 95° C; 12 cycles of 30 s at 92° C, 30 s at 55° C, 30 s at 72° C; 21 cycles of 30 s at 94° C, 30 s at 50° C, 30 s at 72° C, 5 min at 72°C, 10°C hold). The DNA fragments were separated by electrophoresis through a polyacrylamide (PAA) gel (PAA gel: Crosslinker concentration = 10.4%, Total acrylamide– bisacrylamide monomer concentration = 3.7%) and visualized by silver staining [17]. For every PCR amplification, 25 µL of a mastermix containing 1 U of Taq polymerase (Invitek, Berlin, Germany), 50 ng of genomic DNA, 1% formamide and PCR reaction buffer was added.

In the case of allele distribution, the number of chromosomes, rather than the number of test persons, forms the basis for calculation. Chromosome number= number of test persons x 2 = 97x2= 194 chromosomes.

Statistical analysis

The statistical analyses were performed using the computer program SPSS for Windows Version 17.0 (IBM). Metric data were tested for normal distribution using the Kolmogorov- Smirnov test and for variance homogeneity using the Levene test. The Student t-test for normal distribution and the Mann-Whitney U-test for non-normally distributed variables were used for independent samples. Categorical data were analyzed in contingency tables using the Pearson Chi-square test with Yates correction. For the genotype-phenotype association studies, recessive, dominant and co-dominant genetic models were tested as hypotheses. Binary logistic regression (stepwise forward) was used to study the influence of genetic polymorphism on the development of a popliteal aneurysm. In general, $p < 0.05$ was defined as statistically significant. The calculation of the Hardy-Weinberg distribution of the examined genotypes was performed with the help of the Excel program from Microsoft Office.

Ethics

The Ethics Committee of the University of Göttingen has approved the performance of genetic tests of the -94 ins/delATTG promoter polymorphism in the transcription factor NF-kB on patients in this study (reference: 31/3/17).

Results

Association of male gender, age and smoking for diagnosis of popliteal aneurysm

The popliteal aneurysm occurs predominantly in men (93.8% versus 6.3%, p<0,0001). The risk for men to develop a popliteal aneurysm is: Odds ratio = (unadjusted) 25.6 (95% confidence interval 7.0 to 100). The majority of patients were or are still active smokers (22.9% or 68.8% versus 8.3%, (p<0.0001). The unadjusted risk for prevalence of popliteal aneurysm is: OR=8.8 (95% confidence interval 2.7 to 28.6) (Table 2).

Table 2: Association of male gender, age and smoking for diagnosis of popliteal aneurysm

	V (control group without aneuryms) N=49	**P with popliteal aneurysms N=48**	***p*-value**
Gender	% within diagnosis	% within diagnosis	
female	31 (63.3%)	3 (6.3%)	
male	18 (36.7%)	45 (93.8%)	< 0.0001
Ex	5 (10.2%)	11 (22.9%)	
Smoking	21 (42.9%)	33 (68.8%)	< 0.0001
No smoking	23 (46,9%)	4 (8.3%)	

Ex: ex smoking
Popliteal aneurysm occurs predominantly in male patients and in smokers.

Allele distribution i or d allele

The allele i was found in 60.2% of the control group and 60.4% in patients with a popliteal aneurysm, the allele d in 39.8% of the control group and 39.6% in patients with a popliteal aneurysm. No differences in the allele distribution i and d between patients with a popliteal aneurysm and the control group were found (Table 3).

Table 3: Distribution i or d allele

	V N=49 (control group without aneuryms)	**P N=48 (patient with aneuryms)**	***p*- value**
i (n=117, 60.%)	59 (60.2%)	58 (60.4%)	
d (n=77, 39.7%)	39 (39.8%)	38 (39.6%)	
			1.0
Odd ratio (95% CI)	0.996 (0.749-1.323)	1.004 (0.751-1.344)	

No differences in the allele distribution i and d between patients with a popliteal aneurysm and the control group.

Distribution of NF-κB genotypes

Table 3 shows the distribution of NFkappaB genotypes in patient and control group. Genotype id is the most frequently encountered genotype with 50.5% (46.9% in the control group

versus 54.2% in patients with popliteal aneurysm). Genotype ii follows with 35.1% (36.7% in the control group versus 33.3% in patients with popliteal aneurysm). Genotype dd was found least frequently with 14.4% (16.3% in the control group versus 12.5% in patients with a popliteal aneurysm). However, there was no significant difference in the distribution of genotypes between the two groups (Table 4).

