PROGRAMA DE DOCTORADO EN MEDICINA Y CIENCIAS DE LA SALUD

TESIS DOCTORAL

CARACTERÍSTICAS CLÍNICAS Y MARCADORES GENÉTICOS DE SUSCEPTIBILIDAD DE LA ARTERITIS DE CÉLULAS GIGANTES DE FENOTIPO EXTRACRANEAL

PhD THESIS

CLINICAL MANIFESTATIONS AND GENETIC SUSCEPTIBILITY OF EXTRACRANIAL GIANT CELL ARTERITIS

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A mis padres

Por vuestro amor y apoyo incondicional

Por todo vuestro esfuerzo para que pudiese conseguir mis metas

Por acompañarme siempre en cada paso, desde el más pequeño hasta el más grande

A Gabriel

Por creer siempre en mí y formar parte de todos mis proyectos

Por darme fuerza, amor y confianza para conseguir todo lo que me proponga

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A todos los pacientes y sus familiares porque sin su colaboración nada de esto sería posible.

A mi familia y amigos por su indispensable apoyo en el día a día.

ÍNDICE

1. INTRODUCCIÓN

1. INTRODUCCIÓN

1.1 Estado actual de la Arteritis de Células Gigantes: el espectro clínico está cambiando.

La Arteritis de Células Gigantes (ACG) es la vasculitis más común en pacientes mayores de 50 años procedentes de países occidentales [1,2]. La ACG se caracteriza por la inflamación granulomatosa de la pared de vasos de arterias mediano y gran calibre [1,2]. La primera descripción de esta vasculitis se la debemos al Dr. Bayard T. Horton quién describió en 1932 el caso de dos pacientes en la sexta década de la vida que ingresaron en la Clínica Mayo (Rochester, Estados Unidos) por un cuadro subagudo consistente en cefalea, alteraciones visuales y manifestaciones sistémicas que, además, presentaban tumefacción y dolor a la palpación a lo largo del recorrido de las arterias temporales. La biopsia de arterias temporales reveló inflamación granulomatosa de la pared vascular[3].

Clásicamente la ACG se ha descrito como una vasculitis con especial tropismo por las arterias craneales, en especial por las arterias temporales, por lo que a esta entidad también se le ha denominado durante años Arteritis de la Temporal[4]. Sin embargo, en los últimos años se ha evidenciado la existencia de un subgrupo de pacientes con ACG en los que existe una afectación predominante de vasos extracraneales, como es la aorta y sus principales ramas, que incluso puede ocurrir en ausencia de síntomas sugestivos de afectación clásica craneal. Estos pacientes presentan rasgos demográficos y clínicos diferentes a los pacientes con el fenotipo craneal cásico de la ACG[5–9]. En este sentido, la ACG se considera actualmente una entidad heterogénea en la que se describen dos patrones clínicos, fenotipo craneal cásico y fenotipo extracraneal, que a menudo pueden solaparse entre sí y con la polimialgia reumática (PMR) [9–12] **(Figura 1).**

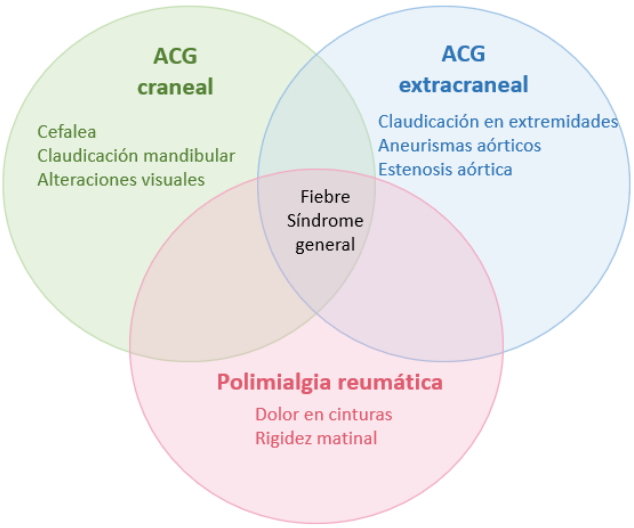

Figura 1. Espectro clínico de la ACG

Las manifestaciones clínicas de la ACG craneal clásica son bien conocidas, incluyendo cefalea, claudicación mandibular y síntomas visuales que pueden evolucionar hacia la ceguera en ausencia de tratamiento [4,13]. Sin embargo, las manifestaciones de la ACG extracraneal son más inespecíficas y por tanto más difíciles de diagnosticar. La ACG extracraneal suele debutar a edades más tempranas con un cuadro polimiálgico refractario al tratamiento convencional con corticoides y que, generalmente, se asocia a síntomas constitucionales como fiebre, astenia y pérdida de peso, y a claudicación vascular en extremidades [5–9]. En estos pacientes la elevación de parámetros analíticos de inflamación, como son la proteína C reactiva (PCR) y la velocidad de sedimentación globular (VSG), suele ser menos marcada [8,14]. Se ha observado en varios estudios que los pacientes con ACG extracraneal tienen menor riesgo de desarrollo de complicaciones isquémicas craneales. Pero, mayor riesgo de desarrollo de aneurismas, estenosis y disección aórtica [6,15]. En estos pacientes la biopsia de arteria temporal, al contrario que en la forma clásica, es generalmente negativa lo que dificulta y retrasa el diagnóstico. En ausencia de una alta sospecha clínica, la ACG extracraneal es a menudo infradiagnosticada, lo que puede conducir hacia graves complicaciones **(Tabla 1).**

Tabla 1.*Diferencias entre la ACG de fenotipo craneal y la ACG de fenotipo extracraneal.*

	ACG fenotipo craneal	**ACG fenotipo extracraneal**
Edad al diagnóstico	65-85 años	50-70 años
Síntomas constitucionales	++	+++
Manifestaciones craneales	+++	+
Biopsia de arteria temporal positiva	++	+/-
Complicaciones visuales isquémicas	+	+/-
Polimialgia reumática	++	+++
Claudicación vascular en extremidades	+/-	+

1.2 Epidemiología de la Arteritis de Células Gigantes

Se considera que probablemente la prevalencia e incidencia de la ACG es más alta que la descrita en los estudios clásicos en los que únicamente se incluyeron pacientes con ACG que cumplían los criterios de clasificación del Colegio Americano de Reumatología (ACR) de 1990[16] o con biopsia de arteria temporal probada [2,17]. El metaanálisis más reciente sobre epidemiología de la ACG ha revelado una incidencia media de 10.0 [9.2-10.8] casos por cada 100.000 pacientes mayores de 50 años, con una edad media de diagnóstico de 79 años y un predominio de mujeres (ratio 2.5:1) [17]. Las incidencias más altas se han encontrado en países escandinavos 10.9 [8.8-13.0], Norteamérica 10.9 [8.8-13-0] y países europeos no-escandinavos 7.3 [6.1-8.5], observando incidencias hasta 6 veces inferiores en países de Asia y África [17]. Los datos epidemiológicos más recientes en España han mostrado una incidencia media de 10.1 [8.9-11.5] casos por cada 100.000 habitantes mayores de 50 años[2,18]. Existen escasos estudios epidemiológicos dirigidos específicamente a estudiar la incidencia de la ACG de fenotipo extracraneal. Un estudio italiano publicado recientemente ha observado una incidencia anual de ACG de 8.3 casos por cada 100.000 habitantes mayores de 50 años, con una incidencia anual de ACG extracraneal de 3.4 casos por cada 100.000 habitantes mayores de 50 años[19]. Este estudio ha revelado importantes diferencias epidemiológicas entre pacientes con ACG con fenotipo craneal clásico y con fenotipo de ACG extracraneal. La incidencia de ambos fenotipos

fue similar en los pacientes menores de 70 años. Sin embargo, en el rango de edad entre 70 y 90 años, la incidencia del fenotipo craneal fue prácticamente el doble que del fenotipo extracraneal [19]. En un estudio escandinavo realizado en 889 autopsias, la prevalencia de ACG extracraneal fue del 1.4-1.7%, teniendo en cuenta que sólo un 20% de estos pacientes tenían diagnóstico previo de ACG craneal[6]. En estudios realizados sobre muestras histológicas obtenidos de cirugías cardiovasculares se observó una prevalencia de ACG extracraneal que oscilaba entre el 1-8.4%[6].

1.3 Inmunopatogenia de la Arteritis de Células Gigantes

La inmunopatogenia de la ACG es compleja y aún no se conoce por completo. Los principales estudios sostienen que la ACG es una enfermedad inmunomediada por linfocitos T en la que el principal factor patogénico es un desequilibrio en la diferenciación de linfocitos T reguladores hacia la formación de linfocitos Th1 y Th17[20,21] **(Figura 2)**. En la ACG parece existir una maduración anormal de las células dendríticas en la pared vascular. En condiciones normales las células dendríticas mantienen la tolerancia inmunogénica en la adventicia de los vasos. Sin embargo, en la ACG las células dendríticas expresan moléculas de superficie y liberan citocinas que activan células de la inmunidad innata, como monocitos y fibroblastos, y además promueven el reclutamiento de linfocitos T que se diferencian hacia linfocitos Th1 productores de interferón gamma (IFN-γ) y linfocitos Th17 productores de IL-17[20,21]. Las respuestas Th1 y Th17 activan los macrófagos que en la adventicia secretan IL1 e IL-6 que a su vez perpetúan y retroalimentan la respuesta inflamatoria. Los macrófagos en la lámina media producen metaloproteasas y destruyen la lámina elástica interna promoviendo la migración y proliferación de miofibroblastos hacia la íntima lo que produce hiperplasia de la íntima y oclusión progresiva del lumen vascular [20,21]. El interferón gamma promueve la diferenciación de los macrófagos hacia la formación de células gigantes multinucleadas, que dan nombre a la enfermedad, y que a su vez secretan más citocinas y factores de crecimiento endotelial [20,21].

El tratamiento con corticoides parece bloquear rápidamente la respuesta Th17 que se ha relacionado con las manifestaciones inflamatorias sistémicas de la ACG y la clínica polimiálgica. Sin embargo, la respuesta Th1 productora de interferón gamma, que se ha relacionado con el desarrollo de manifestaciones isquémicas, suele ser más resistentes al tratamiento corticoideo[22].

Una marcada expresión de IL-6, que a su vez es inductora de la respuesta Th17, se ha asociado con mayor respuesta inflamatoria y menor riesgo de manifestaciones craneales [23]. Por el contrario, la expresión de IL-1β e IFN-γ en la pared de arterias temporales se ha asociado a un aumento de riesgo de complicaciones isquémicas craneales[23,24]. En este sentido es posible que la respuesta Th-17 esté más implicada en la ACG de fenotipo extracraneal, mientras que la respuesta Th-1 sea la dominante en la ACG de fenotipo craneal clásico.

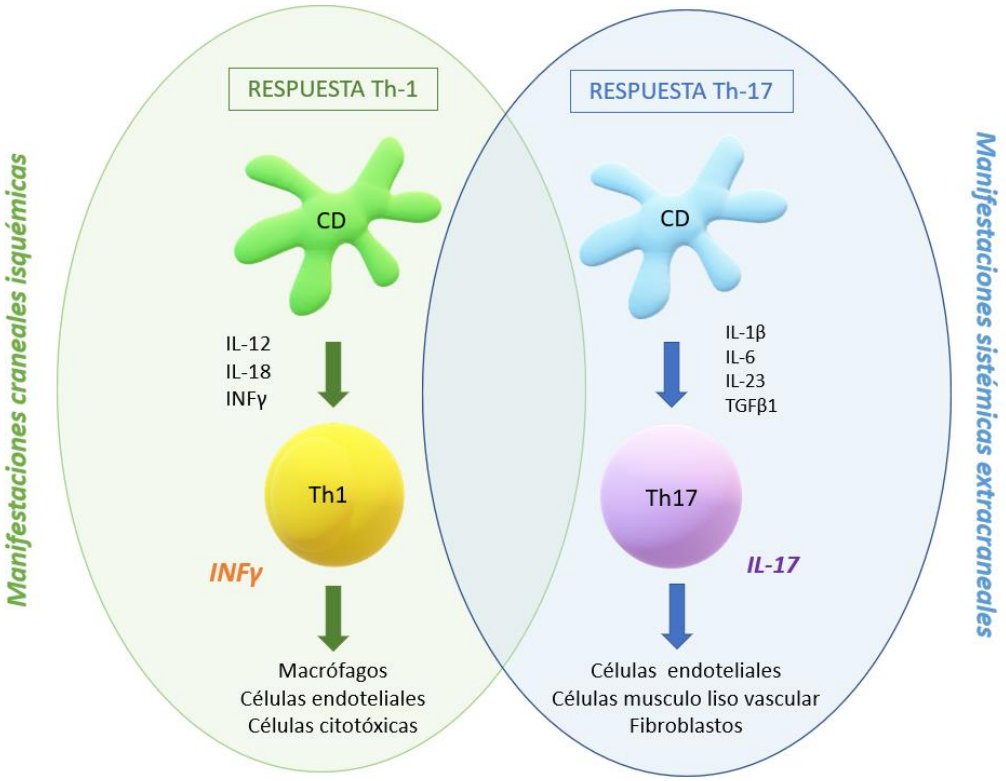

Figura 2. Inmunopatología de la ACG.

1.4 Histopatología de la Arteritis de Células Gigantes

A nivel histológico las muestras de las biopsias de arterias temporales de pacientes con ACG craneal y las muestras de la aorta o sus principales ramas obtenidas durante intervenciones quirúrgicas por complicaciones vasculares en pacientes con ACG extracraneal han mostrado hallazgos similares. Los rasgos histológicos característicos son la presencia de infiltrado inflamatorio transmural compuesto de forma predominante por macrófagos y linfocitos CD4 positivos con presencia de células gigantes hasta en el 50% de las muestras. Otros hallazgos característicos son la fragmentación de la lámina elástica interna, hiperplasia de la íntima y formación de nuevos capilares[1,25–27].

1.5 Diagnóstico de la Arteritis de Células Gigantes

Los criterios ACR 1990 para la ACG [16] resultaron de gran utilidad a lo largo de las últimas décadas para la identificación de pacientes que presentan manifestaciones clínicas predominantemente craneales. Estos criterios incluyen: 1) edad mayor o igual a 50 años al comienzo de los síntomas; 2) cefalea de reciente aparición o distinta a la existente; 3) Alteraciones en el aspecto de las arterias temporales; 4) velocidad de sedimentación globular mayor o igual a 50 mm/h; 5) biopsia de arteria temporal que evidencie vasculitis con predominio de infiltrado inflamatorio mononuclear con formación de granulomas. La presencia de al menos 3 de estos criterios permite establecer el diagnóstico de ACG con una sensibilidad del 93% y una especificidad del 91.2% [16].

Sin embargo, los criterios ACR 1990 no permiten el diagnóstico de pacientes con ACG que debutan con manifestaciones predominantemente extracraneales. Para el diagnóstico de la ACG extracraneal son fundamentales las pruebas de imagen[28–30]. Entre las técnicas de imagen recomendadas por las últimas guías de la Sociedad Europea de Reumatología (EULAR) para el diagnóstico de las vasculitis de grandes vasos se encuentra la ecografía, la angio-resonancia

magnética (RM), la angio-tomografía computarizada (TC) y la tomografía por emisión de positrones (PET)/TC con 18F-fluorodesoxiglucosa (FDG)[31].

