C-Reactive Protein Gene Polymorphisms in Biopsy-proven Giant Cell Arteritis from Northwestern Spain

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ABSTRACT. ***Objective.*** To investigate the potential implication of several polymorphisms of the C-reactive protein (*CRP*) gene in the predisposition to or clinical expression of giant cell arteritis (GCA).

Methods. A total of 125 patients diagnosed with biopsy-proven GCA and 234 ethnically matched controls from the Lugo region of Northwestern Spain were included in our study. Four functional gene polymorphisms for *CRP* rs1417938, rs1800947, rs1205, and rs3093059 variants were assessed using a polymerase chain reaction system with predeveloped TaqMan allelic discrimination assay.

Results. Although we observed a significant increase in the frequency of heterozygotes for rs1417938 A/T [odds ratio (OR) = 1.70; 95% confidence interval (CI) 1.04–2.80; p = 0.03] and rs1205 C/T (OR 1.73; 95% CI 1.07–2.78; p = 0.02) in patients with GCA, no statistically significant differences in the allelic frequencies of these 2 polymorphisms were found between patients with GCA and controls. A marginal significant increase in the frequency of rs3093059 allele T in patients with GCA compared to controls was observed (OR 1.81; 95% CI 0.97–3.39; p = 0.04). However, the increased frequency of patients with GCA homozygous for rs3093059 T/T in patients with GCA compared to controls was out of the range of significance (OR 1.77; 95% CI 0.92–3.40; p = 0.07). No significant differences were found when we stratified patients with GCA according to the presence of polymyalgia rheumatica or severe ischemic complications of the disease.

Conclusion. The functional *CRP* gene polymorphisms assessed in our study do not seem to play a major role in the pathogenesis of GCA in individuals from Northwestern Spain. (First Release Dec 1 2008; J Rheumatol 2009;36:341–6; doi:10.3899/jrheum.080707)

Key Indexing Terms:
GIANT CELL ARTERITIS DISEASE SUSCEPTIBILITY C-REACTIVE PROTEIN
GENETIC STUDIES GENE POLYMORPHISMS

Giant cell (temporal) arteritis (GCA) is the most common type of systemic vasculitis affecting Caucasian individuals over age 50 years[1]. It is characterized by the granulomatous involvement of large and medium-size blood vessels of the aorta with predilection for the extracranial branches of the carotid artery[1,2].

Inflammation-induced angiogenic activity has been shown to counteract the risk of ischemic complications in patients with GCA[3]. In this regard, GCA patients without ischemic complications have higher tissue angiogenesis scores than those with ischemic events[3]. Markers of inflammation, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are usually elevated, often dramatically, in patients with GCA[4]. According to some investigators, CRP may be a more sensitive indicator of disease activity than ESR in GCA[5]. Circulating CRP is one of the principal downstream mediators of the acute-phase response and is primarily derived via interleukin 6 (IL-6)–dependent hepatic biosynthesis. Proinflammatory cytokines seem to contribute to different patterns of disease expression. Hernández-Rodríguez, *et al* found that expression of IL-6 in tissue from temporal artery samples, at both the mRNA and protein level, and circulating IL-6 levels were significantly lower in GCA patients with vascular occlusive events than in those who never developed ischemic complications[6]. These investigators showed that IL-6 is able to induce a functional program related to angiogenesis in endothelial cells and that IL-6 induces angiogenesis in *ex vivo* and *in vivo* models[6]. Due to this, IL-6 seems to play a protective role against the development of severe ischemic complications in GCA by promoting angiogenesis[6].

To our knowledge, there are 84 polymorphisms in the *CRP* gene. Twenty-one of them are common (minor allele frequency > 0.05) in Caucasians. Except for one single-nucleotide polymorphism (SNP) (rs876538) that is located at the 3' end of this region and that is not in linkage disequilibrium (LD) with any other SNP, the other 20 SNP

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Accepted for publication September 4, 2008.

belong to 4 complete-LD groups[7]. Interestingly, some functional *CRP* gene polymorphisms (rs1417938, rs1800947, rs1205, and rs3093059) that are located at the intronic, exonic, 3′UTR, and promoter region, respectively, and belong to each one of the 4 clusters mentioned, have been shown to have a strong association with plasma CRP levels[7-17], cardiovascular risk[7,8,10,14,15], some autoimmune diseases such as systemic lupus erythematosus[17,18], and other conditions such as type 2 diabetes mellitus[19].

Taking into account all these considerations, an important step forward in our understanding of the pathogenesis of GCA might be to establish whether functional *CRP* gene polymorphisms are implicated in the susceptibility to GCA and/or the potential risk of developing severe ischemic complications in the setting of this vasculitis.

