Cranial and extracranial giant cell arteritis do not exhibit differences in the *IL6 -174 G/C* gene polymorphism

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Abstract

Objective

Since interleukin-6 (IL-6) is a pivotal proinflammatory cytokine implicated in the pathogenesis of giant cell arteritis (GCA), we aimed to determine the potential association of the functional IL6 -174 G/C polymorphism with GCA as well as if the single base change variation at the promoter region in the human IL-6 gene may account for differences in the clinical spectrum of GCA between cranial and extracranial large-vessel vasculitis (LVV)-GCA.

Methods

The IL6 -174 G/C polymorphism (rs1800795) was genotyped in 191 patients with biopsy-proven GCA who had typical cranial manifestations of the disease, 109 patients with extracranial LVV-GCA, without cranial ischaemic manifestations of GCA, and 877 ethnically matched unaffected controls. A comparative study was carried out between patients with cranial and extracranial LVV-GCA and controls.

Results

*No significant differences in genotype and allele frequencies of IL6 –174 G/C polymorphism were found between the whole cohort of GCA patients and healthy controls. It was also the case when cranial and extracranial LVV-GCA were compared or when each of these subgroups was compared to controls. Moreover, no significant results in genotype and allele frequencies of IL6 –174 G/C polymorphism were disclosed when the whole cohort of GCA patients were stratified according to the presence of polymyalgia rheumatica, severe ischaemic manifestations, including permanent visual loss and peripheral arteriopathy, and HLA-DRB1*04:01 status.*

Conclusion

Our results show that the IL6 –174 G/C polymorphism does not influence the phenotypic expression of GCA.

Key words

giant cell arteritis, large-vessel vasculitis, *IL6 -174 G/C (rs1800795)*, polymorphism

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Introduction

Giant cell arteritis (GCA) is the most common vasculitis in people over 50 years of age in Western countries (1). This systemic granulomatous vasculitis involves medium-sized and large arteries (1). The classic clinical picture is the result of vasculitis affecting the cranial vessels derived from the carotid artery, giving rise to the typical findings of the disease such as headache, jaw claudication or blindness (2). However, with the help of new imaging techniques, recent studies have shown that the spectrum of the disease is not restricted to the cranial arteries and that involvement of the aorta and its extracranial branches is not uncommon (3, 4). Currently we can identify two different phenotypes of the disease depending on the presence of predominant cranial or extracranial manifestations (5, 6). In this regard, while patients with the predominant classic cranial phenotype complain of headache and are at increased risk of permanent visual loss (2), patients with the predominant pattern of extracranial large-vessel vasculitis (LVV) pattern of the disease often present with nonspecific manifestations, such as constitutional syndrome, fever of unknown origin, or refractory/atypical polymyalgia rheumatica (PMR) and may develop peripheral artery disease more frequently than those with the predominant cranial phenotype. Furthermore, these patients with a predominant extracranial LVV-GCA phenotype are younger and have more disease relapses. Furthermore, in these patients, cranial manifestations are less common (7, 8).

The pathogenesis of GCA is not fully understood. Besides a number of cells, cytokines play a key role in its pathogenesis. With respect to this, interleukin-6 (IL-6) is a pleiotropic cytokine that has been linked to GCA activity (9, 10). Macrophages in temporal artery tissue biopsies synthesise IL-6 specific mRNA and produce IL-6 (11). IL-6 serum levels were significantly elevated in GCA patients with active disease (12). In this regard, anti-IL-6 receptor-tocilizumab therapy has proved to be useful both in clinical trials and in real -life patients (13-16). The use of this targeted therapy allowed a reduction of the cumulative prednisone dose and the number of relapses in GCA patients (13, 15). However, we do not know if the two different clinical phenotypes are the result of differences in the immunogenetic background and/or cytokine expression between patients with classic cranial pattern and the extracranial LVV-GCA pattern. In this sense, a strong contribution of the HLA to GCA susceptibility was described (16). However, the HLA region does not appear to influence the phenotype expression of GCA as both cranial and extracranial LVV-GCA showed similar *HLA-DRB1* and *HLA-B* association (17, 18).

rs1800795 is a single nucleotide polymorphism (SNP) in the promoter of the *IL6* gene, affecting the levels of this important cytokine. It is also referred to as the *IL6 -174 G/C* polymorphism. It tends to be quite polymorphic in Caucasians (19). In a former study of our group that included a series of 62 biopsy-proven GCA patients, we observed that the *IL6 -174 G/C* polymorphism may have some implication in GCA disease susceptibility. We observed that the presence of allele C at the position -174 in the promoter region of the *IL6* gene might be a marker for PMR in biopsy-proven GCA. It was especially true among *HLADRB1*04* negative patients (20). However, this study was based on a small series of patients as only included 30 patients with PMR associated with GCA. Nevertheless, considering that LVV-GCA patients have more commonly PMR than those with cranial GCA and that the frequency of *HLA-DRB1*04* is slightly lower in the subgroup of extracranial LVV-GCA than in the classic cranial phenotype (17, 18), in the present study we aimed to explore the potential association of *IL6 -174 G/C* polymorphism with GCA as well as if the single base change variation at the promoter region in the human *IL6* gene may account for differences in the clinical spectrum of GCA between cranial and extracranial LVV-GCA.

