Cranial and extracranial large-vessel giant cell arteritis share a genetic pattern of *interferon-gamma* pathway

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Abstract

Objective

Two main different clinical phenotypes of giant cell arteritis (GCA) have been described, the classic cranial pattern and the extracranial large-vessel (LV) pattern. Since interferon gamma (IFNG) has shown to be a pivotal cytokine in the pathophysiology of GCA, our aim was to evaluate for the first time the influence of IFNG *and* IFNG receptor 1 (IFNGR1) *polymorphisms in the different clinical phenotypes of GCA.*

Methods

Two IFNG *polymorphisms (rs2069718 G/A and rs1861493 A/G) and one polymorphism in* IFNGR1 *(rs1327474 G/A) were genotyped in 191 patients with biopsy-proven cranial GCA, 109 with extracranial LV-GCA and 490 healthy controls. A comparative study was conducted between patients with cranial and extracranial LV-GCA.*

Results

No significant differences in genotype, allele, and haplotype frequencies of IFNG *polymorphisms were found between GCA patients with the classic cranial pattern and the extracranial LV-GCA pattern. Similar results were found for genotype and allele frequencies of* IFNGR1 *polymorphism. It was also the case when patients with extracranial LV-GCA were compared with healthy controls.*

Conclusion

Our results show that IFNG *and* IFNGR1 *polymorphisms do not influence the clinical phenotype of expression of GCA. Classic cranial GCA and extracranial LV-GCA seem to share a genetic pattern of* IFNG *pathway.*

Key words

giant cell arteritis, large-vessel vasculitis, interferon-gamma, interferon-gamma receptor, polymorphisms

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Introduction

Giant cell arteritis (GCA) is a granulomatous vasculitis of large and medium vessels that affects people aged 50 years and older. In addition to the classic cranial phenotype of GCA, some patients present with a predominant clinical pattern characterised by extracranial large-vessel vasculitis (LV) (1-4). Most of the clinical manifestations observed in the classic cranial pattern of GCA are the result of the involvement of the arterial branches derived from the external carotid artery. However, visual ischaemic manifestations, the most feared complications seen in patients with the classic cranial pattern of GCA, are due to involvement of the ophthalmic arteries derived from the internal carotid artery (5, 6). These manifestations first described by Horton in 1932 include mainly headache, scalp tenderness, visual disturbances and jaw claudication (5, 6). The use of imaging techniques has allowed us to identify patients with a predominantly extracranial GCA pattern that is a consequence of vascular involvement of the aorta and its extracranial branches (7-10). Patients with the predominant extracranial LV-GCA phenotype are usually younger than those with the classic cranial phenotype and often present with polymyalgia rheumatica (PMR) and systemic inflammatory symptoms, such as fever, weight loss, or asthenia. In this subgroup of patients, visual ischaemic complications are uncommon, and a biopsy of the temporal artery is often negative (7-10).

The striking differences between the two clinical phenotypes of GCA raise the possibility that different immunogenetic backgrounds and/or cytokine expression may exist in patients with the classic cranial pattern and the extracranial LV-GCA pattern. Certainly, the pathophysiology of GCA is still not fully understood (11-14). In genetically predisposed individuals, activated dendritic cells in the adventitial layer of the vessel wall promote the differentiation of $CD4^+$ helper T cells into Th-17 and Th-1cells. Th1 cells stimulate the production of interferon-gamma (IFNG), a pivotal mediator of granulomatous inflammation (11-14).

IFNG is a cytokine that plays a pivotal role in both innate and adaptative immunity. It is one of the most important activators of macrophages up-regulating antigen processing and presentation pathways. IFNG also enhances natural killer cell activity and regulates B cell functions (15). IFNG needs to bind to the cell surface IFNG receptor (IFNGR) to mediate its biological functions. IFNGR activates intracellular signalling pathways leading to the regulation of gene expression(16). Previous studies revealed that IFNG pathway polymorphisms induce susceptibility to different conditions such as mixed connective tissue disease, Kawasaki disease and systemic lupus erythematosus (17-20).