MATERIALS AND METHODS

Patients. We began the genetic study on GCA in Northwestern Spain in 1997. Patients from the Lugo region diagnosed with biopsy-proven GCA at the Rheumatology Division of Hospital Xeral-Calde before 1997 were invited to attend the hospital for blood collection. Those who agreed to participate in the study were included in the analysis. Since 1997 blood sample collection is performed for all patients with biopsy-proven GCA from the Lugo region diagnosed at the Rheumatology Division who agree to be included in the genetic studies on this vasculitis.

A total of 125 patients diagnosed with biopsy-proven GCA and 234 healthy controls from the general population of the Lugo region were included in our study. The control population was matched by ethnicity, age, and sex with GCA patients.

The case:control ratio was 1:1.9. All patients and controls were of Spanish Caucasian origin from the Lugo region. All patients had a positive temporal artery biopsy showing disruption of the internal elastic laminae with infiltration of mononuclear cells into the arterial wall with or without giant cells[20]. In addition, all of them met the 1990 American College of Rheumatology criteria for the classification of GCA[21].

Patients with GCA were considered to have an associated polymyalgia rheumatica (PMR) if they had severe bilateral ache and pain involving the neck, the shoulder, and/or the pelvic girdles, associated with morning stiffness[22,23]. As reported[24,25], patients were considered to have severe ischemic manifestations if they experienced at least one of the following complications: visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, or diplopia), cerebrovascular accidents (stroke and/or transient ischemic attacks), jaw claudication, or large-artery stenosis of the extremities that caused signs of occlusive manifestations (limb claudication) of recent onset. Patients and controls were included in our study after written informed consent. We obtained approval for the study from the local ethical committee.

Patients with GCA have consistently elevated acute-phase reactant levels, including CRP levels, and this is not a differential feature in this disease. However, different CRP expression (assessed by determination of CRP serum levels) among patients might be associated with genetic variability of the *CRP* gene. Due to this, the relationship between *CRP* gene polymorphisms and CRP serum level was explored in this series. However, when available, to minimize the effect of corticosteroid treatment, patients' CRP serum levels were analyzed only if they were determined prior to the onset of corticosteroid therapy or within the first 12 h after the onset of this medication. CRP levels were measured in patients diagnosed before 2003 by nephelometry and since then by a latex immunoturbidity method. CRP values were considered abnormal if greater than 5 mg/l[4].

Genotyping methods. DNA from patients and controls was obtained from peripheral blood, using standard methods. Samples were genotyped for *CRP* rs1417938, rs1800947, rs1205, and rs3093059 variants using a polymerase chain reaction (PCR) system with predeveloped TaqMan allelic discrimination assay (Applied Biosystems, Foster City, CA, USA). Allele-specific probes were labeled with the fluorescent dyes VIC and FAM, respectively. PCR reaction was carried out in a total reaction volume of 5 µl with the following amplification protocol: denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 92°C for 15 s, and finished with annealing and extension at 60°C for 1 min. Post-PCR, the genotype of each sample was attributed automatically by measuring the allelic-specific fluorescence on the ABI Prism 7900 Sequence Detection System using SDS 2.3 software for allelic discrimination (Applied Biosystems). Duplicate samples and negative controls were included to check the accuracy of genotyping.

Statistical analysis. We used the chi-squared test to assess Hardy-Weinberg equilibrium. Strength of association between GCA and alleles or genotypes of the *CRP* gene polymorphisms was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined using contingency tables by either chi-squared or Fisher's exact analysis. The same method was used to examine the strength of association between GCA patient subgroups with or without PMR, severe ischemic manifestations, and high or low CRP serum levels and *CRP* gene polymorphisms. Also, means of CRP values were compared using the 2-tailed Student's t test. OR and 95% CI were calculated according to Woolf's method using the Statcalc program (Epi Info 2002, Centers for Disease Control and Prevention, Atlanta, GA, USA). p values < 0.05 were considered statistically significant.

RESULTS

Patient and control genotype distributions were in Hardy-Weinberg equilibrium. The main clinical features of this series of patients with biopsy-proven GCA are summarized in Table 1.

Allele and genotype distribution of *CRP* gene polymorphisms in biopsy-proven GCA and controls are shown in Table 2. Although we observed a significant increase in the

Table 1. Main clinical features of 125 patients with biopsy-proven GCA from the Lugo region of Northwest Spain. Number in parentheses indicates the total proportion of patients with a particular variable.