La ecografía permite la exploración de las ramas más superficiales de la aorta, como son las arterias axilares y subclavias **(Figura 3)**. Está técnica es útil para detectar, de forma precoz y no invasiva, la presencia de afectación extracraneal en pacientes con ACG[32]. Sin embargo, su utilidad es limitada a la hora de evaluar vasos más profundos, como son la aorta torácica y abdominal. En casos de alta sospecha clínica, necesitaremos otras pruebas de imagen para poder descartar por completo esta entidad[30].

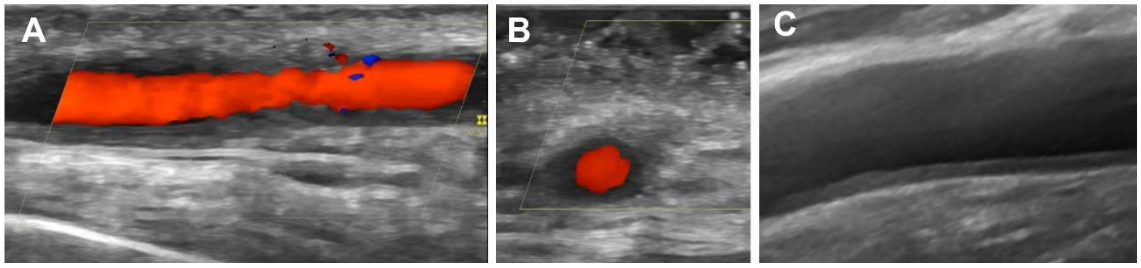

Figura 3. Signo del halo en las arterias temporales y axilares: (A) Corte longitudinal de rama parietal de la arteria temporal (B) Corte transversal de la rama parietal de la arteria temporal (C) Corte longitudinal de la arteria axilar. Imágenes obtenidas por la Dra. Prieto-Peña del Servicio de Reumatología del Hospital Universitario Marqués de Valdecilla.

Tanto la angio-RM, la angio-TC como la 18FDG-PET/TC han demostrado alta sensibilidad y especificidad para el diagnóstico de las vasculitis de grandes vasos permitiendo además descartar daño vascular estructural, como estenosis, oclusiones y aneurismas[28,30]. La decisión de utilizar una prueba de imagen frente a otra dependerá de la disponibilidad y experiencia en cada centro, eligiendo en cada caso la más adecuada según las comorbilidades de cada paciente[31]. Estas técnicas de imagen, en especial la 18FDG-PET/TC **(Figura 4)**, ofrecen la ventaja de descartar en una misma exploración otras enfermedades que también pueden cursar con síndrome polimiálgico y síntomas constitucionales, como neoplasias u otras enfermedades inflamatorias sistémicas, ya que no es excepcional presencia de entidades que imitan una polimialgia reumática [33,34].

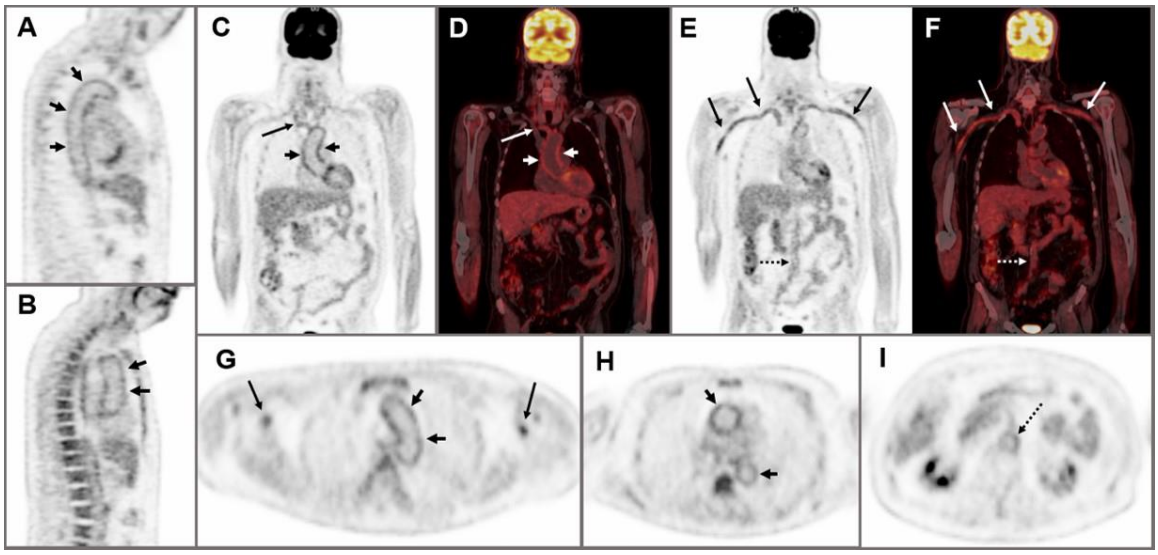

Figura 4. Imágenes de PET/TAC de un paciente con diagnóstico de ACG extracraneal: Corte sagital (A,B), coronal (C,D,E,F) y axial (G,H,I) mostrando hipermetabolismo de la pared vascular del tronco braquiocefálico, arterias subclavias (flechas), aorta torácica (flechas cortas) y aorta abdominal (flecha punteada) sugestivo de vasculitis de grandes vasos. Imagen cedida por la Dra. Martínez-Rodríguez del Servicio de Medicina Nuclear del Hospital Universitario Marqués de Valdecilla.

1.6 Tratamiento de la Arteritis de Células Gigantes

Actualmente, el abordaje terapéutico de la ACG de fenotipo extracraneal es similar al de la ACG de fenotipo craneal. Sin embargo, se desconoce si estos dos subtipos de ACG podrían beneficiarse de diferentes estrategias terapéuticas [35,36]. En ese sentido se ha observado una mayor tendencia a presentar recaídas en pacientes con ACG con fenotipo extracraneal [37], lo que podría implicar la necesidad de un abordaje terapéutico diferente en este subgrupo de pacientes.

Las últimas guías EULAR para el manejo de la ACG no especifican distinciones entre pacientes con ACG con fenotipo craneal y extracraneal[38]. El tratamiento de la ACG se basa en el inicio temprano de corticoides para evitar complicaciones vasculares irreversibles. La dosis inicial de prednisona recomendada es de 40-60 mg/día durante 4 semanas con una pauta posterior descendente disminuyendo 5mg cada 2 semanas hasta alcanzar la dosis de 25mg/día. Luego disminuir 2.5-5mg cada 2-4 semanas hasta llegar a dosis de 10mg/día y posteriormente disminuir 2.5mg cada 2 meses[38]. En casos graves de ACG clásica craneal con clínica visual se

recomienda la administración de bolos de metilprednisolona 500mg-1g ev/día x 3 días consecutivos.

En pacientes con ACG refractaria a tratamiento convencional con glucocorticoides o que presenten efectos adversos/intolerancia a los mismos, se recomienda inicio de tratamiento con inhibidor del receptor de la IL 6, Tocilizumab (TCZ) (162 mg semanal sc o 4-8 mg/kg/ev mensual), y de forma alternativa con Metotrexato (10-25 mg/semanal preferiblemente subcutáneo)[38]. El ensayo clínico pivotal, GiACTA trial [39], que demostró la efectividad de TCZ y permitió su aprobación en ficha técnica para el tratamiento de la ACG incluyó tanto pacientes con fenotipo craneal como extracraneal. Un estudio observacional multicéntrico posterior liderado por nuestro grupo que incluyó 134 pacientes con ACG confirmó la efectividad de TCZ en la práctica clínica real [40]. Sin embargo, actualmente, se desconoce si la respuesta terapéutica a TCZ es diferente en función del patrón de afectación craneal o extracraneal de la ACG, o si el bloqueo de otras dianas terapéuticas podría se más o menos beneficioso dependiendo del patrón clínico de la ACG.

1.7 Justificación del estudio

Las diferencias descritas en cuanto a la epidemiología y presentación clínica entre la ACG de fenotipo craneal y la ACG de fenotipo extracraneal plantean la posibilidad de que podría existir una predisposición genética diferente que explicase estas diferencias. La profundización en el conocimiento de las bases inmunogénicas de los diferentes subtipos de ACG podría ser fundamental en un futuro próximo a la hora de realizar un diagnóstico precoz y poder ofrecer tratamientos dirigidos individualizados.

Hasta donde sabemos, la ACG es una enfermedad poligénica en la cual los genes del antígeno leucocitario humano (HLA) parecen jugar un papel crucial. En este sentido, se ha postulado que la ACG se asocia principalmente con los genes HLA de clase II (fundamentalmente con *HLA*-

*DRB1*04*), aunque los genes HLA de clase I (*HLA-B *15*) también parecen contribuir a la susceptibilidad para el desarrollo de la enfermedad[41–46].

En la década de 1990, estudios pioneros trataron de dilucidar si los pacientes con ACG craneal y los pacientes con PMR aislada, entidades a menudo solapantes pero con rasgos clínicos muy diferentes, presentaban una susceptibilidad genética diferente [47,48]. Los pacientes con ACG clásica craneal asociada o no a PMR presentaron una clara asociación con *HLA-DRB1*0401* y más débilmente con *HLA-DRB1*0101* y *HLA-DRB1*0102*. Sin embargo, esta asociación no se observó en los pacientes con PMR aislada, donde se encontró una asociación con *HLA-DRB1*13* y *HLA-DRB1*14* [47,48]. Tomando ahora el relevo de estos estudios, y en base al descubrimiento en los últimos años del fenotipo de ACG extracraneal, nos planteamos si la susceptibilidad genética en pacientes con ACG extracraneal es similar a la de los pacientes con ACG craneal clásica o si por el contrario es diferente.

2. HIPÓTESIS GENERAL Y OBJETIVOS

2. HIPÓTESIS GENERAL Y OBJETIVOS

2.1 Hipótesis General

En base a las diferencias clínicas y epidemiológicas que existen entre los pacientes con ACG con fenotipo craneal clásico y los que presentan un fenotipo predominantemente extracraneal, nos planteamos que podría existir una susceptibilidad genética diferente que explicase estas diferencias fenotípicas. Los resultados derivados de la presenta tesis doctoral permitirán contribuir a esclarecer si existen diferencias en la fisiopatogenia de la ACG craneal clásica y la ACG extracraneal lo que podría tener implicaciones en el diagnóstico y tratamiento de los pacientes con ACG.

2.2 Objetivos

1) Identificar y reclutar una cohorte de pacientes con ACG extracraneal y describir sus rasgos clínicos.
2) Evaluar la implicación de los genes HLA (clase I y II) en una cohorte de pacientes con ACG con fenotipo extracraneal y compararla con una cohorte de pacientes con ACG con fenotipo craneal clásico y con controles sanos.
3) Determinar el potencial papel de otras variantes genéticas implicadas en la fisiopatología de la ACG en una cohorte de pacientes con ACG con fenotipo extracraneal y compararla con una cohorte de pacientes con ACG con fenotipo craneal clásico y con controles sanos.

3. PUBLICACIONES

3. RELACIÓN DE LOS ARTÍCULOS QUE COMPENDIAN LA TESIS DOCTORAL

Las publicaciones que compendian este trabajo de tesis doctoral son las siguientes:

- **Artículo 1:** *Predictors of positive 18F-FDG PET/CT-scan for large vessel vasculitis in patients with persistent polymyalgia rheumatica.*
- **Artículo 2:** *Cranial and extracranial giant cell arteritis share similar HLA-DRB1 association.*
- **Artículo 3:** *The presence of both HLA-DRB1*04:01 and HLA-B*15:01 increases the susceptibility to cranial and extracranial giant cell arteritis.*
- **Artículo 4:** *Vascular Endothelial Growth Factor haplotypes are associated with severe ischemic complications in Giant Cell Arteritis regardless of the disease phenotype.*

El **artículo 1** constituyó el primer paso para la consecución del primer objetivo de la presente tesis doctoral. Este artículo permitió identificar y reclutar una cohorte inicial de pacientes con ACG extracraneal y describir sus rasgos clínicos. En los **artículos 2 y 3** se evaluó la implicación de los genes HLA (clase I y II) en una cohorte de pacientes con ACG con fenotipo extracraneal y se comparó con una cohorte de pacientes con ACG con fenotipo craneal clásico y con controles sanos, cumpliendo así con el segundo objetivo de la presente tesis doctoral. Finalmente, el tercer objetivo que consistía en estudiar el potencial papel de otras variantes genéticas implicada en la fisiopatología de la ACG, se completó en el **artículo 4** en el que se estudió la influencia de polimorfismos de nucleótido único del gen del factor de crecimiento endotelial vascular (*VEGF*), en una cohorte de pacientes con ACG con fenotipo extracraneal comparándola con una cohorte de pacientes con ACG con fenotipo craneal clásico y con controles sanos.

ARTÍCULO 1

ARTÍCULO 1

Título: ***Predictors of positive 18F-FDG PET/CT-scan for large vessel vasculitis in patients with persistent polymyalgia rheumatica.***

Autores: Prieto-Peña D, Martínez-Rodríguez I, Loricera J, Banzo I, Calderón-Goercke M, Calvo-Río V, González-Vela C, Corrales A, Castañeda S, Blanco R, Hernández JL, González-Gay MÁ.

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PREDICTORS OF POSITIVE 18F-FDG PET/CT-SCAN FOR LARGE VESSEL VASCULITIS IN PATIENTS WITH PERSISTENT POLYMYALGIA RHEUMATICA

Authors

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Abbreviations

18F-FDG: 18F-Fluorodeoxyglucose

CI: confidence interval

CRP: C-reactive protein

CT: computed tomography

ESR: erythrocyte sedimentation rate

GCA: giant cell arteritis

IQR: interquartile range

LVV: large-vessel vasculitis

OR: odds ratio

PMR: polymyalgia rheumatica

PET/CT: positron emission tomography/computed tomography

SD: standard deviation

ABSTRACT

Objective: Polymyalgia rheumatica (PMR) is often the presenting manifestation of giant cell arteritis (GCA). Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) scan often discloses the presence of large vessel vasculitis (LVV) in PMR patients. We aimed to identify predictive factors of a positive PET/CT scan for LVV in patients classified as having isolated PMR according to well-established criteria.

Methods: A set of consecutive patients with PMR from a single hospital were assessed. All of them underwent PET/CT scan between January 2010 and February 2018 based on clinical considerations. Patients with PMR associated to other diseases, including those with cranial features of GCA, were excluded. The remaining patients were categorized in classic PMR (if fulfilled the 2012 EULAR/ACR classification criteria at disease diagnosis; n=84) or atypical PMR (who did not fulfill these criteria; n=16). Only information on patients with classic PMR was assessed.

Results: The mean age of the 84 patients (51 women) with classic PMR was 71.4±9.2 years. A PET/CT scan was positive in 51(60.7%). Persistence of classic PMR symptoms was the most common reason to perform a PET/CT scan. Nevertheless, patients with positive PET/CT scan often had unusual symptoms. The best set of predictors of a positive PET/CT scan were bilateral diffuse lower limb pain (OR=8.8, 95% CI 1.7-46.3; p=0.01), pelvic girdle pain (OR=4.9, 95% CI 1.50-16.53; p=0.01) and inflammatory low back pain (OR=4.7, 95% CI 1.03-21.5; p=0.04).

Conclusion: Inflammatory low back pain, pelvic girdle and diffuse lower limb pain are predictors of positive PET/CT scan for LVV in PMR.

Key words: polymyalgia rheumatica, giant cell arteritis, large vessel vasculitis, PET/CT scan, predictors.

Running Tittle: Predictors of positive PET for LVV in PMR.

1. INTRODUCTION

Polymyalgia rheumatica (PMR) is a relatively common disease among individuals of European background [1,2]. It occurs mainly in people older than 50 years [1,2]. Pain and stiffness involving the shoulder girdle and the proximal aspects of the arms are typical features of this condition [3]. Other common manifestations are pain and stiffness in the neck, pelvic girdle and thighs [3]. In most cases, PMR is associated with elevation of acute phase proteins, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [3].