Table 4: Distribution of NF-κB genotypes

	V N=49 (control group without aneuryms)	P N=48 (patient with aneuryms)	*p*- value
ii (n=34, 35.1%)	18 (36.7%)	16 (33.3%)	
id (n=49, 50.5%)	23 (46.9%)	26 (54.2%)	
dd (n=14, 14,4%)	8 (16.3%)	6 (12.5%)	
			0.749

Genotype constellations in relation to the popliteal aneurysm

The summary of genotypes with deletion ii versus di + dd is shown in Table 5. The genotype ii was detected in 18 subjects of the control group (36.7% within diagnosis) and 16 of the patients with a popliteal aneurysm (33.3% within diagnosis). The genotype di + dd was found in 31 subjects of the control group (63.3% within diagnosis), and in 32 patients with a popliteal aneurysm (66.7% % within diagnosis). Also, for the distribution of genotype constellations ii versusu di+dd, id versus ii+dd, dd versus ii+id, id versus ii+dd and dd versus ii+id no significant differences could be found between healthy volunteers and patients with a popliteal aneurysm (Table 5).

Table 5: NF-κB genotype constellations in relation to the popliteal aneurysm

	V N=49 (control group without aneuryms)	P N=48 (patient with aneuryms)	*p*- value
ii (n=34, 35.1%)	18 (36.7%)	16 (33.3%)	
di + dd (n=63, 64.9%)	31 (63.3%)	32 (66.7%)	
del vs. ins (ii/di+dd)			*0.832*
ii + dd (n=48, 49.5%)	26 (53.1%)	22 (45.8%)	
id (n=63, 64.9%)	23 (49.6%)	26 (54.2%)	
id vs. others			*0.545*
ii + id (n=83, 85.6%)	41 (83.7%)	87.5%)	
dd (n=14, 14.4%)	8 (16.3%)	6 (12.5%)	
dd versus others			*0.774*

Odd ratio (95% CI)	V N=49 (control group without aneuryms)	P N=48 (patient with aneuryms)
del vs. ins (ii/di+dd)	1.076 (0.718-1.612)	0.926 (0.602-1.426)
id vs. others	1.154 (0.777-1.714)	0.864 (0.576-1.295)
dd versus others	0.864 (0.523-1.430)	1.181 (0.622-2.242)

No significant differences in NF-κB genotype constellations between healthy volunteers and patients with a popliteal aneurysm

Influence of age, sex, smoking, NF-κB genotypes on the diagnosis popliteal aneurysm, multivariate analysis with binary logistic regression

The multivariate analysis with binary logistic regression shows a clear dependence on the male sex and age with regard to the influence of age, smoking, gender and NF-κB genotypes both in the overall group and under different genotype combinations. Nicotine abuse and NF- κB genotypes have no influence on the popliteal aneurysm (Table 6).

Table 6: Influence of age, male gender, smoking and NFkappa B genotypes for diagnosis of popliteal aneurysm

	Regression coefficient B	Standard error	Sig.	Odds ratio
Gender male	-3.978	1.358	0.003	0.019
age	0.240	0.063	0.000	1,272
all smokers (currently +ex)	1.146	1.180	0.331	3.145
NFkappaB genotypes ii versus others	-0.031	0.653	0.963	0.970
NFkappaB genotypes id versus others	-0.432	0.909	0.635	0.649
NFkappaB genotypes dd versus others	0.340	1.229	0.782	1.405

No influence of NF-κB genotypes on the popliteal aneurysm

Discussion

In this study we investigated the influence of NF-κB polymorphism -94ins/del ATTG especially the distribution of allele i and d and genotypes ii, id and dd of the NF-κB gene on popliteal aneurysm. For the allele i and d we could not detect any statistically relevant distribution differences (60.2% in control group versus 60.4% for allele i in patients with a popliteal aneurysm, and 39.8% for allele d patients with a popliteal aneurysm versus 39.6% in control group). The distribution of genotypes showed no significant differences for deletion ii versus id+dd (36.7% for ii in control group and 33.3% in in patients with popliteal aneurysm, versus 63.3% for ii + dd within in control group versus 66.7% in patients with popliteal aneurysm. control group. The risk of popliteal aneurysm is independent of NF-κB genotype polymorphism.