Studies on temporal artery biopsies from GCA patients showed that IFNG positively correlated with intimal hyperplasia, and consequently, with ischaemic symptoms (21, 22). Furthermore, IFNG was associated with the presence of cranial ischaemic symptoms and the formation of giant cells in the granulomatous infiltrates (23). In contrast, GCA patients with fever showed a lower expression of *IFNG* mRNA (17). A study conducted by our group found that an *IFNG* microsatellite polymorphism was associated with the development of ischaemic visual manifestations in patients with cranial GCA (24). However, the influence of the *IFNG* pathway has not been specifically explored in patients with the LV-GCA phenotype. In this regard, since ischaemic manifestations are more commonly found in patients with the cranial GCA phenotype, and fever, as a systemic inflammatory manifestation, is more likely to occur in the setting of extracranial LV-GCA, we wondered if *IFNG* and *IFNGR* polymorphisms show differences between patients with cranial and extracranial LV-GCA.

Taking these considerations into account, we evaluated for the first time whether *IFNG* and *IFNGR1* polymorphisms were associated with the different clinical phenotypes of GCA.

Methods

Patients

A total of 191 patients with biopsy-proven cranial GCA and 109 with LV-

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).

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.

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

	Classic cranial GCA pattern n=191	LV-GCA pattern n=109	*p*
Age at diagnosis (mean ± SD)	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; LV: large-vessel; SD: standard deviation; TAB: temporal artery biopsy.

Patients with classic cranial phenotype of GCA

Patients were classified into the cranial phenotype if they fulfilled the American College of Rheumatology (ACR) 1990 classification criteria (25) 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 LV involvement. All of them had a positive temporal artery biopsy consistent with the diagnosis of GCA.

Patients with extracranial LV-GCA phenotype

A well-differentiated subset of patients with the extracranial LV-GCA phenotype was identified by experienced rheumatologists based on the presence of consistent clinical manifestations along with confirmatory imaging techniques. All patients fulfilled the revised criteria for LV-GCA defined in the protocol of GiACTA trial (26, 27) and exhibited LV involvement confirmed by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), angiographic magnetic resonance (MRI-A) and/or computed tomography angiography (CT-A). For the purposes of this study and to establish two well-differentiated disease patterns, patients with extracranial LV-GCA disease presenting cranial symptoms were excluded from the analysis. Patients with other underlying inflammatory conditions, infections or neoplastic diseases that could present with LV involvement were also excluded.

Healthy controls

A cohort of 490 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.

IFNG and IFNGR1 polymorphisms selection and genotyping

Genomic DNA was extracted from peripheral blood using the REALPURE "SSS" kit (RBME04, REAL, Durviz S.L., Valencia, Spain), as previously described (28).

All patients were genotyped for *IFNG* rs2069718 G/A and rs1861493 A/G, as well as for *IFNGR1* rs1327474 G/A by TaqMan assays, previously assessed in several autoimmune conditions (17–20). 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).

For the comparative analysis of genotype and allele frequencies we considered each *IFNG* and *IFNGR1* polymorphism independently. Both genotype and allele frequencies of *IFNG* rs2069718 and rs1861493, as well as *IFNGR1* rs1327474 were calculated and compared between patients with the cranial and the extracranial LV-GCA phenotype as well as between patients with the extracranial LV-GCA phenotype and healthy controls 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).

In a further analysis, allelic combinations (haplotypes) of *IFNG* rs2069718 and rs1861493 were carried out. Haplotype frequencies were calculated by the Haploview v4.2 software (http://broad.mit.edu/mpg/haploview) and then compared by chi-square or Fisher tests between the groups mentioned above. Strength of associations was

estimated by OR and 95% CI. Two-tailed *p*-values lower than 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

Genotyping quality control

The *IFNG* rs2069718 and rs1861493, as well as *IFNGR1* rs1327474 genotype distribution was in HWE. Genotype and allele frequencies were in agreement with the data of the 1000 Genomes Project for Europeans.

