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Genetic control of chemokines in severe human internal carotid artery stenosis

Giorgio Ghilardi [a,*], Maria Luisa Biondi [b], Olivia Turri [b], Francesca Pateri [b], Gianvico Melzi d'Eril [a,b], Roberto Scorza [a]

[a] *Dipartimento MCO, Università degli Studi di Milano, Via A. Di Rudinì, 8, I-20142 Milano, Italy*
[b] *Laboratorio di Chimica Clinica e Microbiologia, Ospedale S. Paolo, Via A. Di Rudinì, 8, I-20142 Milano, Italy*

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Abstract

Background and purpose: Atherosclerosis is an inflammatory disease. Chemokines and chemokine receptors are known to be involved in atherogenesis. Common single nucleotide polymorphisms (SNPs) affect transcription in response to inflammatory stimuli. The aim of this study was to evaluate the correlations between MCP-1, RANTES, SDF-1, CCR2, and CCR5 gene polymorphisms with increased risk of internal carotid artery (ICA) stenosis. *Methods:* Hundred and twelve patients, consecutively recruited for ICA occlusive disease, and 282 controls were genotyped for MCP-1-2518G, RANTES-403A, CCR5Δ32, CCR2 V64I, and SDF-1-801A polymorphisms. *Results:* The frequency of the SDF-1A allele was significantly different between cases and controls: 0.32 vs. 0.20, respectively (OR 1.81; 95% CI 1.25–2.60; $p = 0.007$). The frequency of the RANTES-403G allele was significantly higher in patients with stenosis >70% (OR, 2.45; 95% CI 1.12–5.71; $p = 0.015$). No significant differences were observed with the other polymorphisms. *Conclusion:* The reported results seem to correlate the polymorphisms of the genes encoding for SDF-1, RANTES with pathogenesis and progression of ICA occlusive disease. Although suggestive, these results need confirmation in prospective cross-sectional studies.

Keywords: Chemokines; Polymorphisms; Internal carotid artery; Atherosclerosis

1. Introduction

Arteriosclerosis is a multi-factorial condition which is determined both by environmental and genetic factors, involving a strong inflammatory component [1,2]. Atherogenesis requires a complex interplay between mononuclear cells, endothelial cells, vascular smooth muscle cells, growth factors, and cytokines [3]. The formation of atherosclerotic lesions proceeds through a sequence from fatty streak to fibrofatty matrix and fibrous plaque. Monocyte arrest on vascular endothelial lining is not only considered to be an initial step, but appears to play a causative role in the ensuing pathological process [4]. The mechanisms by which monocytes arrest on the luminal surface of vessels prone to form artherosclerotic lesion are incompletely understood. Chemokines are a superfamily of structurally related small chemotactic cytokines involved in leukocyte trafficking and activation. Binding of chemokines to their receptors elicits a variety of cellular responses including an increas in intracellular free calcium concentration, integrin activation, and leukocyte migration [5].

The Regulated upon Activation Normal T-cell Expressed and Secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1), and stromal cell-derived factor 1β (SDF-1β) chemokines have been implicated in atherogenesis [6–8]. RANTES is a potent chemoattractant for monocytes, lymphocytes, eosinophilis, and basophilis [9]. RANTES interacts with the chemokine receptors CCR1, CCR3, and CCR5, and has been implicated in cardiac inflammatory disorder after organ transplantation [10,11]. Systemic blockage

* Corresponding author. Fax: +39 0281843043.
E-mail address: giorgio.ghilardi@unimi.it (G. Ghilardi).

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of RANTES receptors inhibits neointima formation and macrophage infiltration in carotid arteries of ApoE−/− mice [11].

MCP-1 has been implicated in the recruitment of monocytes into early atherosclerotic lesions, the development of intima hyperplasia after angioplasty, vasculogenesis and thrombosis [12,13].

SDF-1 is a potent platelet agonist implicated in lymphocyte arrest on inflamed endothelium [14].

Genetic variations commonly occur in the regulatory regions of chemokine genes: such polymorphisms affect chemokine gene transcription in response to inflammatory stimuli, most likely by modulating leucocyte recruitment and activation in inflammation foci [15].