Although PMR symptoms may be observed in a large spectrum of conditions that sometimes mimic a "pure" PMR [4], the most remarkable association of PMR is with giant cell arteritis (GCA) [5]. As occurs with PMR, GCA is also more common in people older than 50 years of European descent, in particular those with Scandinavian background [1,2].

PMR and GCA are often overlapping conditions, and PMR may be the presenting manifestation of GCA [5]. Although in a population based-study almost 50% of patients with classic biopsy-proven GCA had PMR manifestations [6], most studies indicate that the frequency of patients with PMR who have concomitant GCA is approximately 20% [7,8].

The classic pattern of GCA is characterized by the presence of cranial ischemic manifestations. Nevertheless, some patients with GCA present large-vessel vasculitis (LVV) features without headache, abnormal temporal arteries on physical examination or other typical manifestations of this entity [9]. In these cases, the temporal artery yield is lower than in the classic cranial form of GCA [9]. With respect to this, the advent of new imaging techniques has allowed us to identify a large proportion of GCA patients who have LVV involvement without cranial ischemic manifestations. This is especially true when we use fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) [10].

Despite a major advance in the diagnosis of GCA, an issue that remains a challenge for the clinicians who treat PMR is to identify those individuals who have a "silent" underlying LVV. Interestingly, a positive 18F-FDG PET/CT scan showing the presence of LVV is observed in at least a third of the patients presenting with PMR [3]. Although PMR and GCA exhibit a rapid response to corticosteroids in most cases, the initial dose required for the management of these conditions is certainly different. Thus, whereas 12.5-25 mg/day of prednisone/prednisolone is the initial dose of glucocorticoid recommended by the EULAR expert Committee for the management of PMR [11], this dose is in most cases insufficient to prevent severe ischemic manifestations in patients with GCA [12,13]. Moreover, in some cases, patients initially diagnosed as having isolated PMR experience a relapse that include features of a previously silent GCA [13]. In this regard, Narvaez et al. retrospectively reviewed a series of 167 patients with GCA. Seventy-nine percent of them were diagnosed with GCA by a positive temporal artery biopsy and the remaining by well-established classification criteria. Eighteen (11%) of these 167 patients were initially diagnosed with isolated PMR. At that time, they did not have clinical manifestations of GCA and all of them showed a rapid response to 10-20 mg/day of prednisone, with normalization of the acute-phase proteins. However, during the follow-up, 17 patients had relapses with cranial ischemic manifestations of GCA and 1 patient suffered an upper extremity vascular insufficiency due to stenotic involvement of the left subclavian and axillary arteries. Moreover, 9 of these 18 patients initially diagnosed as having isolated PMR suffered severe ischemic complications of GCA, including visual ischemic complications in 7, with permanent visual loss in 2 of them [13]. These observations highlight the need for a close-follow-up of patients diagnosed as having "pure" isolated PMR. In this regard, an issue of major relevance is to identify those patients with PMR who have LVV involvement in the setting of GCA. Although 18F-FDG PET/CT scan is useful to demonstrate the presence of LVV in patients presenting with PMR, this technique is expensive and associated with radiation exposure.

Taking all these considerations into account, in the present study, we aimed to identify predictive factors of a positive 18F-FDG PET/CT scan for LVV in patients presenting with well-defined PMR without cranial manifestations of GCA.

2. PATIENTS AND METHODS

Patients

A set of consecutive patients were prospectively included in the study. They were diagnosed with PMR at a single tertiary care center were assessed. All of them underwent 18F-FDG PET/CT scan between January 2010 and February 2018, based on clinical considerations, to identify the presence of LVV involvement.

Inclusion and exclusion criteria and clinical definitions

During the recruitment period, patients with polymyalgia symptoms associated with cranial ischemic manifestations suggestive of GCA were excluded. In this regard, none of the patients included in the present study fulfilled the 1990 American College of Rheumatology classification criteria for GCA [14]. Patients with PMR symptoms associated with another underlying inflammatory or neoplastic disease that could mimic PMR were also excluded [3,4].

The remaining patients were categorized into classic PMR (if fulfilled the 2012 EULAR/ACR classification criteria at disease diagnosis) or atypical PMR (patients with PMR symptoms who did not fulfill these criteria) [15]. Most patients (n= 84) were classified as having classic (typical) PMR. At the time of disease diagnosis, these patients were older than 50 years old, had predominant inflammatory shoulder pain and elevation of acute phase proteins (ESR and/or CRP). All of them tested negative for rheumatoid factor and anti-cycle citrullinated peptide antibodies and did not exhibit peripheral arthritis. Based on the attending physician's decision, a temporal artery biopsy of at least 1 cm in length was performed in 36 of them. In all cases the histology was informed as normal (negative for GCA). A few patients (n= 16) had polymyalgia

manifestations but they did not fulfill the 2012 EULAR/ACR classification criteria. Six of them were under 50 years of age at the time of PMR diagnosis (range of age in these 6 patients: 43-48 years). Another 10 patients did not complain of relevant pain and stiffness in the arms and shoulder girdle at any time. However, they had typical inflammatory pain involving the pelvic girdle and the proximal aspects of the limbs. In addition, these 16 patients had elevation of acute phase proteins (ESR and/or CRP). No other conditions were found to be responsible for the polymyalgia syndrome in these 16 patients after at least one year of follow-up since the onset of polymyalgia symptoms. Moreover, none of them developed cranial ischemic manifestations over the extended follow-up period.

The reasons for requesting a PET/CT scan in patients with classic PMR were the following: 1) Persistence of typical classic PMR features despite receiving a treatment with at least 15 mg/day of prednisone. 2) Occurrence of unusual manifestations, such as inflammatory low back pain or bilateral diffuse lower limb pain (including in some cases intermittent claudication pain on movement in the lower extremities). 3) Development of marked constitutional symptoms (with or without fever) in the follow-up period despite receiving glucocorticoid therapy. 4) Unexplained increase of acute phase proteins (ESR and/or CRP) despite therapy.

In PMR patients who did not fulfill the 2012 EULAR/ACR classification criteria, a PET/CT scan was requested because of the unusual presentation of symptoms or if PMR patients were under 50 years of age.

Epidemiological differences between patients with classic and atypical PMR are shown in Table 1. Patients with atypical PMR were younger and had a shorter duration of symptoms when a 18F-FDG PET/CT scan was requested than those with classic PMR. However, the percentage of positive 18F-FDG PET/CT scans was similar in both groups of patients. In an attempt to identify the presence of LVV in patients with well-defined PMR, only patients with classic presentation

at the time of disease diagnosis, who at that time were included in the category of classic PMR were included in the analysis.

Definitions of atypical manifestations

Inflammatory low back pain was considered to be present if the patient presented low back pain that improved with movement but not with rest, and it was usually predominant at night. Bilateral diffuse lower limb pain was defined when the patient complained of pain in both legs, in the thighs as well as anywhere between the knees and the ankles. Patients with these symptoms often complained of muscle pain on mild exertion such as walking, predominantly in the calves, which improved by a short period of rest [16]. Constitutional symptoms were considered to be present if the patient had asthenia, anorexia and/or weight loss greater than 5% of the normal body weight during the last six months. Fever was defined if the temperature was ≥ 38ºC without any evidence of infectious or neoplastic underlying disease.

Laboratory data

All patients with classic PMR had initially been treated with prednisone at an initial dose of least 15 mg/day. They were still taking prednisone (mean± standard deviation [SD]: 12.1±6.3 mg/day) when the 18F-FDG PET/CT scan was performed. CRP was considered to be abnormal at the time of performing 18F-FDG PET/CT scan if the value was higher than 0.5 mg/dL. At that time, an ESR level above 20 mm/1st hour was considered elevated.

PET/CT scan equipment and protocol

Patients had to be in a low carbohydrate diet 48 hours before the scan, with reduced physical exercise for 24 hours and fasting state for at least 6 hours before 18F-FDG administration. Serum glucose level was lower than 160 mg/dL in all the patients. Whole-body PET/CT scan was acquired 180 minutes after intravenous injection of 7 MBq/kg of 18F-FDG using a Biograph LSO Pico 3D (Siemens Healthcare Molecular Imaging, Hoffman Estates, Illinois, USA). A low dose CT

scan for attenuation correction and anatomic localization was first obtained, followed by a PET scan (acquiring 250 s/bed position). Images were reconstructed using the ordered subsets-expectation maximization (OSEM) algorithm (2 iterations, 8 subsets). Images were visually evaluated by two experienced nuclear medicine specialists according to the intensity of the 18F-FDG uptake by the vessel wall at the supraaortic trunks, thoracic aorta, abdominal aorta, iliac arteries and femoral/tibioperoneal arteries. PET/CT images were visually evaluated grading the vascular FDG uptake in comparison to liver uptake. PET/CT scans were considered positive for active LVV when a pattern of linear uptake was found in the aorta wall and its branches (when involved) with an intensity similar or higher than the liver, according to previous reports [17-19] and the recently published recommendations of the EANM, SNMMI, and the PET Interest Group, and endorsed by the American Society of Nuclear Cardiology [20]. Figures 1A and 1B shows two representative cases of PMR with negative and positive PET/CT scan for LVV, respectively.

Statistical analysis

All continuous variables were tested for normality, and results were expressed as mean ±SD or as median and interquartile range (IQR) as appropriate. Student's t test or Mann-Whitney U-test were used to compare continuous variables, and □2-test for categorical variables. Multivariable stepwise logistic regression analyses were conducted to identify the independent set of predictors for a positive 18F-FDG PET/CT scan. The predicted probability for a positive imaging result was calculated from the regression model for each patient. The reliability of the model was evaluated using the Hosmer-Lemeshow goodness-of-fit test. The area under the ROC curve and its 95% CI tested the discriminative ability of the regression model. A p value <0.05 was considered as statistically significant in all the calculations. Data management and analysis were performed using SPSS (v19.0) [21].

3. RESULTS

The mean age of the 84 patients (51 women/33 men) with classic PMR was 71.4±9.2 years. A PET/CT scan was positive in 51(60.7%) of them.

Persistence of classic PMR symptoms, alone or associated to the presence of unusual manifestations and/or constitutional symptoms, was the most common reason for requesting a PET/CT scan (Table 2).

Differences between patients with classic PMR according to PET/CT scan results

The main clinical and laboratory differences between patients with classic PMR who had a positive 18F-FDG PET/CT scan for LVV and those in whom this procedure was negative are shown in Table 2. No differences in the age and sex between those with positive and negative 18F-FDG PET/CT scan were observed. It was also the case for the presence of classic cardiovascular risk factors. With regard to the typical PMR features, patients with positive 18F-FDG PET/CT scans had more commonly pelvic girdle involvement than those with negative 18F-FDG PET/CT scans (86.3% versus 36.4%; $p<0.01$). More importantly, patients with classic PMR who had a positive 18F-FDG PET/CT scan showed more commonly atypical PMR features, such as inflammatory low back pain (29.4% versus 9.1%; $p= 0.027$) or diffuse lower limb pain (52.9% versus 6.1%; $p<0.01$) at the time of PET/CT scan performance (Figures 2A and 2B). However, no differences between patients with positive and negative 18F-FDG PET/CT scan were observed according to the presence of constitutional symptoms (including fever in this category). Also, the values of laboratory markers of inflammation and the dose of prednisone at the time of 18F-FDG PET/CT scan were similar in both groups (Table 2).

Multivariate logistic regression model showing the best set of predictors for the presence of LVV in the PET/CT scan

Table 3 shows the best set of predictors of a positive 18F-FDG PET/CT-scan for LVV. They were bilateral diffuse lower limb pain (odds ratio-OR=8.8, 95% confidence interval [CI] 1.7-46.3; p=0.01), pelvic girdle pain (OR=4.9, 95% CI 1.50-16.53; p=0.01) and inflammatory low back pain (OR=4.7, 95% CI 1.03-21.5; p=0.04) once adjusted for age and sex. Further adjustments, including for diabetes status, did not virtually change these results.

Figure 3 shows the ROC analysis of the full predictive model for a positive 18F-FDG PET/CT scan result showing LVV in patients with classic PMR (area under the curve 0.85 [95% CI 0.76- 0.93]; p<0.0001). A cut-off point of 0.55 yielded a sensitivity of 86% and a specificity of 64%. The correspondent figures for a cut-off point of 0.70 were 65% and 91%.

4. DISCUSSION

The present study confirms that patients who fulfill well-established classification criteria for PMR often have LVV. Interestingly, besides the classic pelvic girdle involvement, the presence of atypical symptoms, such as inflammatory low back pain or bilateral diffuse pain in the lower extremities, was a predictor of underlying LVV in these patients at the time of PET/CT scan evaluation.

Experts in the field consider that PET/CT scans may show LVV involvement in at least a third of patients with PMR [22-24]. The results of our study suggest that the prevalence of LVV in patients with well-defined PMR may be higher, reaching in our series up to 60%. Our results were in keeping with a former prospective study of our group that included 40 consecutive patients (27 women/13 men, 68.10±10.27 years) with PMR assessed by 18F-FDG PET/CT scan. In that study, this imaging technique disclosed LVV in 26 of the 40 patients [25]. The high percentage of LVV in our PMR series can be explained in part by the criteria used for the interpretation of PET/CT scan images. As Lavado-Pérez et al. did, we used a more delayed acquisition protocol in comparison to that applied in oncological patients, because it has

demonstrated a better visualization of the vessel wall uptake, due to the decrease of the blood pool activity and the increase in the lesion/background ratio [18,19].

Early detection of LVV in patients with PMR is of potential relevance to determine the actual spectrum of the disease [26-28]. 18F-FDG PET/CT has demonstrated to be very sensitive to make an early diagnosis of LVV [29-36]. However, information aimed to identify clinical and laboratory predictors of a positive 18F-FDG PET/CT for LVV in patients with PMR is scarce [37]. In this sense, in a multicenter retrospective study that included patients with GCA, PMR and other inflammatory disorders assessed by 18F-FDG PET/CT scan, Hooisma et al. reported that an elevated ESR was a positive predictor whereas arthralgia was a negative predictor for LVV [37]. Nevertheless, they concluded that a reliable prediction of the result of the 18F-FDG PET/CT based only on these two parameters was not possible [37]. In the present study we assessed patients with well-defined PMR, including for this purpose only those who fulfilled 2012 EULAR/ACR classification criteria [15]. According to our results, besides pelvic girdle pain, atypical manifestations, such as inflammatory low back pain and lower diffuse limb pain, were predictors of a positive 18F-FDG PET/CT scan result for LVV in patients with PMR. Noteworthy, 18F-FDG PET/CT was negative for LVV in all our patients when it was performed because of a marked unexplained elevation of serum CRP and ESR levels not associated to typical or atypical manifestations of the disease. Thus, it seems that a reliable prediction of a positive result for LVV in 18F-FDG PET/CT, based only on an elevation of acute phase proteins is not possible.

A potential limitation of our study may be that our patients were taking prednisone at the time of PET/CT scan assessment. In this regard, glucocorticoids decrease the intensity of vessel wall 18F-FDG uptake [19,38,39]. However, Cimmino et al. [40], demonstrated that 18F-FDG PET/CT scan is useful for the evaluation of LVV in patients with PMR despite a previous treatment with low-dose glucocorticoids. This is especially true if PET/CT scan is performed within the first 3 days after the onset of glucocorticoid therapy [20].