Association of IFNG with classic cranial GCA and extracranial LV-GCA

We compared the *IFNG* genotype, allele, and haplotype frequencies between the cohort of 191 patients with the classic cranial GCA pattern and the cohort of 109 patients with the extracranial-LV-GCA pattern. However, no statistically significant genetic differences were found between these groups (Table II).

Association of IFNGR1 with classic cranial GCA and extracranial LV-GCA

Furthermore, we also assessed whether differences in the *IFNGR1* genotype and allele frequencies might exist between GCA patients with the cranial and extracranial phenotype. As shown in Table II, no statistically significant differences were disclosed between GCA patients with the classic cranial pattern and the extracranial LV-GCA pattern.

Difference in IFNG and IFNGR1 between patients with LV-GCA phenotype and healthy controls

Finally, genetic frequencies of IFNG and IFNGR1 were compared between patients with LV-GCA phenotype and healthy controls. As shown in Table III, no statistically significant genetic differences were found between these groups.

Discussion

Two edges have been described in the overlapping clinical spectrum of GCA: the classic cranial phenotype and the extracranial LV-GCA pheno-

Table II. Genetic frequencies of *IFNG* and *IFNGR1* in patients with LV-GCA pattern and classic cranial GCA pattern.

Polymorphism	LV-GCA pattern % (n)	Classic cranial GCA pattern % (n)	*p*	OR [95% CI]
IFNG rs2069718				
GG	38.0 (41)	40.8 (78)	-	Ref.
GA	45.4 (49)	44.0 (84)	0.69	1.11 [0.66-1.86]
AA	16.6 (18)	15.2 (29)	0.64	1.18 [0.59-2.38]
G	60.7 (131)	62.8 (240)	-	Ref.
A	39.3 (85)	37.2 (142)	0.60	1.10 [0.78-1.55]
IFNG rs1861493				
AA	54.1 (59)	57.3 (98)	-	Ref.
AG	37.6 (41)	36.8 (63)	0.76	1.08 [0.65-1.80]
GG	8.3 (9)	5.9 (10)	0.41	1.49 [0.57-3.89]
A	72.9 (159)	75.7 (259)	-	Ref.
G	27.1 (59)	24.3 (83)	0.46	1.16 [0.79-1.71]
IFNGR1 rs1327474				
AA	32.7 (35)	39.3 (75)	-	Ref.
AG	49.5 (53)	47.6 (91)	0.41	1.25 [0.74-2.11]
GG	17.8 (19)	13.1 (25)	0.18	1.63 [0.79-3.34]
A	57.5 (123)	63.1 (241)	-	Ref.
G	42.5 (91)	36.9 (141)	0.18	1.26 [0.90-1.78]
IFNG Haplotypes*	LV-GCA pattern % (n)	Classic cranial GCA pattern % (n)	*p*	OR [95% CI]
GA	60.7 (131)	63.7 (218)	-	Ref.
AG	27.3 (59)	24.3 (83)	0.41	1.18 [0.79-1.76]
AA	12.0 (26)	12.0 (41)	0.84	1.06 [0.62-1.81]

CI: confidence interval; GCA: giant cell arteritis; LV: large-vessel; OR: odds ratio.
*The polymorphism order was rs2069718 and rs1861493.

Table III. Genetic frequencies of *IFNG* and *IFNGR1* in patients with LV-GCA pattern and healthy controls.