Characteristic	n
Age, yrs, at the time of diagnosis, median (range)	75 (60–92)
Sex	
Women/men	71/54
Women (%)	57
Headache	109 (87)
Abnormal temporal artery on examination	95 (76)
Polymyalgia rheumatica	47 (38)
Jaw claudication	51 (41)
Visual ischemic manifestations*	27 (22)
Permanent visual loss	12 (10)
Stroke	4 (3)
Arm claudication due to ischemia of the humeral artery	1 (1)
Severe ischemic manifestations**	65 (52)
ESR > 40 mm/h	125 (100)

* If they had transient visual loss including amaurosis fugax, permanent visual loss, or diplopia. ** If they experienced at least one of the following features: visual manifestations, cerebrovascular accidents (stroke and/or transient ischemic attacks), jaw claudication, or limb claudication of recent onset. ESR: erythrocyte sedimentation rate. GCA: giant cell arteritis..

Table 2. CRP gene polymorphisms in a series of biopsy-proven GCA and matched controls.

CRP Polymorphisms	GCA Patients, n (%)	Controls, n (%)	p	OR (95% CI)
rs1417938	n = 116	n = 192		
A/A	6 (5.2)	15 (7.8)	0.37	0.64 (0.22–1.84)
A/T	56 (48.3)	68 (35.4)	0.03	1.70 (1.04–2.80)
T/T	54 (46.6)	109 (56.8)	0.08	0.66 (0.41–1.08)
A	68 (29.3)	98 (25.5)	0.30	1.21 (0.83–1.77)
T	164 (70.7)	286 (74.5)	0.30	0.83 (0.57–1.21)
rs1800947	n = 120	n = 224		
C/C	100 (83.3)	189 (84.4)	0.80	0.93 (0.49–1.76)
C/G	19 (15.8)	32 (14.3)	0.70	1.13 (0.58–2.18)
G/G	1 (0.8)	3 (1.3)	0.56	0.62 (0.02–6.75)
C	219 (91.3)	410 (91.5)	0.90	0.97 (0.54–1.75)
G	21 (8.8)	38 (8.5)	0.90	1.03 (0.57–1.87)
rs1205	n = 118	n = 222		
C/C	41 (34.7)	95 (42.8)	0.15	0.71 (0.44–1.16)
C/T	66 (55.9)	94 (42.3)	0.02	1.73 (1.07–2.78)
T/T	11 (9.3)	33 (14.9)	0.15	0.59 (0.27–1.27)
C	148 (62.7)	284 (64.0)	0.75	0.95 (0.67–1.33)
T	88 (37.3)	160 (36.0)	0.75	1.06 (0.75–1.48)
rs3093059	n = 123	n = 234		
C/C	0 (0)	3 (1.3)	0.21	0.47 (0.29–1.03)
C/T	13 (10.6)	39 (16.7)	0.12	0.62 (0.32–1.20)
T/T	110 (89.4)	192 (82.1)	0.07	1.77 (0.92–3.40)
C	13 (5.3)	45 (9.6)	0.04	0.55 (0.29–1.03)
T	233 (94.7)	423 (90.4)	0.04	1.81 (0.97–3.39)

CRP: C-reactive protein; GCA: giant cell arteritis.

frequency of heterozygotes for rs1417938 A/T (OR 1.70; 95% CI 1.04–2.80; p = 0.03) and rs1205 C/T (OR 1.73; 95% CI 1.07–2.78; p = 0.02) in patients with GCA, no statistically significant differences in the allelic frequencies for these 2 polymorphisms between patients with GCA and controls were found. Also, a marginally significant increase in the frequency of rs3093059 allele T in patients with GCA compared to controls was observed (OR 1.81; 95% CI 0.97–3.39; p = 0.04). However, the frequency of patients homozygous for rs3093059 T/T in this series of individuals with GCA compared to controls was out of the range of significance (OR 1.77; 95% CI 0.92–3.40; p = 0.07; Table 2). Moreover, no significant differences were found when we stratified patients with GCA according to the presence of PMR or characteristic features of the disease such as severe ischemic complications, or more specifically visual ischemic manifestations (data not shown).

Considering the incidence of biopsy-proven GCA in the population of Lugo (11/100,000 individuals age 50 yrs or older)[1], the estimated power of our study for an estimated OR between 1.5 and 2.0 was 60%–98%.

Based on the criteria applied for the assessment of serum CRP levels, the association between *CRP* gene polymorphisms and CRP serum level was explored in 61 patients from this series. In all cases serum CRP values were elevated. As reported[4], patients were stratified in 2 groups according to CRP serum levels [GCA patients with CRP levels ≤ 50 mg/l (24 patients) and those with CRP > 50 mg/l (37 patients)]. Moreover, the mean serum CRP values for each CRP genotype were calculated. However, no significant association between CRP serum levels and *CRP* gene polymorphisms was found (data not shown).