As occurs in the majority of studies of this type, another limitation was the absence of histological confirmation of LVV. Moreover, the size of the study group could also be considered as a potential limitation. However, we think that our series of patients with classic PMR was large enough to disclose predictors of LVV in PMR patients undergoing 18F-FDG PET/CT scan. Moreover, to the best of our knowledge, the present study constitutes the first attempt to identify the best set of predictors for LVV in a series of patients classified as having PMR according to the 2012 EULAR/ACR classification criteria.

5. CONCLUSIONS

In conclusion, our findings indicate that in patients with classic PMR, besides pelvic girdle pain, the presence of inflammatory low back pain and diffuse lower limb pain may have clinical relevance to identify a LVV by 18F-FDG PET/CT scan. In agreement with experts in the field [28], we feel that higher physician awareness and broader use of vascular imaging techniques to disclose LVV involvement is needed in patients with PMR.

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FIGURE LEGENDS

Figure 1A. An 88-year-old man with PMR. Although the patient experienced a rapid response to prednisone (15 mg/day), he suffered an unexplained increase of ESR/CRP not associated with polymyalgia symptoms. Because of that, a PET/CT-scan was performed to exclude LVV. Coronal (A), sagittal (B) and axial (C) 18F-FDG PET images ruled out inflammation of large vessels.

Figure 1B. A 69-year-old woman with PMR and persistence of classic PMR symptoms despite prednisone therapy along with unusual symptoms (inflammatory low back pain) at the time of assessment. Sagittal PET (A) and fused PET/CT (B), axial PET (C) and fused PET/CT (D), and coronal PET (E) images (E) showed inflammation along the thoracic aorta wall (head arrows) and supra-aortic trunks (arrows).

Figure 2. A 63-year-old woman, who initially had with typical PMR features, started to complain of diffuse lower limb pain and intermittent vascular claudication associated to persistent pelvic girdle pain when prednisone dose was tapered. Besides typical bursitis in the setting of PMR demonstrated by 18F-FDG PET/CT in the shoulders and cervical and lumbar interspinous spaces, trochanteric and ischiatic regions of both hips (arrows) (Figure 2A), the images also disclosed the presence of LVV with increased 18F-FDG uptake involving the femoral arteries (Figure 2B). A mild 18F-FDG uptake was also observed at the thoracic aortic wall (Figure 2A).

Figure 3. ROC analyzing the performance of the full predictive model of a positive 18F-FDG PET/CT scan result for LVV in patients with classic PMR.

ROC: Receiver operating characteristics.

Table 1. Epidemiological differences between classic and atypical PMR.

	Total PMR (N=100)	**Classic PMR (N=84)**	**Atypical PMR (N=16)**	**P**
Age (years), mean ±SD	69.34 ± 10.6	71.4 ± 9.2	58.4 ± 10.9	**< 0.01**
Sex (women), n (%)	61 (61.0)	51 (60.7)	10 (62.5)	0.89
Duration of symptoms* (mo), median [IQR]	12.0 [6.0-40.0]	14.0 [6.0-40.0]	6.0 [3.5-11.5]	**0.004**
Positive PET/CT scan result, n (%)	63 (63.0)	51 (60.7)	12 (75.0)	0.29

PET/CT: positron emission tomography complemented by computed tomography; PMR: polymyalgia rheumatica; IQR: interquartile range; SD: standard deviation. ***** At the time of PET/CT scan performance.

Table 2. Main clinical features and laboratory findings of 84 patients with classic PMR when the PET/CT scan was performed.

	Classic PMR (N=84)		
	Positive PET/CT (N= 51)	**Negative PET/CT (N=33)**	***P***
Sex (women), n (%)	31 (62.7)	19 (57.6)	0.64
Age (years), mean ±SD	70.0 ± 9.2	73.7 ± 9.0	0.09
Cardiovascular risk factors, n (%)			
Hypertension	29 (56.9)	24 (72.7)	0.14
Dyslipidemia	18 (35.3)	16 (48.5)	0.23
Diabetes mellitus	10 (19.6)	12 (36.4)	0.09
Current smokers	5 (9.8)	1 (3.0)	0.40
Polymyalgia symptoms, n (%)			
Neck pain	9 (17.6)	9 (27.3)	0.29
Shoulder girdle pain	33 (64.7)	26 (78.8)	0.17
Pelvic girdle pain	44 (86.3)	12 (36.4)	**< 0.01**
Morning stiffness	11 (21.6)	10 (30.3)	0.44
Unusual symptoms, n (%)			
Inflammatory low back pain	15 (29.4)	3 (9.1)	**0.027**
Diffuse lower limb pain	27 (52.9)	2 (6.1)	**< 0.01**
***Constitutional symptoms,* n (%)**			
Fever	2 (3.9)	2 (6,1)	0.64
Asthenia	15 (29.4)	8 (24.2)	0.60
Hyporexia	4 (7.8)	7 (21.2)	0.08
Weight los	9 (17.6)	8 (24.2)	0.46
Laboratory markers,			
Hb (g/dL), mean ± SD	12.7 ± 1.3	12.2 ± 1.6	0.09
Platelet count ($\times 10^9$/l), mean ± SD	281.4 ± 84.9	263.7 ± 100.3	0.19
CRP (mg/dL), median [IQR]	2.0 [0.6-4.4]	2.0 [1.1-5.3]	0.28
ESR (mm/1st h), median [IQR]	33.0 [12.0-65.0]	48.0 [29.5-73.0]	0.15
Treatment,			
Glucocorticoids, n (%)	51 (100.0)	33 (100.0)	0.99
Dose of Prednisone (mg), mean ± SD	12.0 ± 5.7	12.3 ± 7.3	0.88
Months of treatment with Prednisone, median [IQR]	4 [1.0-15.0]	7 [2.5-15.5]	0.31
Methotrexate, n (%)	11 (21.6)	4 (12.1)	0.27
Reasons for PET/CT scan request, n (%)			
Persistence of classic PMR symptoms*	8 (15.7)	10 (30.3)	0.19
Presence of unusual symptoms without classic PMR symptoms*	1 (2.0)	1 (3.0)	0.69
Presence of constitutional symptoms without classic PMR or unusual symptoms*	1 (2.0)	2 (6.1)	0.69
Unexplained increase of ESR/CRP not associated with classic PMR symptoms or unusual symptoms	0 (0.0)	4 (12.1)	**0.04**
Persistence of classic PMR symptoms + unusual symptoms*	25 (49.0)	5 (15.2)	**0.003**
Persistence of classic PMR symptoms + constitutional symptoms*	4 (7.8)	9 (27.3)	**0.04**
Persistence of classic PMR symptoms + constitutional symptoms + unusual symptoms*	12 (23.5)	2 (6.1)	0.07

CRP: serum C reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; PET/CT: positron emission tomography complemented by computed tomography; PMR: polymyalgia rheumatica; IQR: interquartile range; SD: standard deviation. *In most cases associated with mild or moderate elevation of ESR and/or CRP.

Table 3. Multivariate logistic regression model showing the best set of predictors of a positive result for LVV in ^{18}F-FDG PET/CT scan in patients with classic PMR.

Variable	Beta	OR	95% CI	*P*
Classic PMR				
Diffuse low back pain	1.55	4.7	1.03-21.5	**0.04**
Lower limb pain	2.17	8.8	1.70-46.3	**0.01**
Pelvic girdle pain	1.58	4.9	1.50-16.3	**0.01**

CI: confidence interval; OR: odds ratio; PMR: polymyalgia rheumatica.

FIGURE 1A

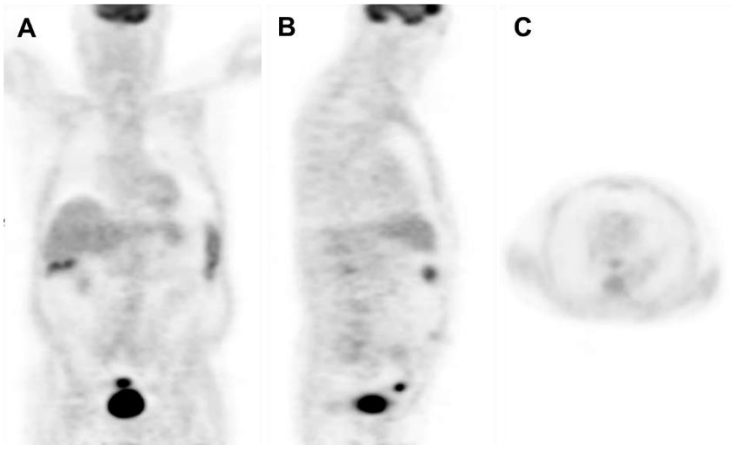


FIGURE 1B

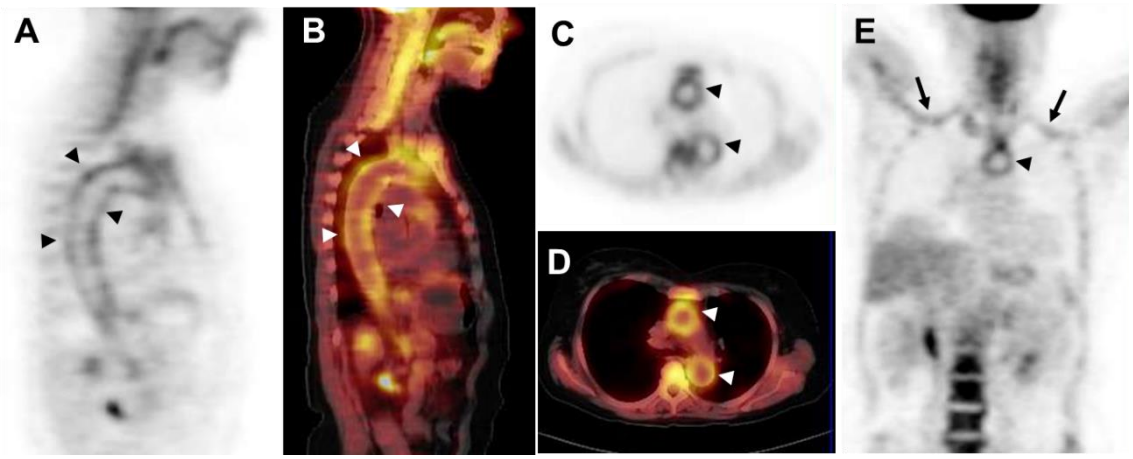


FIGURE 2A

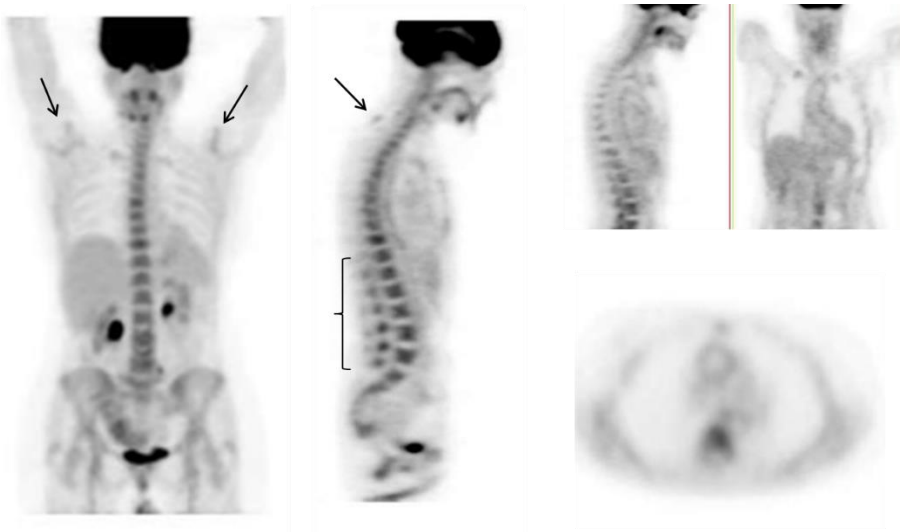


FIGURE 2B

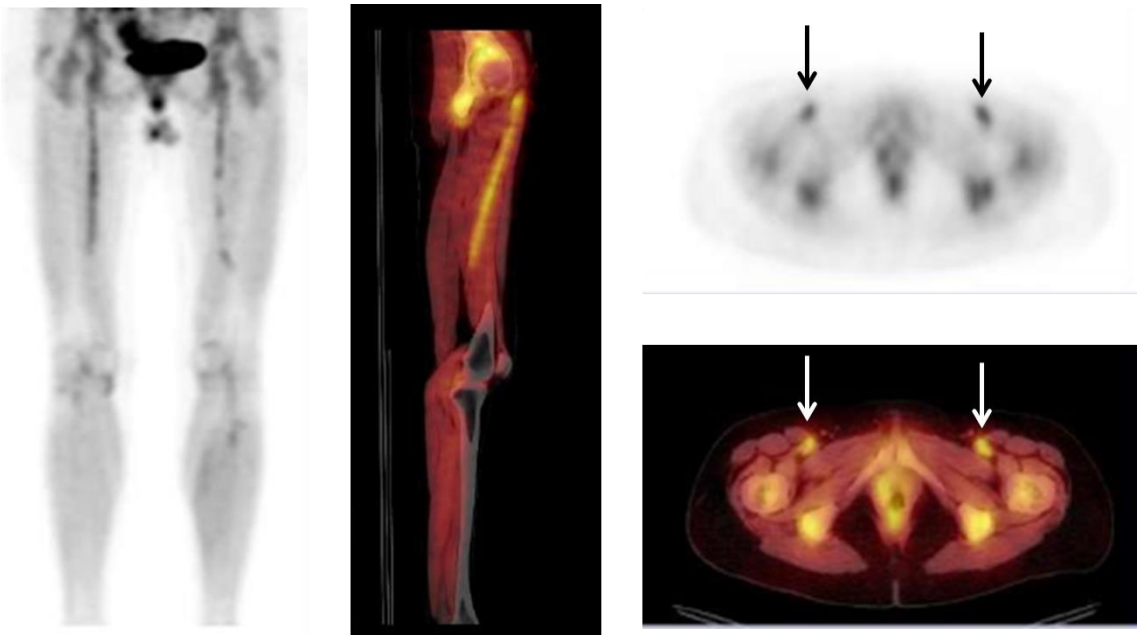
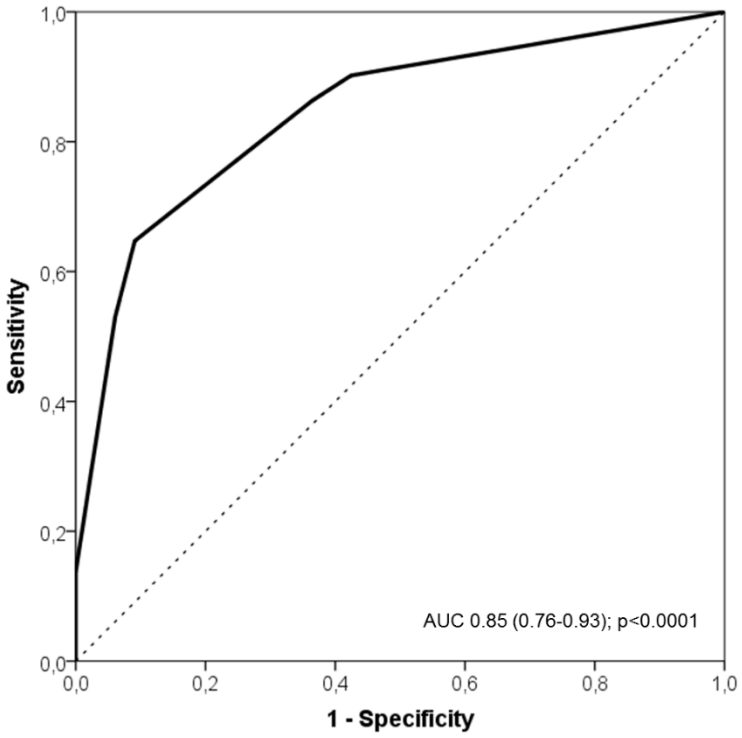


FIGURE 3



ARTÍCULO 2

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Título: ***Cranial and extracranial giant cell arteritis share similar HLA-DRB1 association.***

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CRANIAL AND EXTRACRANIAL GIANT CELL ARTERITIS SHARE SIMILAR *HLA-DRB1* ASSOCIATION

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Short title: *HLA-DRB1* in cranial and extracranial giant cell arteritis.