Methods

Patients

A total of 191 patients with biopsy-proven GCA who had typical cranial

manifestations of the disease and 109 with extracranial LVV-GCA without cranial ischaemic manifestations of GCA were included in the study (Table I). All patients were Spanish of European ancestry. They were recruited in ten collaborative centres: Hospital Universitario Marqués de Valdecilla (Santander, Spain), Hospital Universitario de Basurto (Bilbao, Spain), Hospital de León (León, Spain), Hospital Universitario de La Princesa (Madrid, Spain), Hospital Universitario y Politécnico La Fe (Valencia, Spain), Hospital Universitario Virgen del Rocío (Sevilla, Spain), Hospital Universitario de Pontevedra (Pontevedra, Spain), Hospital Universitario Lucus Augusti (Lugo, Spain), Hospital Universitario San Cecilio (Granada, Spain) and Hospital San Agustín (Avilés, Spain).

Regardless of the GCA phenotype, all patients were treated with high-dose prednisone, generally starting at 40-60 mg/day. Those with severe ischaemic manifestations were initially treated with methylprednisolone pulses, usually methylprednisolone 500 mg or 1000 mg intravenously/day for three consecutive days followed by prednisone 60 mg daily. Then, the dose of prednisone was gradually tapered. In relapsing patients, methotrexate or the anti-IL-6 receptor tocilizumab was used regardless of the clinical phenotype.

The study was approved by the Ethics Committee of clinical research of Cantabria for Hospital Universitario Marqués de Valdecilla as well as by the remaining participant centres mentioned above. All subjects provided informed written consent before being enrolled in the study. The procedures followed were in accordance with the ethical standards of the approved guidelines and regulations, according to the Declaration of Helsinki.

GCA patients with the classic cranial phenotype of GCA

The patients were classified into the cranial phenotype if they fulfilled the American College of Rheumatology (ACR) 1990 classification criteria (21) and presented with the classic cranial manifestations of GCA in the absence of limb claudication or any other symptoms of peripheral arterial disease suggestive of extracranial LVV involvement. All of them had a positive temporal artery biopsy consistent with the diagnosis of GCA that in most cases also had positive findings in the ultrasonography of the temporal arteries. However, we excluded from this group of cranial GCA those patients who also had abnormality in the axillary arteries when ultrasonography was carried out. Due to the typical findings for GCA and the histologic confirmation as well as the positive ultrasonography of the temporal artery in many of them, PET-CT or any other imaging technique was not performed in the vast majority of them.

GCA patients with the extracranial LVV-GCA phenotype

A well-differentiated subset of patients with the extracranial LVV-GCA phenotype was identified by experienced rheumatologists based on the presence of consistent clinical manifestations along with confirmatory imaging techniques, such as 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT), angiographic magnetic resonance (MRI-A) and/or computed tomography angiography (CT-A).

To establish two well-differentiated disease patterns, patients with extracranial LVV-GCA disease presenting cranial symptoms were not included in the study. Therefore, those patients with GCA with cranial manifestations were excluded from the extracranial LVV group.

Patients with other underlying inflammatory conditions, infections or neoplastic diseases that could present with LVV involvement were also excluded.

Unlike patients with cranial-GCA, in the few patients with extracranial LVV-GCA in whom the temporal artery biopsy was positive, the histological findings were similar to those of the classic cranial GCA patients, showing a disruption of the internal elastic lami-

Table I. Main clinical features of patients with classic cranial GCA and extracranial LVV-GCA pattern.

	Classic cranial GCA pattern n=191	LVV-GCA pattern n=109	*p*
Age at diagnosis (mean ± SD) years	74.1 ± 10.2	68.5 ± 9.9	<0.01
Women, n (%)	127 (66.5%)	77 (70.6%)	0.46
Positive TAB, n (%)	191 (100%)	3/37 (8.1%)	<0.01
Headache, n (%)	152 (79.6%)	0 (0%)	<0.01
Abnormal temporal artery on physical examination, n (%)	113 (59.2%)	0 (0%)	<0.01
Jaw claudication, n (%)	75 (39.3%)	0 (0%)	<0.01
Polymyalgia rheumatica, n (%)	76 (39.7%)	90 (82.6%)	<0.01
Visual manifestations, n (%)	49 (25.7%)	0 (0%)	<0.01
Permanent visual loss, n (%)	23 (12%)	0 (0%)	<0.01
Peripheral arteriopathy, n (%)	0 (0%)	13 (11.9%)	<0.01
Stroke, n (%)	8 (4.2%)	0 (0%)	0.05
ESR > 40 mm/1st h. at diagnosis, n (%)	188 (98.4%)	87 (79.8%)	<0.01

ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; LVV: large-vessel vasculitis; SD: standard deviation; TAB: temporal artery biopsy.