Internal carotid artery (ICA) occlusive disease has been recognized as a major cause of stroke. Carotid endarterectomy has been validated by several large trials as effective in prevention of stroke secondary to severe ICA stenosis [16–19].

Rupture of atherosclerotic plaques is crucial in the pathogenesis of acute coronary syndromes and strokes [20,21]. Interactions, within the ICA stenosing plaque, between connective tissue and the cells embedded into the fibrous cap overlying the inner core appear to determine the history of the ICA stenosis: plaque rupture or ulceration, intraplaque haemorrhage and luminal thrombosis are recognized causes of stroke [20,21]. Specific markers to identify *in vivo* ruptured plaques, or plaques prone to rupture, are not available.

The aim of this study was to investigate whether RANTES, MCP-1, SDF-1, CCR2, and CCR5 polymorphisms are associated with the presence of severe ICA occlusive disease and/or are involved in plaque stability in humans.

2. Subjects and methods

We studied 112 subjects affected with ICA occlusive disease consecutively referred to our vascular surgery unit and 282 unselected volunteer outpatients (controls) consecutively referred to our vascular ultrasound laboratory, with no evidence of ICA occlusive disease upon ultrasound colour Doppler (USCD) examination. Informed consent was obtained.

All 394 subjects underwent vascular evaluation, including history, clinical examination, thorough USCD of the accessible arterial tree, and ECG at rest. Within the patients group, 35% were found to be affected with coronary artery disease, 2% with peripheral arterial occlusive disease and 2% with abdominal aortic aneurysm. There was no relevant atherosclerotic finding in the control group. Patients underwent additional neurological evaluation and cerebral CT to assess symptoms and/or cerebral infarction related to ICA stenosis.

Hypertension was defined according to the 7th JNC Report on hypertension [22].

Smoker definition included both ex-smokers and active smokers.

Hypercholesterolemia was defined as total serum cholesterol levels >200 mg/dL.

Carotid stenosis was assessed by USCD and confirmed by multidetector helical angio-CT (MHACT). In this paper, the degree of stenosis is reported in percentages equivalent to the NASCET definition [23,24].

According to the AHA criteria [25], some 87 patients with >50% symptomatic stenosis and >70% asymptomatic stenosis underwent eversion endarterectomy and 25 asymptomatic subjects were not operated upon. 82 plaques were inspected in the operating room by a pathologist and macroscopic observations were recorded in the operation report file. Carotid plaques were classified according to the AHA statement [26]. For the purpose of this paper, plaques were also defined as soft or hard, according to the relative content of lipids, debris or intraplaque haemorrhage, and calcium. The macroscopic examination was then matched to the preoperative MHACT examination and a substantial agreement was found in any instance. Given the ability of MHACT to accurately estimate the calcium content of the plaque [27], a cut-off of 33% calcium content was established to define soft plaques (<33% calcium content) and hard plaques (>33% calcium content). Patients with bilateral lesions were considered only once in this study (first operation).

Whole blood from patients and controls was collected into potassium EDTA. DNA was prepared with commercial extraction kits. The PCR reaction for MCP-1, RANTES, CCR5, CCR2, SDF-1 was carried out as described elsewhere [28].

Differences between groups were examined by χ^2 tests. Odds ratios were calculated as an index of the association of the different genotypes with each phenotype. For each odds ratio, 2-tailed probability values and 95% confidence intervals were calculated.

Multiple logistic regression analysis was used to calculate the odds ratio of ICA stenosis and its 95% CI in subjects exposed to specific risk factors. Only the factors which were significantly associated with the development of carotid plaque on univariate analysis were included in the logistic regression analysis.

All statistical analyses were two-sided and were performed with Stata Statistical Software (Stata Corporation, College Station, TX).

Statistical analysis was assumed significant for a probability value of <0.05.

3. Results

Allele frequencies in both control and patient populations were within Hardy Weinberg equilibrium.

Gender frequency was similar between the two groups ($p = 0.71$); controls were slightly younger (mean ages: patients 68 ± 6 yrs. controls 65 ± 7: $p = 0.02$) (Table 1).