ABSTRACT

Objective: To determine whether giant cell arteritis (GCA) patients with the typical pattern of cranial ischemic manifestations and those with the extracranial large-vessel (LVV)-GCA phenotype exhibit different *HLA-DRB1* association.

Methods: 178 biopsy-proven GCA patients who had cranial ischemic features but no LVV manifestations, 100 patients with LVV-GCA without cranial ischemic manifestations and 486 ethnically matched healthy controls were recruited. All patients and controls were Spanish of European ancestry. We compared *HLA-DRB1* phenotype frequencies between the three groups.

Results: Both GCA subgroups had well-differentiated clinical features. Patients with LVV-GCA were younger (68.0 ± 10.0 years *versus* 74.0 ± 10.4 years; $p < 0.01$) and presented more commonly with polymyalgia rheumatica symptoms (81% *versus* 39.3%; $p < 0.01$) than those with the classic cranial GCA phenotype. *HLA-DRB1*04* phenotype frequency was significantly increased in patients with classic cranial GCA compared to controls (42.1% *versus* 23.5%, respectively; $p < 0.01$; odds ratio-OR [95% confidence interval-CI] =2.38 [1.62-3.47]). This association was mainly due to the *HLA-DRB1*04:01* allele (20.8% *versus* 5.3%, respectively; $p < 0.01$; OR [95% CI] =4.64 [2.63-8.26]). *HLA-DRB1*04* association was also observed in LVV-GCA patients when compared to controls (46.0% *versus* 23.5%, respectively; $p < 0.01$; OR [95% CI] =2.78 [1.73-4.44]). Similar to cranial GCA, the association was also mainly due to the *HLA-DRB1*04:01* allele (19.0% *versus* 5.3%, respectively; $p < 0.01$; OR [95% CI] =4.15 [2.06-8.19]). Cranial and LVV-GCA patients did not exhibit *HLA-DRB1* allele differences.

Conclusion: Cranial and extracranial LVV-GCA share similar *HLA-DRB1* association.

Keywords: Giant cell arteritis, Large vessel vasculitis, HLA, Genetics

Abbreviations:

ACR: American College of Rheumatology

CI: confidence intervals

CT-A: computed tomography angiography

^{18}F-FDG: ^{18}F - fluorodeoxyglucose

GCA: giant cell arteritis.

LVV: large-vessel-vasculitis

MRI-A: angiographic magnetic resonance

OR: odds ratios

PET/CT: positron emission tomography/computed tomography

PMR: polymyalgia rheumatica

SD: standard deviation

1. INTRODUCTION

Giant cell arteritis (GCA) is the most common vasculitis affecting elderly people of European descent [1]. It was classically described as a large vessel vasculitis that involved the cranial arteries [2]. However, wide evidence supports that GCA is a heterogeneous disease, which can also affect extracranial large vessels, such as the aorta and its main branches, even in the absence of cranial manifestations [3-7].

Patients with the classic cranial GCA pattern present with ischemic manifestations such as acute headache, scalp tenderness, jaw and tongue claudication, and visual loss, [8]. GCA patients with predominant extracranial large-vessel-vasculitis (LVV-GCA) are usually younger and may present more commonly as a polymyalgia rheumatica (PMR), often refractory to the usual glucocorticoid dose indicated for this condition. Besides arm or leg claudication, fever, night sweats, weight loss, and back or diffuse limb pain are often found in LVV-GCA patients [9]. Due to the high frequency of non-specific clinical features and the lower frequency of positive temporal artery biopsies, extracranial LVV-GCA is often underdiagnosed [9,10]. However, in the absence of high suspicion, severe vascular complications, such as stenosis, aneurysm and aortic dissection, may occur [11-14]. In addition, GCA patients with predominant LVV involvement usually experience more relapses and require longer glucocorticoid therapy [14]. The wide range of clinical manifestations from the classic cranial to the predominantly extracranial LVV-GCA pattern suggests that GCA is a complex disease and that different subsets of GCA may exist, being part of the same continuum [6] or constituting a heterogeneous group of conditions that share in common the vasculitic involvement of large and middle-sized arteries [3]. With respect to this, it is possible that different genetic susceptibility and/or cytokine profile expression may influence this different clinical presentation.

As far as we are concern, GCA follows a polygenic inherit pattern. Most studies have described an association of GCA with *HLA-DRB1*04* alleles [15-19]. However, a different *HLA-DRB1* association in GCA and isolated PMR was reported in some series. In this regard, in Northern

Spain, biopsy-proven GCA patients with the classic cranial pattern of the disease, with or without PMR manifestations, were associated with *HLA-DRB1*04*, whereas those with isolated PMR were associated with *HLA-DRB1*13/14* [20,21].

Since LVV-GCA is frequently found in patients presenting with PMR features without any cranial clinical manifestation [22,23], we aimed to determine if GCA patients with the predominant extracranial pattern of LVV exhibit different *HLA-DRB1* association than those who have the classic cranial phenotype of the disease. For this purpose, we recruited a series of patients with the LVV-GCA phenotype who did not have any cranial manifestation of the GCA and compared them with another cohort of GCA patients confirmed by a positive temporal artery biopsy who presented a classic cranial pattern of the disease.

2. METHODS

2.1 Patients and controls

We recruited a total of 178 patients with biopsy-proven cranial GCA, 100 with LVV-GCA and 486 healthy controls. All patients and controls were Spanish of European ancestry. Blood samples were obtained from patients recruited from Hospital Universitario Marqués de Valdecilla (Santander, Spain), Hospital Universitario de Basurto (País Vasco, 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 (Galicia, Spain), and Hospital Universitario Lucus Augusti (Galicia, Spain).

All patients with GCA and healthy controls signed informed written consent before being included 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. The study was approved by the Ethics Committee of clinical research of Cantabria for Hospital Universitario Marqués de Valdecilla as well as the corresponding centers mentioned above.

2.1.1 Patients with classic cranial phenotype of GCA

All patients with the cranial phenotype of GCA (n=178) fulfilled the American College of Rheumatology (ACR) 1990 classification criteria [24]. Of note, in all of them, a diagnosis was confirmed with a positive temporal artery biopsy for GCA. None of them had vascular ischemic manifestations or any other clinical features suggestive of peripheral arteriopathy.

2.1.2 Patients with extracranial LVV-GCA phenotype

100 ethnically matched patients with LVV-GCA were also included in our study. LVV-GCA diagnosis was established by experienced rheumatologists based on confirmatory imaging techniques, such as ^{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). During the recruitment period, patients with LVV features who presented cranial GCA symptoms were excluded. The exclusion criteria included other patients with underlying inflammatory conditions, infections or neoplastic diseases that could present with LVV involvement. This process allowed us to recruit a well-defined LVV-GCA group of patients that was clinically different from the former one of cranial GCA.

2.1.3 Healthy controls

A total of 486 ethnically matched unaffected control subjects, without history of vasculitis or any other autoimmune disease, identified from blood donors from Hospital Universitario Marqués de Valdecilla (Santander, Spain) and National DNA Bank Repository (Salamanca, Spain), were also included in this study.

***2.2 HLA-DRB1* genotyping**

High-molecular-weight genomic DNA was extracted from whole blood using the Maxwell 16 Blood DNA Purification Kit (Promega Biotech Ibérica, S.L., Spain) according to the manufacturer's instructions. All DNA samples were stored at -20°C until the HLA analysis. DNA-based *HLA-DRB1* typing was performed using the Luminex 100 system (Luminex, Austin, TX, USA) and the Lifecodes HLA typing Kits, and analyzed by using the MatchIT software (Gen-Probe Inc., San Diego, CA, USA) following the manufacturer's instructions.

2.3 Statistical analysis

All continuous variables were tested for normality, and results were expressed as mean ± standard deviation (SD). Categorical variables were described as number of individuals (n) and percentages (%). Student's t test or Mann-Whitney U-test were used to compare continuous variables and chi-squared test for categorical variables. A p-value <0.05 was considered as statistically significant in all the calculations. *HLA-DRB1* allele frequencies were calculated by direct counting. Comparisons between *HLA–DRB1* alleles of patients with classic cranial GCA and healthy controls, patients with extracranial LVV-GCA and healthy controls, and patients with classic cranial GCA and those with the extracranial LVV-GCA pattern were performed. The strength of association was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined using contingency tables and either chi-square test or Fisher's exact test (expected values <5). Results were subjected to Bonferroni adjustment for multiple comparisons. After the adjustment, a value of P_{BNF}<0.05 was considered statistically significant.

All analyses were performed with Stata statistical software version 12/SE (StataCorp., College Station, TX, USA).

3. RESULTS

Clinical features of GCA patients stratified according to the disease phenotype are shown in **Table 1**. With regard to patients with the classic cranial GCA pattern, the mean age at diagnosis was 74.0 ± 10.4 years with a predominance in women (65.2%). Some of them presented with severe cranial ischemic manifestations, such as jaw claudication (39.3%), visual ischemic manifestations (partial or complete visual loss) (24.2%) and stroke (3.9%). PMR symptoms were present in 70 (39.3%) patients. None of them showed peripheral arteriopathy.

Regarding LVV-GCA patients, although none of them had cranial ischemic manifestations, based on the attending physician's decision, a temporal artery biopsy was performed on 36 of them, being positive for GCA in only 3 (8.3%). Interestingly, none of these 3 patients, who had

histological features of GCA in the temporal artery biopsy, experienced headache or any other cranial ischemic symptoms during the follow-up. As shown in **Table 1**, patients with LVV-GCA were younger than those with classic cranial GCA (68.0 ± 10.0 years *versus* 74.0 ± 10.4 years; p < 0.01) and presented more commonly with polymyalgia rheumatica symptoms (81% *versus* 39.3%; p < 0.01). Approximately, half of the patients with LVV-GCA showed at least one constitutional symptom: malaise (53%), weight loss (25%) or fever (19%). In addition, 12 patients presented symptoms due to peripheral arteriopathy, such as arm or leg claudication. Notably, one patient experienced severe lower limb ischemia requiring surgical intervention.

Table 2 summarizes the *HLA-DRB1* allele frequencies observed in patients with classic cranial GCA, patients with extracranial LVV-GCA and healthy controls.

Firstly, we compared *HLA-DRB1* allele frequencies between patients with classic cranial GCA and healthy controls (**Table 2**). In this regard, the frequency of the *HLA-DRB1*04* phenotype was significantly increased in patients with classic cranial GCA compared to healthy controls (42.1% *versus* 23.5%, respectively; p < 0.01; OR [95% CI] =2.38 [1.62-3.47]). This association was mainly due to the *HLA-DRB1*04:01* allele (20.8% *versus* 5.3%, respectively; p < 0.01; OR [95% CI] =4.64 [2.63-8.26]) and remained statistically significant after Bonferroni correction (P_{BNF} < 0.01) (**Table 2**). No statistically significant results were observed regarding other *HLA-DRB1* alleles after the adjustment by Bonferroni.

In a further step, we compared *HLA-DRB1* allele frequencies between patients with extracranial LVV-GCA and healthy controls (**Table 2**). Similar *HLA-DRB1* allele differences to those mentioned above for classic cranial GCA were observed when patients with extracranial LVV-GCA and healthy controls were compared (**Table 2**). This was especially true for *HLA-DRB1*04* that showed a statistically significant increase when compared to healthy controls (46.0% *versus* 23.5%, respectively; p < 0.01; OR [95% CI] =2.78 [1.73-4.44]). Again, this association was also mainly due to the *HLA-DRB1*04:01* allele (19.0% *versus* 5.3%, respectively; p < 0.01; OR [95% CI] =4.15 [2.06-8.19]) and remained statistically significant after Bonferroni correction (P_{BNF} < 0.01)

(**Table 2**). Since three of the extracranial LVV-GCA patients had a positive TAB although they did not exhibit cranial symptoms, *HLA-DRB1*04:01* allele differences between patients with extracranial LVV-GCA (excluding these three patients with positive TAB) and healthy controls was evaluated. Accordingly, a statistically significant increase of the *HLA-DRB1*04:01* allele in patients with LVV-GCA after excluding those with positive TAB compared to healthy controls was also noted (18.0% *versus* 5.3% respectively, $p < 0.01$; OR [95% CI] =3.88 [1.91-7-73], $P_{BNF} < 0.01$). No other *HLA-DRB1* allele differences were observed between patients with extracranial LVV-GCA and healthy controls after the adjustment by Bonferroni (**Table 2**).

We also assessed whether potential *HLA-DRB1* differences might exist between the two different clinical phenotypes of GCA, classic cranial GCA and extracranial LVV-GCA. With respect to this, no significant differences were found. In this regard, a similar *HLA-DRB1* allele distribution between these two groups of patients was observed (**Table 2**). Similar results were observed when patients with classic cranial GCA were compared to those with LVV-GCA after excluding LVV-GCA patients with positive TAB (20.8% versus 18.0% respectively, $p = 0.58$; OR [95% CI] =1.20 [0.62-2.38]).

4. DISCUSSION

In the present study, we assessed for the first time if the widely described association with *HLA-DRB1*04* in patients with cranial GCA was also observed in LVV-GCA. For this purpose, we studied two well-differentiated groups of GCA patients. One of them with the classic phenotype of cranial ischemic manifestations without clinical features of LVV involvement, and another group of patients with LVV-GCA without any cranial manifestation of GCA.

Given that PMR is observed more frequently in the LVV-GCA phenotype and that Spanish patients with PMR without cranial ischemic manifestations of GCA showed no association with *HLA-DRB1*04* [20], we wondered if such a significant association with *HLA-DRB1*04* might be absent in LVV-GCA patients. However, we could not find *HLA-DRB1* differences between LVV-GCA and classic cranial GCA. Both subgroups showed a similar association with *HLA-DRB1*04*,

mainly due to *HLA-DRB1*04:01*. Although in previous studies [20,21] patients with isolated "pure" PMR were associated to *HLA-DRB1*13/14,* we could not find this association in patients with LVV-GCA or in patients with cranial GCA. Therefore, it is possible that *HLA-DRB1*13/14* could be a marker of isolated PMR in the Spanish population but not of PMR associated with LVV-GCA. In regard with previously reported protective alleles [25], we could not find a protective effect of *HLA-DRB1*15* or *HLA-DRB1*16* in patients with cranial GCA or LVV-GCA, probably because our study might not be enough powered to detect these weaker signals. According to our findings, *HLA-DRB1* is not useful to discriminate between cranial and LVV-GCA. As previously reported by Muratore *et al* [14], our patients with LVV-GCA were younger and had more commonly PMR than those with the cranial GCA phenotype. In this regard, we recently reported a series of PMR patients without cranial GCA manifestations, who had atypical features or were refractory to 15 mg/day of prednisone [23]. Many of them turned out to be LVV-GCA when imaging tests such as PET/CT were used [23]. Also, more than two decades ago, we reported that patients with isolated PMR who carried *HLA-DRB1*04* alleles had more commonly relapses than those who did not carry the *HLA-DRB1*04* alleles [26]. Since at that time the imaging techniques for evaluating LVV involvement were not performed on patients with PMR, it is possible that some of them may have in fact been LVV-GCA presenting as a refractory PMR. The results of our cohort of LVV-GCA patients confirm the lower frequency of biopsy-proven GCA observed by other authors [10]. Interestingly, the frequency of biopsy-proven GCA among LVV-GCA patients from the present study was remarkably similar to that reported in patients with PMR from Northern Spain who underwent temporal artery biopsy because of PMR associated with constitutional symptoms or high inflammatory response [27]. This is in line with the classical concept of *polymyalgia arteritica* introduced by Hamrin in 1972 to describe patients with PMR without cranial symptoms who showed histological features of GCA in the temporal artery biopsy [28]. Based on current understandings, some of these patients may have belonged to the LVV-GCA phenotype. Therefore, it is possible that *HLA-DRB1*04:01* can be used as a

genetic marker of susceptibility for the presence of an underlying LVV-GCA in patients with refractory PMR.