Table II. Genotype and allele frequencies of *IL6 -174 G/C* in all patients with GCA and healthy controls.

Genotypes/Alleles	All patients with GCA % (n)	Healthy controls % (n)	*p*	**OR [95% CI]**
GG	45.5 (136)	43.6 (382)	-	Ref.
GC	42.1 (126)	44.8 (393)	0.46	0.90 [0.67-1.20]
CC	12.4 (37)	11.6 (102)	0.93	1.01 [0.65-1.58]
G	66.6 (398)	66.0 (1157)	-	Ref.
C	33.4 (200)	34.0 (597)	0.79	0.97 [0.80-1.19]

CI: confidence interval; GCA: giant cell arteritis; OR: Odds Ratio.

na with a mononuclear infiltrate with or without multinucleated giant cells.

Healthy controls

A cohort of 877 ethnically matched unaffected control subjects, without history of vasculitis or any other autoimmune disease, constituted by blood donors from National DNA Bank Repository (Salamanca, Spain), were also included in this study.

IL6 -174 G/C polymorphism genotyping

Genomic DNA was extracted from peripheral blood using the REALPURE "SSS" kit (RBME04, REAL, Durviz S.L., Valencia, Spain), as previously described (22).

All individuals were genotyped for the *IL6 -174 G/C* (rs1800795) polymorphism by a TaqMan assay. Negative controls and duplicate samples were included to check the accuracy of the genotyping. Genotyping was performed in a QuantStudio™ 7 Flex real-time polymerase chain reaction system (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

All genotype data were checked for deviation from Hardy-Weinberg equilibrium (HWE).

IL6 -174 G/C genotype and allele frequencies were calculated and compared between two groups by chi-square or Fisher tests when necessary (expected values below 5). Strength of association was estimated using odds ratios (OR) and 95% confidence intervals (CI).

p-values <0.05 were considered as statistically significant. All analyses were performed with the STATA statistical software 12/SE (Stata Corp., College Station, TX, USA).

Results

Clinical features of patients with classic cranial GCA and extracranial LVV-GCA pattern

The main clinical features of the patients included in the present study are shown in Table I.

Patients with the classic cranial GCA phenotype were older than those with the extracranial-LVV phenotype (74.1±10.2 *vs*. 68.5±9.9 years; *p*<0.01). In contrast to patients with cranial-GCA the frequency of a positive temporal artery biopsy among the patients with LVV-GCA was less than 10%. Patients with extracranial LVV-GCA had more commonly PMR (82.6% *vs*. 39.7%; *p*<0.01). Other clinical differences are shown in Table I.

Genotyping quality control

The *IL6 -174 G/C* genotype distribution was in HWE. Genotype and allele frequencies were in agreement with the data of the 1000 Genomes Project for Europeans.

Association of IL6 -174 G/C with GCA susceptibility

We compared the frequencies of *IL6 -174 G/C* genotype and allele between the whole cohort of patients with GCA and healthy controls (Table II). In this regard, no significant differences in the genetic frequencies of *IL6 –174 G/C* polymorphism were found (Table II). This was also the case when classic cranial GCA or extracranial LVV-GCA pattern were compared to controls (Tables III and IV).

Association of IL6 -174 G/C with classic cranial GCA and extracranial LVV-GCA

In a further step, we compared *IL6 -174 G/C* genotype and allele frequencies between patients with the classic cranial GCA pattern and those with the extracranial LVV-GCA pattern. Similar *IL6 -174 G/C* genetic frequencies were disclosed between them (Table V).

Table III. Genotype and allele frequencies of *IL6 -174 G/C* in patients with classic cranial GCA pattern and healthy controls.

Genotypes/Alleles	Classic cranial GCA pattern % (n)	Healthy controls % (n)	*p*	OR [95% CI]
GG	44.0 (84)	43.6 (382)	-	Ref.
GC	42.9 (82)	44.8 (393)	0.76	0.95 [0.67-1.35]
CC	13.1 (25)	11.6 (102)	0.67	1.11 [0.65-1.87]
G	65.4 (250)	66.0 (1157)	-	Ref.
C	34.6 (132)	34.0 (597)	0.85	1.02 [0.80-1.30]

CI: confidence interval; GCA: giant cell arteritis; OR: odds ratio.