Polymorphism	LV-GCA pattern % (n)	Healthy controls % (n)	*p*	OR [95% CI]
IFNG rs2069718				
GG	38.0 (41)	44.0 (215)	-	Ref.
GA	45.4 (49)	44.1 (216)	0.46	1.19 [0.74-1.93]
AA	16.6 (18)	11.9 (58)	0.12	1.63 [0.82-3.15]
G	60.7 (131)	66.1 (646)	-	Ref.
A	39.3 (85)	33.9 (332)	0.13	1.26 [0.92-1.73]
IFNG rs1861493				
AA	54.1 (59)	55.8 (273)	-	Ref.
AG	37.6 (41)	39.3 (192)	0.96	0.99 [0.62-1.57]
GG	8.3 (9)	4.9 (24)	0.18	1.74 [0.67-4.11]
A	72.9 (159)	75.5 (738)	-	Ref.
G	27.1 (59)	24.5 (240)	0.44	1.14 [0.80-1.61]
IFNGR1 rs1327474				
AA	32.7 (35)	34.0 (166)	-	Ref.
AG	49.5 (53)	49.7 (243)	0.89	1.03 [0.65-1.66]
GG	17.8 (19)	16.3 (80)	0.71	1.13 [0.61-2.09]
A	57.5 (123)	58.8 (575)	-	Ref.
G	42.5 (91)	41.2 (403)	0.72	1.06 [0.78-1.42]
IFNG Haplotypes*	LV-GCA pattern % (n)	Healthy controls % (n)	*p*	OR [95% CI]
GA	60.7 (131)	66.1 (646)	-	Ref.
AG	27.3 (59)	24.5 (240)	0.27	1.21 [0.85-1.72]
AA	12.0 (26)	9.4 (92)	0.17	1.39 [0.83-2.27]

CI: confidence interval; GCA: giant cell arteritis; LV: large-vessel; OR: odds ratio.
*The polymorphism order was rs2069718 and rs1861493.

type. Whether genetic factors may play a role in the development of these different clinical phenotypes is still being investigated. Several cytokines and inflammatory pathways are involved in the complex pathophysiology of GCA. Among them, IFNG has shown to be a pivotal cytokine that seems to have a particular implication in the development of severe ischaemic manifestations in patients with the classic cranial GCA phenotype (23, 24). Due to this, we aimed to assess for the first time if a different association with *IFNG* and *IFN*GR1 polymorphisms might exist between patients with the classic cranial phenotype and the extracranial LV-GCA phenotype. Our results indicate that *IFNG* and *IFNGR1* polymorphisms do not influence the clinical expression of GCA.

The role of *IFNG* and *IFNGR1* polymorphisms in the genetic susceptibility and severity of classic cranial GCA was assessed in two former studies carried out by our group (20, 24). In the first study (24), a microsatellite polymorphism in the first intron of *IFNG* was evaluated in 59 biopsy-proven cranial GCA patients, 79 PMR patients and 129 ethnically matched controls from the northern Spain (24). The frequency of *IFNG* allele *4 was reduced, and the frequency of allele *3 was increased in patients with cranial GCA who developed visual ischaemic manifestations. However, no statistically significant differences in the allele frequency of *IFNG* microsatellite polymorphisms were found between cranial GCA patients, PMR patients and healthy controls (24). In a subsequent study we assessed the influence of *IFNGR1* polymorphisms in patients with classic cranial GCA (20). However, no significant differences in the genotype or allele distribution between patients with cranial GCA and controls were found. This was also the case when patients with cranial GCA were stratified according the presence of severe ischaemic complications or PMR (20). In keeping with these observations, in the present study, we have not found differences in the genetic frequencies of *IFNG* and *IFNGR1* polymorphisms between patients with the cranial GCA pattern and the extracranial LV-GCA pattern.

Former studies focused on the role of HLA class I and class II genes and *vascular endothelial growth factor (VEGF)* polymorphisms did not reveal any involvement of these genes in the development of the different clinical phenotypes of GCA (29, 30). Despite these results, we cannot exclude that other genetic polymorphisms account for a different genetic susceptibility in cranial and extracranial LV-GCA. The genetic background of GCA can be even more complex than previously thought. More research is needed to help understand the presence of different clinical patterns of expression in GCA, which could have diagnostic and therapeutic implications(31, 32).

In conclusion, according to our results *IFNG* and *IFNGR1* polymorphisms do not influence the clinical phenotype of expression of GCA. Classic cranial GCA and extracranial LV-GCA seems to share a genetic pattern of *IFNG* pathway.

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Competing interests

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