The hypothesis proposed by several authors of cranial GCA and LVV-GCA as being part of the same continuum [3,6], can be supported by the fact that both conditions share the same *HLA-DRB1*04:01* susceptibility. Given that GCA is a polygenic disease [17,18], the additive role of other genes may have an influence on the different clinical phenotype expression and outcome of these conditions. In addition, it has been reported that there is an absence of shared epitope homozygosity in GCA in different regions of the world [29]. This may suggest that some environmental factors may also play a role in the development of different clinical phenotypes.

A potential limitation of our study is the relatively small number of LVV-GCA patients. In this regard, collaboration among different groups would lead to enlarge the number of patients with LVV-GCA in attempt to enhance the power of the study and to perform a genome-wide association study to further elucidate more genetic signals.

In conclusion, our study confirms the strong association of GCA with *HLA-DRB1*04* regardless of the clinical phenotype, but precludes of the use of *HLA-DRB1* assessment analysis as a tool to identify subsets of the disease. Because that, it is important to further investigate other potential genetic differences between the classic cranial GCA pattern and that of LVV-GCA.

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Competing interests

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Table 1. Main clinical features of patients with cranial GCA and LVV-GCA pattern.

	Classic cranial GCA pattern n=178	LVV-GCA pattern n=100	p
Age at diagnosis (mean ± SD)	74.0 ± 10.4	68.0 ± 10.0	< 0.01
Women, n (%)	116 (65.2%)	73 (73%)	0.18
Positive TAB, n (%)	100 (100%)	3/36 (8.3%)	< 0.01
Headache, n (%)	140 (78.7%)	0 (0%)	< 0.01
Abnormal temporal artery on physical examination, n (%)	107 (60.1%)	0 (0%)	< 0.01
Jaw claudication, n (%)	70 (39.3%)	0 (0%)	< 0.01
Polymyalgia rheumatica, n (%)	70 (39.3%)	81 (81%)	< 0.01
Visual manifestations, n (%)	43 (24.2%)	0 (0%)	< 0.01
Permanent visual loss, n (%)	20 (11.2%)	0 (0%)	< 0.01
Peripheral arteriopathy, n (%)	0 (0%)	12 (12%)	< 0.01
Stroke, n (%)	7 (3.9%)	0 (0%)	0.05
ESR > 40 mm/1st h. at diagnosis, n (%)	175 (98.3%)	79 (79%)	< 0.01

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

Table 2. *HLA-DRB1* allele frequencies in patients with a classic cranial GCA pattern, LVV-GCA pattern and healthy controls.

HLA-DRB1		Classic cranial GCA pattern (n=178)	LVV-GCA pattern (n=100)	Healthy controls (n=486)
*DRB1*01*	01:01	16.9 (30)	16.0 (16)	11.5 (56)
	01:02	12.4 (22)	10.0 (10)	10.9 (53)
	01:03	2.8 (5)	2.0 (2)	1.2 (6)
*DRB1*03*	03:01	18.0 (32)	17.0 (17)	22.6 (110)
*DRB1*04*	04:01	**20.8 (37)[a]**	**19.0 (19)[b]**	**5.3 (26)[a, b]**
	04:02	3.4 (6)	2.0 (2)	3.9 (19)
	04:03	0.6 (1)	4.0 (4)	1.0 (5)
	04:04	11.2 (20)	10.0 (10)	7.0 (34)
	04:05	1.7 (3)	4.0 (4)	4.5 (22)
	04:07	1.1 (2)	6.0 (6)	1.2 (6)
	04:08	3.4 (6)	1.0 (1)	0.4 (2)
*DRB1*07*	07:01	38.2 (68)	25.0 (25)	31.7 (154)
*DRB1*08*	08:01	6.2 (11)	6.0 (6)	3.9 (19)
	08:03	0	0	0.8 (4)
*DRB1*09*	09:01	1.1 (2)	1.0 (1)	1.9 (9)
*DRB1*10*	10:01	2.2 (4)	2.0 (2)	4.5 (22)
*DRB1*11*	11:01	9.6 (17)	4.0 (4)	13.2 (64)
	11:02	1.1 (2)	0	3.1 (15)
	11:03	1.7 (3)	1.0 (1)	2.3 (11)
	11:04	3.9 (7)	1.0 (1)	10.9 (53)
*DRB1*12*	12:01	5.1 (9)	3.0 (3)	1.4 (7)
*DRB1*13*	13:01	7.9 (14)	8.0 (8)	12.1 (59)
	13:02	2.8 (5)	10.0 (10)	6.2 (30)
	13:03	5.6 (10)	4.0 (4)	4.3 (21)
*DRB1*14*	14:01	2.8 (5)	8.0 (8)	3.7 (18)
	14:04	0	0	1.6 (8)
*DRB1*15*	15:01	11.2 (20)	16.0 (16)	12.1 (59)
	15:02	2.2 (4)	4.0 (4)	2.5 (12)
*DRB1*16*	16:01	0.6 (1)	2.0 (2)	3.9 (19)

GCA: giant cell arteritis; HLA: human leukocyte antigen; LVV: large- vessel vasculitis.
Values are presented as percentages (number of individuals).
Results that remained statistically significant after Bonferroni adjustment are highlighted in **bold:**
[a]$P < 0.01$, OR=4.64 [95% CI: 2.63-8.26], $P_{BNF} < 0.01$
[b]$P < 0.01$, OR=4.15 [95% CI: 2.06-8.19], $P_{BNF} < 0.01$

ARTÍCULO 3

ARTÍCULO 3

Título: ***The presence of both HLA-DRB1[*]04:01 and HLA-B[*]15:01 increases the susceptibility to cranial and extracranial giant cell arteritis.***

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THE PRESENCE OF BOTH *HLA-DRB1*04:01* AND *HLA-B*15:01* INCREASES THE SUSCEPTIBILITY TO CRANIAL AND EXTRACRANIAL GIANT CELL ARTERITIS

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Short title: *HLA-DRB1*04:01 and HLA-B*15:01 effect on GCA susceptibility*

Keywords: giant cell arteritis, large vessel vasculitis, HLA, genetics

ABSTRACT

Objective: To determine if patients with the predominant extracranial large-vessel-vasculitis (LVV) pattern of giant cell arteritis (GCA) have a distinctive *HLA-B* association, different from that reported in biopsy-proven cranial GCA patients. In a further step we assessed if the combination of *HLA-B* and *HLA-DRB1* alleles confers an increased risk for GCA susceptibility, either for the cranial and extracranial LVV phenotypes.

Methods: A total of 184 patients with biopsy-proven cranial GCA, 105 with LVV-GCA and 486 healthy controls were included in our study. We compared *HLA-B* phenotype frequencies between the three groups.

Results: *HLA-B*15* phenotype was significantly increased in patients with classic cranial GCA compared to controls (14.7% *versus* 5.8%, respectively; $p < 0.01$; OR [95% CI] =2.81 [1.54-5.11]). It was mainly due to the *HLA-B*15:01* allele (12.5% *versus* 4.0%, respectively; $p < 0.01$; OR [95% CI] =3.51 [1.77-6.99]) and remained statistically significant after Bonferroni correction. Similar *HLA-B*15* association was observed in patients with the LVV-GCA (11.4% *versus* 5.8%, $p= 0.04$, OR [95% CI] =2.11 [1.04-4.30]). This association was also mainly due to the *HLA-B*15:01* allele (10.5% *versus* 4.0%, respectively; $p = 0.0054$; OR [95% CI] =2.88 [1.19-6.59]). Noteworthy, the presence of *HLA-B*15:01* together with *HLA-DRB1*04:01* led to an increased risk of developing both cranial and extracranial LVV-GCA.

Conclusion: Susceptibility to GCA is strongly related to the HLA region, regardless of the clinical phenotype of expression of the disease.

INTRODUCTION

Giant cell arteritis (GCA) is a systemic vasculitis characterized by the involvement of middle and large vessels in individuals over 50 years [1]. Classically, GCA was described as a vasculitis with a predilection for the affection of cranial arteries, presenting with cranial ischemic manifestations such as headache, jaw claudication or visual ischemic manifestations [2,3]. However, in the recent years the use of imaging techniques has allowed to identify a different subset of GCA patients with predominant extracranial involvement [4–6]. These patients with the predominant extracranial large-vessel-vasculitis (LVV) pattern of GCA are usually younger than those with the classic cranial phenotype and they often present as a glucocorticoid-resistant polymyalgia rheumatica or as patients with fever or constitutional syndrome of unknown origin [7–9].

Genetic factors seem to play an important role in the pathogenesis of GCA [10]. This vasculitis follows a polygenic inheritance pattern, mostly associated with HLA class II genes [11–14]. However, it remains unknown whether a different genetic susceptibility and/or cytokine profile expression may explain the different clinical phenotypes of GCA. In a first attempt to determine if genetic differences between classic-cranial GCA and LVV-GCA existed, we performed a comparative analysis of *HLA-DRB1** phenotype frequencies between both subgroups. In this study, we could not find any differences as both cranial and extracranial-LVV-GCA shared a strong association with *HLA-DRB1*04*, in particular with *HLA-DRB1*04:01* [15].

Besides the strong association of GCA with HLA class II genes, there is evidence that class I region is also involved in the genetic susceptibility to cranial GCA. In this regard, association with *HLA-B*15* was observed in a cohort of patients with biopsy-proven GCA [16]. This implication of HLA class I genes in the susceptibility to cranial GCA was further confirmed in large-scale studies [12,13].

HLA class I genes also play an important role in the genetic susceptibility of Takayasu arteritis (TAK) [13,17]. LVV-GCA, as well as TAK, usually affects individuals who are younger than patients with the classic cranial pattern of GCA, and are characterized by the affection of larger arteries

that may lead to the development of stenosis, aneurysms and aortic dissection [18,19]. Since TAK and classic cranial GCA differ in HLA association, we aimed to determine if patients with LVV-GCA have a distinctive *HLA-B* association, different from that reported in biopsy-proven cranial GCA patients. In a further step we assessed if the combination of *HLA-B* and *HLA-DRB1* alleles confers an increased risk for GCA susceptibility, either for the cranial and extracranial LVV phenotypes.

METHODS

Patients and controls

A total of 184 patients with biopsy-proven cranial GCA, 105 with LVV-GCA and 486 healthy controls were included in our study. All patients and controls were Spanish of European ancestry. They were recruited in ten collaborative centers: 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 centers 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.

Patients with classic cranial phenotype of GCA

A set of 184 patients with the cranial phenotype of GCA were included in our study. GCA diagnosis was based on the American College of Rheumatology (ACR) 1990 classification criteria **(20)**. In addition, the diagnosis of GCA was confirmed in all patients by a positive temporal artery

biopsy showing the typical histopathologic findings of this vasculitis. Noteworthy, none of them presented clinical symptoms suggesting peripheral arterial involvement.

Patients with extracranial LVV-GCA phenotype

A cohort of 105 ethnically matched patients with the extracranial LVV-GCA phenotype were also included in our study. LVV-GCA diagnosis was established by experienced rheumatologists based on 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).

For the purpose of the present study, in an attempt to assess a well-defined LVV-GCA group of patients who were clinically different from the former ones of cranial GCA, patients with LVV-GCA who presented cranial GCA symptoms were excluded from the analysis (**Table 1**). Patients with other underlying inflammatory conditions, infections or neoplastic diseases that could present with LVV involvement were also excluded.

Healthy controls

A total of 486 ethnically matched unaffected control subjects, without history of vasculitis or any other autoimmune disease, constituted by blood donors from Hospital Universitario Marqués de Valdecilla (Santander, Spain) and National DNA Bank Repository (Salamanca, Spain), were also included in this study.

HLA-B genotyping

High-molecular-weight genomic DNA was extracted from whole blood using the Maxwell 16 Blood DNA Purification Kit (Promega Biotech Ibérica, S.L., Spain) according to the manufacturer's instructions. All DNA samples were stored at -20°C until the HLA analysis. DNA-based *HLA-B* typing was performed using the Luminex 100 system (Luminex, Austin, TX, USA) and the Lifecodes HLA typing Kits, and analyzed by using the MatchIT software (Gen-Probe Inc., San Diego, CA, USA) following the manufacturer's instructions. *HLA-DRB1* typing was performed as previously reported [15].

Statistical analysis

HLA-B phenotype frequencies were calculated by direct counting. Comparisons between *HLA-B* phenotype of patients with classic cranial GCA and healthy controls, patients with extracranial LVV-GCA and healthy controls, and patients with classic cranial GCA and those with the extracranial LVV-GCA pattern were performed. The strength of association was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined using contingency tables and either chi-square test or Fisher's exact test (expected values <5). Results were subjected to Bonferroni adjustment for multiple comparisons. After the adjustment, a value of $P_{BNF} < 0.05$ was considered statistically significant.

All analyses were performed with Stata statistical software version 12/SE (StataCorp., College Station, TX, USA).

RESULTS

HLA-B phenotype frequencies were compared between patients with the classic cranial GCA pattern and healthy controls (**Table 2**). Noteworthy, the frequency of the *HLA-B*15* phenotype was significantly increased in patients with cranial GCA compared to controls (14.7% *versus* 5.8%, respectively; p < 0.01; OR [95% CI] =2.81 [1.54-5.11]). This association was mainly due to the *HLA-B*15:01* allele (12.5% *versus* 4.0%, respectively; p < 0.01; OR [95% CI] =3.51 [1.77-6.99]) and remained statistically significant after Bonferroni correction ($P_{BNF} < 0.01$) (**Table 2**).

Regarding the LVV-GCA phenotype, similar *HLA-B* differences to those mentioned above for the cranial pattern were observed when LVV-GCA patients were compared to controls (**Table 2**). This was especially true for *HLA-B*15*, which was significantly increased in these patients with extracranial LVV-GCA compared to healthy controls (11.4% *versus* 5.8%, p= 0.04, OR [95% CI] =2.11 [1.04-4.30]). This association was also mainly due to the *HLA-B*15:01* allele (10.5% *versus* 4.0%, respectively; p = 0.0054; OR [95% CI] =2.88 [1.19-6.59]) (**Table 2**). These results remained significant after excluding the three patients with extracranial LVV-GCA who had a positive TAB.

When cranial and extracranial LVV-GCA groups were compared, no significant differences in terms of the *HLA-B* phenotype association were observed **(Table 2)**.

Noteworthy, the presence of *HLA-B*15:01* together with *HLA-DRB1*04:01* led to an increased risk of developing both cranial GCA and extracranial LVV-GCA (**Table 3**).