DISCUSSION

GCA is the best example of vasculitis in which a genetic influence has been implicated in both disease susceptibility and severity[26,27]. The familial clustering of GCA supports this genetic component, and there is a strong association with HLA-DRB1*04 in many different populations. Within cohorts of biopsy-proven GCA, HLA-DRB1*04 has also been associated with systemic signs and symptoms, visual manifestations, and corticosteroid resistance[28,29]. Other genes within the major histocompatibility complex (MHC) region have been shown to have effects in the susceptibility to GCA. With respect to this, besides an association with *TNF* microsatellite polymorphisms[30], we have recently reported an independent association of *MICA* and HLA-B genes with the genetic susceptibility to GCA[31], suggesting that several genes within the MHC may have independent effects in the susceptibility to GCA.

In addition to the association between GCA and genes located within the MHC region, other gene polymorphisms have also been implicated in disease susceptibility or clinical expression to this vasculitis[26,27]. Many other studies

have examined genetic variants in key components of immune and inflammatory pathways known to be activated in GCA[32-49]. Most of them have shown an association with susceptibility to the disease or with features of this vasculitis such as PMR or severe ischemic complications or the occurrence of relapses[32,33,35-44,46-49].

GCA is typically characterized by a marked elevation of routine laboratory markers of inflammation[4]. Interestingly, angiogenesis has been found to be more severe in GCA patients with a strong acute-phase response compared with those with a weak systemic inflammatory response[3]. Recent studies have disclosed that a severe inflammation-induced angiogenic activity may counteract the risk of ischemic complications in patients with GCA[3]. In keeping with these observations, we described that a functional variant of vascular endothelial growth factor (*VEGF*) gene was associated with severe ischemic complications in patients with biopsy-proven GCA[49]. The frequency of *VEGF* alleles associated with lower circulating VEGF levels was significantly increased in the subgroup of GCA patients with severe ischemic complications[49].

GCA patients with a strong systemic inflammatory response have elevated tissue expression of proinflammatory cytokines including IL-6[50]. This cytokine has potent effects on promoting angiogenesis in GCA, leading to a reduction of severe ischemic complications in these patients[3,6]. Moreover, IL-6 is directly implicated in the production of serum CRP. However, although polymorphisms in the *CRP* gene have been found to be implicated in the susceptibility to other autoimmune diseases[17,18], we observed no evidence of strong associations between *CRP* gene polymorphisms and susceptibility to GCA. It was also the case when patients were stratified according to the presence of PMR, severe ischemic complications, or visual ischemic events in the setting of this vasculitis.

Since CRP is a main component of the detectable consequences of a complex inflammatory cascade, an important result derived from our study was the lack of significant association between these *CRP* gene polymorphisms and the systemic inflammatory reaction determined by the circulating levels of CRP in patients with biopsy-proven GCA from Northwestern Spain. However, the absence of strong evidence for the association between these *CRP* gene polymorphisms and GCA in Northwestern Spain does not exclude completely a potential implication of CRP in the pathogenesis of GCA. It is possible that complex gene-gene interactions rather than involvement of a single gene may be responsible for the development and phenotype expression of this vasculitis. These interactions may upregulate *CRP* gene expression, leading to high production of serum CRP in patients with GCA. On the other hand, it is possible that the genetic background of the population may also influence the pathogenic role of some gene polymorphisms in polygenic diseases such as GCA. In keeping with this assumption, we have emphasized a lack of concordance between our findings and those reported by other European investigators regarding association of biopsy-proven GCA with genes located within[51,52] and outside the MHC region[32,33,35,36,40,41,43,44]. These observations may be related to the different genetic backgrounds of the European populations.

A potential limitation of our study was the stratification of patients according to clinical manifestations. This decreased the power to find statistically significant differences, as it diminished the sample size in each group. Moreover, it is also important to emphasize that the 4 SNP included in our study are not the only functional polymorphisms in the *CRP* gene. Therefore, our results cannot exclude the role of additional functional SNP in the *CRP* gene, even in the population of Northwestern Spain.

The functional *CRP* gene polymorphisms assessed in our study do not seem to play a major role in the pathogenesis of GCA in individuals from Northwestern Spain. Additional studies on patients with biopsy-proven GCA from different genetic backgrounds are needed to fully exclude the implication of *CRP* gene polymorphisms in the pathogenesis of GCA.

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