Table IV. Genotype and allele frequencies of *IL6 -174 G/C* in patients with LVV-GCA pattern and healthy controls.

Genotypes/Alleles	LVV-GCA pattern % (n)	Healthy controls % (n)	*p*	OR [95% CI]
GG	48.2 (52)	43.6 (382)	-	Ref.
GC	40.7 (44)	44.8 (393)	0.37	0.82 [0.52-1.29]
CC	11.1 (12)	11.6 (102)	0.67	0.86 [0.40-1.72]
G	68.5 (148)	66.0 (1157)	-	Ref.
C	31.5 (68)	34.0 (597)	0.45	0.89 [0.65-1.22]

CI: confidence interval; GCA: giant cell arteritis; LVV: large-vessel vasculitis; OR: odds ratio.

Table V. Genotype and allele frequencies of *IL6 -174 G/C* in patients with LVV-GCA pattern and classic cranial GCA pattern.

Genotypes/Alleles	LVV-GCA pattern % (n)	Classic cranial GCA pattern % (n)	*p*	OR [95% CI]
GG	48.2 (52)	44.0 (84)	-	Ref.
GC	40.7 (44)	42.9 (82)	0.58	0.87 [0.31-1.48]
CC	11.1 (12)	13.1 (25)	0.52	0.78 [0.33-1.77]
G	68.5 (148)	5.4 (250)	-	Ref.
C	31.5 (68)	34.6 (132)	0.44	0.87 [0.60-1.26]

CI: confidence interval; GCA: giant cell arteritis; LVV: large-vessel vasculitis; OR: odds ratio.

*Association of IL6 -174 G/C with GCA according to different clinical features and HLA-DRB1*04:01 allele*

Furthermore, we also assessed whether differences in the *IL6 -174 G/C* genotype and allele frequencies might exist in the whole cohort of GCA patients stratified according to the presence/absence of PMR, severe ischaemic manifestations, visual ischaemic manifestations and/or peripheral arteriopathy, permanent visual loss and/or peripheral arteriopathy, permanent visual loss, as well as *HLA-DRB1*04:01* status. However, no significant associations in the genetic frequencies were obtained (Supplementary Tables S1-6).

Discussion

In the present study we aimed to determine if differences in the *IL6 -174 G/C* promoter gene polymorphisms might exist between patients with cranial GCA and those with extracranial LVV- GCA. However, no differences were observed when these subgroups of patients were compared. It was also the case when the entire group of both cranial and extracranial GCA was compared with healthy controls or when each group was compared separately with controls.

Although frequent overlap between cranial and extracranial GCA exists as imaging techniques often disclose the presence of LVV involvement in patients presenting with the classic cranial phenotype, it is clinically evident that cranial and extracranial LVV-GCA constitute two different phenotypes within the clinical spectrum of GCA. Patients with predominant LVV-GCA features are generally younger than those presenting with cranial manifestations, have more commonly PMR features and ischaemic arteriopathy, more relapses of the disease and less common visual ischaemic manifestations (6-8).

Since GCA is a complex polygenic disease, we wondered if a genetic component could influence the phenotype expression of the disease. However, so far studies to identify potential immunogenetic influences between cranial and extracranial LVV-GCA have been disappointing as both GCA subgroups share similar *HLA-DRB1* class II and *HLA-B* class I genetic association (17, 18). The same occurred when data on functional *vascular endothelial growth factor (VEGF)* polymorphisms associated with an increased risk of major ischaemic complications in unselected GCA patients (23) were replicated in a new larger cohort that included patients with cranial and extracranial LVV-GCA (24). Although two *VEGF* haplotypes were associated with the development of severe ischaemic manifestations, it was independent of the clinical phenotype of GCA (24). The results shown in the present study are in the same line as these previously evaluated gene polymorphisms and do not support differences in the polymorphism of the *IL6 -174 G/C* promoter as being responsible for the different GCA phenotypes.

The *IL6 -174 G/C* polymorphism is functional and it was shown that the G allele is associated with higher production of IL-6 in other conditions. Elevated serum levels of IL-6 constitute a typical feature of GCA (9, 10). We and others have observed that patients with severe cranial ischaemic events, including visual ischaemic manifestations, due to arteritic involvement of cranial blood vessels, exhibit lower inflammatory response when compared with the remaining patients who do not suffer such complications (25, 26). The lack of association between the functional *IL6 -174 G/C* polymorphism with severe ischaemic manifestations of the disease suggest that other gene polymorphism rather that the *IL6 -174 G/C* polymorphism itself may modulate the expression of IL-6 in GCA. Alternatively, it is possible that unknown gene-gene interactions may modulate the expression of IL-6.

In conclusion, the *IL6 -174 G/C* polymorphism does not influence the phenotypic expression of GCA.

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