DISCUSSION

Our study constitutes the first attempt to determine whether there is a different HLA class I susceptibility pattern in GCA patients who present the cranial and the extracranial LVV phenotype. However, we found no *HLA-B* differences between these two subsets of patients. In this regard, a similar association with *HLA-B*15*, mainly due to *HLA-B*15:01,* was observed in patients with GCA, regardless the clinical phenotype. Furthermore, we found that the presence of both *HLA-B*15:01* and *HLA-DRB1*04:01* has an effect increasing the risk of developing both cranial and extracranial LVV-GCA.

A former study that included 98 biopsy-proven GCA patients with the classic cranial pattern of the disease showed an association of this vasculitis with HLA-B genes, in particular with *HLA-B*15:01* [16]. The present study that included 184 biopsy-proven GCA patients confirmed this *HLA-B*15:01* association with cranial GCA. Herein, we also show that a similar association with *HLA-B*15:01* is present in patients with the extracranial LVV-GCA phenotype.

As recently described for *HLA-DRB1* association [15], we could not find any differences in HLA class I genetic predisposition between patients with the extracranial LVV-GCA and the classic cranial GCA pattern. These findings indicate that susceptibility to GCA is strongly related to the HLA region, regardless of the clinical phenotype of expression of the disease. Consequently, it is possible that genes located outside the HLA region might account for the different clinical expression of this vasculitis.

In conclusion, no differences regarding HLA-B genetic susceptibility seem to exist between patients with the classic cranial GCA and the extracranial LVV-GCA pattern. However, the presence of *HLA-B*15:01* together with *HLA-DRB1*04:01* increases the susceptibility to both

cranial and LVV-GCA. Further investigation is underway to determine if specific genetic pathways may explain the different phenotype expression of the disease.

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Competing interests

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TABLE 1. Main clinical features of patients with classic cranial GCA and LVV-GCA pattern

	Classic cranial GCA pattern n=184	LVV-GCA pattern n=105	P
Age at diagnosis, yrs (mean ± SD)	74.0 ± 10.4	67.5 ± 9.8	< 0.01
Women, n (%)	122 (66.3%)	76 (72.4%)	0.24
Positive TAB, n (%)	184 (100%)	3/37 (8.1%)	< 0.01
Headache, n (%)	144 (78.3%)	0 (0%)	< 0.01
Abnormal temporal artery on physical examination, n (%)	109 (59.2%)	0 (0%)	< 0.01
Jaw claudication, n (%)	72 (39.1%)	0 (0%)	< 0.01
Polymyalgia rheumatica, n (%)	74 (40.2%)	86 (81.9%)	< 0.01
Visual manifestations, n (%)	47 (25.5%)	0 (0%)	< 0.01
Permanent visual loss, n (%)	21 (11.4%)	0 (0%)	< 0.01
Peripheral arteriopathy, n (%)	0 (0%)	12 (11.4%)	< 0.01
Stroke, n (%)	8 (4.4%)	0 (0%)	0.05
ESR > 40 mm/1st h. at diagnosis, n (%)	181 (98.4%)	84 (80.0%)	< 0.01

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

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TABLE 2. *HLA-B* frequencies in patients with a classic cranial GCA pattern, LVV-GCA pattern and healthy controls.

HLA-B		**Classic cranial GCA pattern** (n=184)	**LVV-GCA pattern** (n=105)	**Healthy controls** (n=486)
*HLA-B*07*	07:02	13.6 (25)	18.1 (19)	13.8 (67)
	07:05	0	0	2.1 (10)
*HLA-B*08*	08:01	17.4 (32)	13.3 (14)	9.7 (47)
*HLA-B*13*	13:02	7.1 (13)	1.9 (2)	3.3 (16)
*HLA-B*14*	14:01	5.4 (10)	2.9 (3)	3.5 (17)
	14:02	15.2 (28)	10.5 (11)	10.5 (51)
*HLA-B*15*	15:01	**12.5 (23)[a]**	10.5 (11)	**4.0 (19)[a]**
	15:03	0.5 (1)	0	1.0 (5)
	15:17	1.6 (3)	1.0 (1)	0.8 (4)
*HLA-B*18*	18:01	10.9 (20)	9.5 (10)	17.3 (84)
*HLA-B*27*	27:05	6.0 (11)	10.5 (11)	5.1 (25)
*HLA-B*35*	35:01	8.7 (16)	8.6 (9)	7.8 (38)
	35:02	1.1 (2)	0	4.1 (20)
	35:03	4.9 (9)	3.8 (4)	4.3 (21)
	35:08	1.6 (3)	0	4.5 (22)
*HLA-B*37*	37:01	1.6 (3)	1.0 (1)	2.1 (10)
*HLA-B*38*	38:01	4.3 (8)	4.8 (5)	8.6 (42)
*HLA-B*39*	39:01	3.8 (7)	1.9 (2)	2.3 (11)
	39:06	1.1 (2)	1.0 (1)	2.1 (10)
*HLA-B*40*	40:01	5.4 (10)	10.5 (11)	4.1 (20)
	40:02	1.1 (2)	1.9 (2)	1.4 (7)
*HLA-B*41*	41:01	0	1.0 (1)	3.3 (16)
	41:02	0	1.0 (1)	0.6 (3)
*HLA-B*44*	44:02	13.6 (25)	13.3 (14)	13.4 (65)
	44:03	14.1 (26)	15.2 (16)	12.1 (59)
*HLA-B*45*	45:01	1.1 (2)	3.8 (4)	3.1 (15)
*HLA-B*49*	49:01	4.3 (8)	5.7 (6)	7.0 (34)
*HLA-B*50*	50:01	7.1 (13)	7.6 (8)	3.9 (19)
*HLA-B*51*	51:01	16.8 (31)	11.4 (12)	12.8 (62)
*HLA-B*52*	52:01	2.2 (4)	1.9 (2)	3.1 (15)
*HLA-B*53*	53:01	3.2 (6)	5.7 (6)	2.3 (11)
*HLA-B*55*	55:01	1.6 (3)	1.9 (2)	2.5 (12)
*HLA-B*57*	57:01	6.5 (12)	9.5 (10)	5.1 (25)
*HLA-B*58*	58:01	1.1 (2)	2.9 (3)	2.1 (10)

HLA: human leukocyte antigen; GCA: giant cell arteritis; LVV: large-vessel-vasculitis.
Values are presented as percentages (number of individuals).
Results that remained statistically significant after Bonferroni adjustment are highlighted in **bold:** [a]$P < 0.01$, OR=3.51 [95% CI: 1.77-6.99], $P_{BNF} < 0.01$.

TABLE 3. *HLA-B*15:01* and *HLA-DRB1*04:01* are associated with increased susceptibility to classic cranial GCA and LVV-GCA.

Classic cranial GCA patients[+]					
HLA-B*15:01	***HLA-DRB1*04:01***	**Classic cranial GCA** % (n)	**Healthy controls** % (n)	**P**	**OR [95% CI]**
-	-	73.4 (135)	91.4 (444)	-	Ref.
+	-	5.4 (10)	3.3 (16)	0.08	2.06 [0.81-4.94]
-	+	14.1 (26)	4.7 (23)	< 0.001	3.72 [1.96-7.04]
+	+	7.1 (13)	0.6 (3)	< 0.001	14.25 [3.82-78.67]
LVV-GCA patients[+]					
HLA-B*15:01	***HLA-DRB1*04:01***	**LVV-GCA** % (n)	**Healthy controls** % (n)	**P**	**OR**
-	-	75.2 (79)	91.4 (444)	-	Ref.
+	-	6.7 (7)	3.3 (16)	0.05	2.46 [0.98-6.17]
-	+	14.3 (15)	4.7 (23)	< 0.001	3.67 [1.69-7.69]
+	+	3.8 (4)	0.6 (3)	0.002	7.49 [1.23-51.81]
All GCA patients[+]					
HLA-B*15:01	***HLA-DRB1*04:01***	**All GCA** % (n)	**Healthy controls** % (n)	**P**	**OR [95% CI]**
-	-	74.0 (214)	91.4 (444)	-	Ref.
+	-	5.9 (17)	3.3 (16)	0.02	2.20 [1.02-4.76]
-	+	14.2 (41)	4.7 (23)	< 0.001	3.70 [2.10-6.62]
+	+	5.9 (17)	0.6 (3)	< 0.001	11.76 [3.34-63.06]

HLA: human leukocyte antigen; GCA: giant cell arteritis; LVV: large-vessel-vasculitis; OR: odds ratio, CI: confidence interval.

ARTÍCULO 4

ARTÍCULO 4

Título: *Vascular Endothelial Growth Factor* haplotypes are associated with severe ischemic complications in Giant Cell Arteritis regardless of the disease phenotype.

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VASCULAR ENDOTHELIAL GROWTH FACTOR HAPLOTYPES ARE ASSOCIATED WITH SEVERE ISCHEMIC COMPLICATIONS IN GIANT CELL ARTERITIS REGARDLESS OF THE DISEASE PHENOTYPE

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Short title: *Association of VEGF haplotypes with severe ischemic complications in GCA*

Keywords: giant cell arteritis, large vessel vasculitis, VEGF, genetics, haplotypes

ABSTRACT

Objective: To determine whether functional *VEGF* polymorphisms influence the expression of the clinical phenotype of giant cell arteritis (GCA). We also evaluated whether *VEGF* polymorphism is associated with the development of severe ischemic manifestations in patients with GCA regardless of the clinical phenotype, classic cranial GCA or predominantly extracranial GCA large vessel vasculitis (LVV).

Methods: *VEGF* rs833061 T/C, rs2010963 G/C and rs3025039 C/T polymorphisms were genotyped in 185 patients with biopsy-proven cranial GCA, 105 with extracranial LVV-GCA and 490 healthy controls. Allelic combinations (haplotypes) of *VEGF* were carried out. Comparisons were performed between patients with GCA and healthy controls as well as between patients with GCA stratified according to the clinical phenotype and the presence of severe ischemic manifestations.

Results: No significant differences in genotype, allele, and haplotype frequencies of *VEGF* were found between patients with GCA and healthy controls as well as between GCA patients with the classic cranial pattern and the extracranial LVV-GCA pattern of the disease. However, the *VEGF* CGC haplotype (OR= 1.63 [1.05-2.53]) and the CGT haplotype (OR= 2.55 [1.10-5.91]) were significantly more frequent in GCA patients with severe ischemic complications compared to those patients without these complications.

Conclusion: *VEGF* haplotypes seem to play a role in the development of severe ischemic manifestations in GCA patients, regardless of the clinical phenotype of expression of the disease.

INTRODUCTION

Giant cell arteritis (GCA) is the most common vasculitis among individuals over the age of 50 of North European descent which is characterized by granulomatous inflammation of large and medium-sized vessels [1]. The clinical spectrum of GCA involves two different phenotypes that can overlap: the classic cranial GCA pattern and the extracranial large-vessel (LVV)-GCA pattern [2-6]. Classically, GCA has been related to the affection of cranial vessels with a particular predilection for the temporal arteries being responsible of the classic cranial manifestations of GCA such as headache, scalp tenderness or jaw claudication [7]. This is the reason why this vasculitis was classically called temporal arteritis [7]. However, progress in imaging techniques has contributed to identify a subgroup of patients with predominant extracranial manifestations [8,9]. These patients are usually younger at the time of disease diagnosis and present more commonly as refractory polymyalgia rheumatica (PMR) often associated with constitutional symptoms and/or fever of unknown-origin [8-11].

Severe ischemic complications can occur in the setting of GCA as a result of perpetuated inflammation of the vessel wall, particularly in patients with the classic cranial GCA pattern [12,13]. In the absence of early glucocorticoid therapy, severe inflammation of cranial arteries can lead to intimal hyperplasia and luminal occlusion [12,13]. Visual manifestations, including amaurosis fugax and irreversible vision loss, necrosis of the scalp or tongue, and ischemic strokes are the major feared complications [14]. Patients with predominant extracranial LVV involvement can also develop severe vascular complications as a consequence of the structural inflammatory damage in the vessel wall of the aorta and its main branches [15,16]. Patients with extracranial LVV-GCA have an increased risk of developing peripheral arterial disease that can manifest as claudication of the extremities [17].

Vascular endothelial growth factor (VEGF), which is a pivotal mediator of angiogenesis, seems to be implicated in GCA pathogenesis [18-20]. In this regard, high levels of circulating VEGF have been found in patients with GCA and PMR which decrease in response to glucocorticoid therapy

[21,22]. VEGF modulates the formation of new vessels which may compensate the ischemic complications in GCA [23]. However, it also plays a proinflammatory role by inducing the expression of leucocyte adhesion molecules on the endothelial cells [24,25]. An association of some *VEGF* functional polymorphism with the susceptibility to several systemic inflammatory conditions has been reported [26,27], including classic cranial GCA [28-30]. In this regard, in a previous study [28], we found that *VEGF* rs2010963 (-634G/C) polymorphism was associated with the development of severe ischemic manifestations in biopsy-proven GCA patients with predominant classic cranial manifestations. However, the genetic role of *VEGF* in extracranial LVV GCA remains unknown.

Taken all these considerations into account, we aimed to assess for the first time if *VEGF* functional polymorphisms are associated with distinct clinical phenotypes of GCA. In addition, we also aimed to evaluate if *VEGF* functional polymorphisms influence the development of severe ischemic manifestations in both patients with the cranial and the extracranial LVV-GCA pattern.

METHODS

Patients and controls

The study group comprised 185 patients with biopsy-proven cranial GCA, 105 with LVV-GCA and 490 healthy controls. All patients and controls were Spanish of European ancestry. They were recruited in ten collaborative centers: 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 centers 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.

Patients with classic cranial phenotype of GCA

A total of 185 patients with the cranial phenotype of GCA were included in our study. GCA diagnosis was based on the American College of Rheumatology (ACR) 1990 classification criteria [31]. In addition, the diagnosis of GCA was confirmed in all patients by a positive temporal artery biopsy showing the typical histopathologic findings of this vasculitis. None of them presented clinical symptoms suggesting peripheral arterial involvement.

Patients with extracranial LVV-GCA phenotype

A set of 105 ethnically matched patients with the extracranial LVV-GCA phenotype were also included in our study. LVV-GCA diagnosis was established by experienced rheumatologists based on 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).

For the present study, in an attempt to evaluate a well-defined group of LVV-GCA patients who were clinically different from those with classic cranial GCA, patients with LVV-GCA presenting symptoms of cranial GCA were excluded from the analysis (**Table 1**). Patients with other underlying inflammatory conditions, infections or neoplastic diseases that could present with LVV involvement were also excluded.

GCA patients with severe ischemic manifestations

As previously reported [28,32], patients were considered to have severe ischemic manifestations if they had at least one of the following complications: visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, or diplopia), cerebrovascular strokes, jaw claudication, or large-artery stenosis of the extremities that caused signs of occlusive manifestations (limb claudication) of recent onset.

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.

***VEGF* polymorphisms genotyping**

Genomic DNA was extracted from peripheral blood using the REALPURE "SSS" kit (RBME04, REAL, Durviz S.L., Valencia, Spain), as previously described [33].

All patients and healthy controls were genotyped for *VEGF* rs833061 T/C, rs2010963 G/C, and rs3025039 C/T by TaqMan assays. 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).

First, comparisons were performed considering each *VEGF* polymorphism independently. Both genotype and allele frequencies of rs833061, rs2010963 and rs3025039 were calculated and compared between patients with GCA and healthy controls as well as between patients with GCA stratified according to the clinical phenotype (cranial and extracranial LVV-GCA) and the presence of severe ischemic manifestations 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).