The adjusted odds ratios associated with the presence of the G/A SDF-1 genotype (G/A + AA versus GG) and A

Table 1
General characteristics and selected risk factors for carotid artery occlusive disease

	Patients ($n = 112$)	(%)	Controls ($n = 282$)	(%)	OR (95%CI)	p
Age	68 ± 6		65 ± 7			0.02
Men: women	75/:37		184:98		1.07 (0.66–1.77)	0.74
Hypertension	70/110	64	100/278	36	3.11(1.92–5.07)	0.0001
Cigarette smoking	84/112	75	124/275	45	3.65(2.18–6.18)	0.0001
Diabetes mellitus	25/108	23	44/275	16	1.58(0.86–2.82)	0.10
Hypercholesterolemia	82/105	78	179/275	65	1.91(1.10–3.38)	0.014

allele were 1.82 (95% CI, 1.14–2.90; $p = 0.0076$) and 1.81 (95% CI, 1.25–2.60; $p = 0.0007$), respectively (Table 2).

No differences were noted in-2518A/G MCP-1, -403G/A RANTES, CCR5Δ32 and CCR2 V64I variants distribution compared to controls (Table 2).

Twenty patients had had TIA, 32 had had strokes or silent cerebral infarction and 60 were asymptomatic. No differences in clinical signs and symptoms (e.g.: transient ischemic attacks and stroke or silent cerebral infarction) were found in correlation with the five genotypes.

In patients, -403G/A RANTES genotype was significantly correlated with a higher grade of stenosis, expressed as percentage of ICA occlusion (Table 3). To confirm this data the mean percentage of carotid occlusion was 75.3 ± 11.4 vs 80.3 ± 11.2 (GG vs GA + AA); $p = 0.036$.

Among patients, -2518A/G MCP-1 genotype distribution showed some degree of correlation with the stenosis percentage, G allele being more represented in more severely affected subjects, but the difference did not reach statistical significance ($p = 0.09$) (Table 3).

4. Discussion

Gene polymorphisms that modify expression and/or bioavailability of chemokines and their cellular receptors may affect leucocyte trafficking in inflammatory diseases, including atherosclerosis [15].

In our study, the SNPs SDF-1 A, and RANTES A-403 were significantly associated with susceptibility and clinical course of ICA stenosis disease. The other three gene variants studied (MCP-1 G, CCR2 I, CCR5Δ32) did not show

Table 2
Genotype of chemokines in ICA stenosis patients and controls

CCR5	Patients ($n = 112$)	Controls ($n = 282$)	OR (CI%)	p
Wt/Wt	99 (88)	252 (89)	0.9 (0.43–1.97)	0.78
Wt/Δ32	12 (11)	28 (10)		
Δ32/Δ32	1 (1)	2 (1)		
Δ32 frequency	0.06	0.05	0.9 (.045–1.86)	0.75
SDF-1				
G/G	53 (47)	175 (62)	1.82(1.14–2.90)	0.0076
G/A	47 (42)	99 (35)		
A/A	12 (11)	8 (3)		
A frequency	0.32	0.20	1.81(1.25–2.60)	0.0007
MCP-1				
A/A	65 (58)	152 (54)	1.18 (0.74–1.88)	0.45
A/G	43 (38)	104 (37)		
G/G	4 (4)	26 (9)		
G frequency	0.23	0.27	1.79 (0.89–1.90)	0.15
RANTES				
G/G	74 (66)	196 (70)	0.85 (0.52–1.40)	0.50
G/A	32 (28)	80 (28)		
A/A	6 (6)	6 (2)		
A frequency	0.20	0.16	0.79 (0.52–1.21)	0.26
CCR2				
Val/Val	90 (81)	211 (75)		
Val/Iso	20 (18)	68 (24)		
Iso/Iso	2 (1)	3 (1)	1.37 (0.78–2.48)	0.50
Iso frequency	0.19	0.13	1.25 (0.75–2.14)	0.35

Data are expressed as absolute values (genotype frequency, %). The ORs were calculated as wild type homozygots vs mutants (heterozygots plus homozygots).