Functional polymorphisms of the NF-κB 1 gene play a crucial role in etiology of dilated cardiomyopathy [19], of epithelial ovarian cancer [20], of papillary thyroid carcinoma [21], and of coronary artery disease [22].

In the pathogenesis of aneurysms, the malfunction of endothelial cells initiated by deviation of normal wall shear stress (WSS) was identified as a key factor [23]. An increase of WSS above 15 dyne/cm2) leads to an increased activity of PGE2, EPN2, COX 2 and nuclear factor kappa B. A special role is played by the activation of factor NF-κB, which itself initiates inflammatory cell adhesion via the expression of vascular cell adhesion molecule-1 (VCAM- 1), intracellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1) [23]. A down- regulation of NF-κB expression by inhibition of COX-2 or EP2 is associated with a reduced incidence of CA formation [24,25]. In experimental studies, the blocking of intracellular Nf-kB signaling led to inhibition of intimal hyperplasia and the migration and accumulation of smooth muscle cells [26,27].

In the etiology of intracranial aneurysms (IA) a clear association between NF-κB 1 -94 insertion/deletion ATTG polymorphism was found. Whereas NF-κB 1 -94ins/del ATTG polymorphism represents an increased risk for intracranial aneurysms, a significantly decreased risk of IA was observed in the ATTG1/ATTG2 and ATTG2/ATTG2 genotypes compared with the ATTG1/ATTG1 genotype ATTG1/ATTG2 vs. ATTG1/ATTG1 (odds ratio [OR]=0.58, 95% confidence interval [95% CI]=0.39-0.87, p=0.007; ATTG2/ATTG2 vs. ATTG1/ATTG1: OR=0.12, 95% CI=0.06-0.23, p<0.001, and also the ATTG2 allele, ATTG2 vs. ATTG1: OR=0.41, 95% CI=0.32-0.54, p<0.001) [19]. Beyond the role of NF-κB signalling in the endothelium as the key step in aortic aneurysm formation, a clear association was determined between AAA and the thoracic aneurysm genes ACTA2, COL3A1, EFEMP2, FBN1, MYH11, MYLK, SMAD3, TGBF2, TGFBR1, TGFBR2, and MTHFR [28]. The AAA risk allele was identified in LRP1 and SORT1 [29], DAP21P [30], ANRIL [31] and SORT1 [32].

Genetic studies on popliteal aneurysms have so far only been performed in cases of coincidence with an aortic aneurysm [33,34]. In such constellations the Marfan gene fibrillin 1 mutation was identified as the main finding [35]. A novel variant in FBN1 presenting with Bilateral Popliteal Artery Aneurysm was found in patients with Marfan syndrome in the presence of general aneurysm [36].

Apart from ACE-receptor polymorphism, mutations of PKD1/2, COL4A1, FBN1, EFEMP2, TGFBR1/2, MYH11, ACTA2, COL3A1 etc. seem to play a major role in the development of aneurysms in Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos type IV and familial TAA with patent ductus arteriosus [37-40].

In the submitted study, no significant differences in the genotype constellations between ii versus di + dd, id versus ii + dd, dd versus ii + id, were found. We could only establish a dependence on male gender and age in relation to popliteal aneurysm. A positive association could not be demonstrated for smoking nor for NF-κB genotypes and the underlying pathomechanisms of popliteal aneurysms seem to be different from those of AAA and intracranial aneurysms. The central role of the NF-κB gene in the initiation of inflammation in the development of poplitea artery aneurysms seems to play a rather minor role. Further investigations must clarify the role of other pathomechanisms such as degradation of elastin fibres and apolipoproteine-E-polymorphismus in the development of popliteal aneurysm.

Conclusions

The -94 ins/delATTG promoter polymorphism in the transcription factor NF-kB plays a major role in the aetiology of aneurysms, but according to the results of this study not in patients with a popliteal aneurysm. The aetiology of popliteal aneurysms seems to differ due to a completely different mechanism in comparison to abdominal aortic aneurysms.

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