Table 3
Genotype of Chemokines in ICA stenosis patients according to the severity of the stenosis

CCR5	<70 ($n = 46$)	>70 ($n = 66$)	OR (CI%)	p
Wt/Wt	43 (93)	56 (84)	2.55 (0.6–15.2)	0.16
Wt/Δ32	2 (4)	10 (16)		
Δ32/Δ32	1 (3)	0		
Δ32 frequency	0.04	0.07	1.84 (0.51–8.3)	0.30
SDF-1				
G/G	24 (52)	29 (44)	1.39 (0.61–3.17)	0.39
G/A	17 (37)	30 (45)		
A/A	5 (11)	7 (11)		
A frequency	0.29	0.39	1.20 (0.65–2.24)	0.52
MCP-1				
A/A	31 (67)	34 (52)	1.94 (0.83–4.61)	0.09
A/G	13 (28)	30 (45)		
G/G	2 (5)	2 (3)		
G frequency	0.18	0.30	1.53 (0.76–3.15)	0.20
RANTES				
G/G	36 (78)	38 (57)	2.65 (1.05–6.97)	0.022
G/A	9 (20)	23 (35)		
A/A	1 (2)	5 (8)		
A frequency	0.12	0.25	2.45 (1.12–5.71)	0.015
CCR2				
Val/Val	36 (79)	54 (82)	0.80 (0.28–2.31)	0.64
Val/Iso	9 (19)	11 (17)		
Iso/Iso	1 (2)	1 (1)		
Iso frequency	0.19	0.13	0.80 (0.31–2.09)	0.61

Data are expressed as absolute values (genotype frequency, %). The ORs were calculated as wild type homozygots vs mutants (heterozygots plus homozygots).

any statistically supported correlation with ICA stenosis nor with its severity.

Recruitment of circulating monocytes to the arterial intima contributes to the formation of atherosclerotic lesions and may participate in their destabilization [4]. Leukocyte emigration from blood into arterial wall tissue is mediated by multiple adhesion molecules and chemokines, depending on their expression patterns of chemokine receptors [5].

Carriers of the A allele in the SDF-1 gene were at increased risk of developing ICA occlusive disease compared with individuals homozygous for the G. The -801A variant of the SDF-1 gene has been associated with genetic restriction of AIDS pathogenesis, as well as with enhanced CD34+ progenitor cell mobilisation from bone marrow [29,30]. Soriano et al. have shown an association between high plasma SDF-1 levels and the SDF-1 A allele [31]. However, other studies demonstrated that SDF-1, at least in high concentrations, may mediate anti-inflammatory and matrix-stabilizing effects in unstable angina.

The -403A variant of the RANTES gene resulted in up to 8-fold increased constitutive transcriptional activity after transient transfection in human mast-cell and T-cell lines [32]. Data in mice demonstrated that Met-RANTES (RANTES receptor antagonist) reduced plaque formation and these effects could be linked to a decrease in leukocyte infiltration with inhibition of neointima formation [11]. Recently RANTES-403A has been associated with several inflammatory disease in humans [32–34]. In atherosclerosis Simeoni et al. [35] showed that the RANTES-403A allele was associated with CAD independently from conventional cardiovascular risk factors, Data confirmed in our results that could demonstrate a genetic component in the development of ICA stenosis in some way linked to the more active RANTES gene variant.

The lack of correlations between clinical signs of stroke and the examined SNPs on RANTES, and SDF-1 gene could actually be affected by the size of the sample and the fact that carotid surgery is indicated and effective in the prevention of cerebral ischemia. Therefore, further investigations would be suggested.

Polymorphisms in other chemokine genes have also been associated with atherosclerosis. The rare Val64Ile polymorphism in the CCR2 gene was associated with reduced coronary calcification, as well as MCP-1 G2518 homozygosity [36,37]. On the contrary Brenner et al. demonstrated a A2518 association with increased IMT [38]. However, this association was not found for ICA occlusive disease in the present study, in accordance with Tabara et al. study that demonstrated a lack of association with carotid intima-media thickness in Japanese [39]. These differences could be explained by different patients populations or the disease state. In a recently published study we demonstrated that the CCR5Δ32 polymorphism can be regarded as a risk factor for abdominal aortic aneurysm and its tendency to rupture [40]. Others reported on the protective effect of this deletion polymorphism against premature myocardial infarction [41]. In the present study ICA occlusive disease seems to be indifferent to this variant.

In conclusion, our results successfully try to correlate the polymorphisms of the genes encoding for SDF-1, and RANTES with pathogenesis and progression of ICA occlusive disease. Although suggestive, these results need confirmation in prospective cross-sectional studies.

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