Subsequently, allelic combinations (haplotypes) of *VEGF* were carried out. Haplotype frequencies were calculated by the Haploview v4.2 software (http:// broad. mit. edu/ mpg/ haplo view) and then compared by chi-square or Fisher tests between the groups mentioned above. Strength of associations was estimated by OR and 95% CI. 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 rs833061, rs2010963, and rs3025039 genotype distribution was in HWE. Genotype and allele frequencies were in agreement with the data of the 1000 Genomes Project for Europeans.

Association of VEGF with classic cranial GCA and extracranial LVV-GCA

Genotype, allele, and haplotype frequencies of *VEGF* were compared between the whole cohort of patients with GCA and healthy controls. As shown in **Table 2**, no statistically significant genetic differences were found between these groups. This was also the case when patients with the classic cranial GCA pattern and patients with the extracranial-LVV GCA pattern were compared to healthy controls (**Suppl Tables 1 and 2)**. We also examined whether differences in the genotype, allele and haplotype frequencies of *VEGF* could exist between patients with GCA stratified according to the clinical phenotype of GCA. However, no statistically significant differences were found in this regard between GCA patients with the classic cranial pattern and the LVV-GCA extracranial pattern (**Table 3**).

Association of VEGF with severe ischemic manifestations

In an additional step, we also evaluated the differences in *VEGF* frequencies among the entire cohort of the GCA patient group (both cranial and extracranial LVV-GCA) stratified according to the presence or absence of severe ischemic complications. In this regard, no statistically significant differences in the genotype and allele frequencies of each *VEGF* polymorphism were disclosed between them, except for rs2010963 GC genotype which showed a decreased frequency in patients with ischemic manifestations (**Table 4**).

Nevertheless, when *VEGF* haplotypes were analyzed, we found that the CGC haplotype (OR= 1.63 [1.05-2.53]) and the CGT haplotype (OR= 2.55 [1.10-5.91]) were significantly more frequent among GCA patients with severe ischemic complications compared to those patients without these complications (**Table 4**).

DISCUSSION

GCA patients can present different clinical phenotypes and outcomes that might be influenced by a different genetic susceptibility. *VEGF* seems to play an important role in the pathogenesis of GCA and the development of ischemic complications. In this regard, we wondered if *VEGF* could influence the development of different GCA phenotypes and severity of the disease. We found no implication of *VEGF* polymorphisms in the genetic predisposition to cranial and extracranial LVV-GCA. However, two haplotypes of *VEGF* were associated with the development of severe ischemic manifestations, regardless of the clinical phenotype of GCA.

Interestingly, in the present study the two *VEGF* haplotypes that were associated with severe ischemic complications carried the G allele of rs2010963. In accordance, a previous study that included 103 biopsy-proven GCA patients with the classic cranial pattern of the disease showed that the G allele of rs2010963 (-634G/C) was significantly overrepresented in cranial GCA patients with ischemic manifestations [28]. Therefore, we confirm the possible implication of *VEGF* in the development of severe ischemic manifestations in GCA patients with the classic cranial and the extracranial LVV-GCA pattern. Of note, the presence of the G allele of rs2010963 (-634G/C) has also been related to the development of vascular complications in other systemic vasculitis. In this regard, the frequency of the G allele was significantly higher in patients with Kawasaki disease with coronary artery lesions [34]. Furthermore, a previous study observed that the G allele of rs2010963 (-634G/C) is associated with a reduced *VEGF* transcription and, consequently, with a lower production of VEGF [35], which may explain the increased risk of ischemic complications.

Although previous studies observed an association of *VEGF* in GCA susceptibility [29,30], we did not find an implication of *VEGF* rs833061, rs2010963 and rs3025020 in GCA genetic predisposition. Furthermore, we did not observe a role of *VEGF* in the development of different clinical phenotypes of GCA. Similarly, in former studies, we could not find differences in HLA class I and class II genetic predisposition between patients with the cranial and the extracranial

LVV-GCA phenotype [36,37]. Thereby, more studies are needed to assess the possible implication of other genes that may explain the different clinical expression of GCA.

In conclusion, our study reveal that *VEGF* haplotypes may play a role in the development of severe ischemic manifestations in GCA patients with both the cranial and the extracranial-LVV pattern.

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Competing interests

Disclosures that might be interpreted as constituting of possible conflict(s) of interest for the study: DP-P has received research support from UCB Pharma, Roche, AbbVie and Lilly. BA-M received grants/research supports from Kern Pharma, AbbVie, Pfizer, Celgene and GSK. RB received grants/research supports from Abbvie, MSD and Roche, and had consultation fees/participation in company sponsored speaker´s bureau from Abbvie, Lilly, Pfizer, Roche, Bristol-Myers, Janssen, UCB Pharma and MSD. MAG-G received grants/research supports from Abbvie, MSD. Jansen and Roche and had consultation fees/participation in company sponsored speaker´s bureau from Abbvie, Pfizer, Roche, Sanofi, Lilly, Celgene and MSD. The remaining authors declare do not have conflict of interest.

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Table 1. Main clinical features of patients with classic cranial GCA and extracranial LVV-GCA pattern.

	Classic cranial GCA pattern n=185	LVV-GCA pattern n=105	P
Age at diagnosis (mean ± SD)	74.0 ± 10.4	67.5 ± 9.8	< 0.01
Women, n (%)	122 (65.9%)	76 (72.4%)	0.24
Positive TAB, n (%)	185 (100%)	3/37 (8.1%)	< 0.01
Headache, n (%)	145 (79.2%)	0 (0%)	< 0.01
Abnormal temporal artery on physical examination, n (%)	110 (60.1%)	0 (0%)	< 0.01
Jaw claudication, n (%)	73 (39.5%)	0 (0%)	< 0.01
Polymyalgia rheumatica, n (%)	74 (40.0%)	86 (81.9%)	< 0.01
Visual manifestations, n (%)	47 (25.4%)	0 (0%)	< 0.01
Permanent visual loss, n (%)	21 (11.4%)	0 (0%)	< 0.01
Peripheral arteriopathy, n (%)	0 (0%)	12 (11.4%)	< 0.01
Stroke, n (%)	8 (4.3%)	0 (0%)	0.05
ESR > 40 mm/1st h. at diagnosis, n (%)	182 (98.4%)	84 (80.0%)	< 0.01

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

Table 2. Genotype, allele, and haplotype frequencies of *VEFG* in all patients with GCA and healthy controls.

Polymorphism	**All patients with GCA % (n)**	**Healthy controls % (n)**	**p**	**OR [95% CI]**
VEGF rs833061				
TT	30 (85)	28 (135)	-	Ref.
TC	48 (138)	48 (233)	0.73	0.94 [0.67-1.33]
CC	22 (64)	24 (122)	0.38	0.83 [0.55-1.25]
T	54 (308)	51 (503)	-	Ref.
C	46 (266)	49 (477)	0.37	0.91 [0.74-1.12]
VEGF rs2010963				
GG	42 (123)	48 (237)	-	Ref.
GC	46 (133)	40 (197)	0.10	1.30 [0.95-1.77]
CC	12 (34)	12 (56)	0.52	1.17 [0.72-1.89]
G	65 (379)	68 (671)	-	Ref.
C	35 (201)	32 (309)	0.20	1.15 [0.93-1.43]
VEFG rs3025039				
CC	72 (210)	75 (368)	-	Ref.
CT	27 (78)	23 (110)	0.21	1.24 [0.89-1.74]
TT	1 (2)	2 (12)	0.11	0.29 [0.06-1.32]
C	86 (498)	86 (846)	-	Ref.
T	14 (82)	14 (134)	0.80	1.04 [0.77-1.40]
Haplotype*	**All patients with GCA % (n)**	**Healthy controls % (n)**	**p**	**OR [95% CI]**
TGC	34 (198)	33 (326)	-	Ref.
CGC	26 (149)	29 (288)	0.24	0.85 [0.65-1.11]
TCC	15 (86)	13 (132)	0.67	1.07 [0.78-1.48]
CCC	10 (60)	10 (100)	0.95	0.99 [0.69-1.42]
CGT	4 (25)	5 (51)	0.41	0.81 [0.48-1.34]
TCT	4 (22)	4 (39)	0.79	0.93 [0.53-1.61]
CCT	6 (32)	3 (38)	0.20	1.39 [0.84-2.29]

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

*The polymorphism order was rs833061, rs2010963 and rs3025039.

Table 3. Genotype, allele, and haplotype frequencies of *VEFG* in patients with LVV-GCA pattern and classic cranial GCA pattern.

Polymorphism	**LVV-GCA pattern % (n)**	**Classic cranial GCA pattern % (n)**	**p**	**OR [95% CI]**
VEGF rs833061				
TT	31 (32)	29 (53)	-	Ref.
TC	45 (46)	50 (92)	0.51	0.83 [0.47-1.46]
CC	24 (24)	21 (40)	0.99	0.99 [0.51-1.94]
T	54 (110)	54 (198)	-	Ref.
C	46 (94)	46 (172)	0.93	0.98 [0.70-1.39]
VEGF rs2010963				
GG	48 (50)	39 (73)	-	Ref.
GC	44 (46)	47 (87)	0.32	0.77 [0.47-1.28]
CC	8 (9)	14 (25)	0.14	0.53 [0.23-1.22]
G	70 (146)	63 (233)	-	Ref.
C	30 (64)	37 (137)	0.11	0.75 [0.52-1.07]
VEFG rs3025039				
CC	71 (75)	73 (135)	-	Ref.
CT	29 (30)	26 (48)	0.67	1.13 [0.66-1.92]
TT	0 (0)	1 (2)	-	-
C	86 (180)	86 (318)	-	Ref.
T	14 (30)	14 (52)	0.94	1.02 [0.63-1.66]
Haplotype*	**LVV-GCA pattern % (n)**	**Classic cranial GCA pattern % (n)**	**p**	**OR [95% CI]**
TGC	37 (76)	33 (122)	-	Ref.
CGC	27 (55)	25 (94)	0.78	0.94 [0.61-1.46]
TCC	12 (24)	17 (62)	0.09	0.62 [0.36-1.08]
CCC	10 (20)	11 (40)	0.48	0.80 [0.44-1.47]
CGT	4 (9)	4 (16)	0.82	0.90 [0.38-2.15]
TCT	4 (9)	4 (13)	0.82	1.11 [0.45-2.72]
CCT	5 (10)	6 (22)	0.44	0.73 [0.33-1.72]

CI: confidence interval; GCA: giant cell arteritis; LVV: large- vessel vasculitis; OR: Odds Ratio.
*The polymorphism order was rs833061, rs2010963 and rs3025039.

Table 4. Genotype, allele, and haplotype frequencies of *VEFG* in patients with GCA according to the presence of severe ischemic manifestations.

	Ischemic manifestations			
Polymorphism	**Yes % (n)**	**No % (n)**	**p**	**OR [95% CI]**
VEGF rs833061				
TT	28 (31)	30 (54)	-	Ref.
TC	44 (48)	51 (90)	0.80	0.93 [0.53-1.63]
CC	28 (30)	19 (34)	0.20	1.54 [0.79-2.97]
T	50 (110)	56 (198)	-	Ref.
C	50 (108)	44 (158)	0.23	1.23 [0.88-1.73]
VEGF rs2010963				
GG	49 (53)	39 (70)	-	Ref.
GC	38 (41)	51 (92)	**0.04**	**0.59 [0.35-0.98]**
CC	13 (15)	10 (19)	0.92	1.04 [0.49-2.24]
G	67 (147)	64 (232)	-	Ref.
C	33 (71)	36 (130)	0.41	0.86 [0.60-1.23]
VEFG rs3025039				
CC	72 (78)	73 (132)	-	Ref.
CT	28 (31)	26 (47)	0.69	1.12 [0.66-1.90]
TT	0 (0)	1 (2)	-	-
C	86 (187)	86 (311)	-	Ref.
T	14 (31)	14 (51)	0.97	1.01 [0.62-1.64]
Haplotype*	**Yes % (n)**	**No % (n)**	**p**	**OR [95% CI]**
TGC	30 (66)	37 (132)	-	Ref.
CGC	31 (67)	23 (82)	**0.03**	**1.63 [1.05-2.53]**
TCC	17 (37)	14 (49)	0.12	1.51 [0.90-2.54]
CCC	8 (17)	12 (43)	0.47	0.79 [0.42-1.49]
CGT	6 (14)	3 (11)	**0.03**	**2.55 [1.10-5.91]**
TCT	3 (7)	4 (15)	0.89	0.93 [0.36-2.40]
CCT	5 (10)	6 (22)	0.82	0.91 [0.41-2.03]

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

*The polymorphism order was rs833061, rs2010963 and rs3025039.

Supplementary Table 1. Genotype, allele, and haplotype frequencies of *VEFG* in patients with classic cranial GCA pattern and healthy controls.

Polymorphism	**Classic cranial GCA pattern % (n)**	**Healthy controls % (n)**	**p**	**OR [95% CI]**
VEGF rs833061				
TT	29 (53)	28 (135)	-	Ref.
TC	50 (92)	48 (233)	0.98	1.01 [0.68-1.50]
CC	21 (40)	24 (122)	0.46	0.84 [0.52-1.35]
T	54 (198)	51 (503)	-	Ref.
C	46 (172)	49 (477)	0.47	0.92 [0.72-1.16]
VEGF rs2010963				
GG	39 (73)	48 (237)	-	Ref.
GC	47 (87)	40 (197)	0.05	1.43 [0.99-2.06]
CC	14 (25)	12 (56)	0.18	1.45 [0.85-2.49]
G	63 (233)	68 (671)	-	Ref.
C	37 (137)	32 (309)	0.06	1.28 [0.99-1.64]
VEFG rs3025039				
CC	73 (135)	75 (368)	-	Ref.
CT	26 (48)	23 (110)	0.39	1.19 [0.80-1.76]
TT	1 (2)	2 (12)	0.31	0.45 [0.10-2.06]
C	86 (318)	86 (846)	-	Ref.
T	14 (52)	14 (134)	0.86	1.03 [0.73-1.46]
Haplotype*	**Classic cranial GCA pattern % (n)**	**Healthy controls % (n)**	**p**	**OR [95% CI]**
TGC	33 (122)	33 (326)	-	Ref.
CGC	25 (94)	29 (288)	0.39	0.87 [0.64-1.19]
TCC	17 (62)	13 (132)	0.22	1.26 [0.87-1.81]
CCC	11 (40)	10 (100)	0.76	1.07 [0.70-1.63]
CGT	4 (16)	5 (51)	0.56	0.84 [0.46-1.53]
TCT	4 (13)	4 (39)	0.73	0.89 [0.46-1.73]
CCT	6 (22)	3 (38)	0.13	1.55 [0.88-2.72]

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

*The polymorphism order was rs833061, rs2010963 and rs3025039.

Supplementary Table 2. Genotype, allele, and haplotype frequencies of VEFG in patients with LVV-GCA pattern and healthy controls.

Polymorphism	**LVV-GCA pattern % (n)**	**Healthy controls % (n)**	**p**	**OR [95% CI]**
VEGF rs833061				
TT	31 (32)	28 (135)	-	Ref.
TC	45 (46)	48 (233)	0.47	0.83 [0.51-1.37]
CC	24 (24)	24 (122)	0.53	0.83 [0.46-1.49]
T	54 (110)	51 (503)	-	Ref.
C	46 (94)	49 (477)	0.50	0.90 [0.67-1.22]
VEGF rs2010963				
GG	48 (50)	48 (237)	-	Ref.
GC	44 (46)	40 (197)	0.65	1.11 [0.71-1.72]
CC	8 (9)	12 (56)	0.49	0.76 [0.35-1.64]
G	70 (146)	68 (671)	-	Ref.
C	30 (64)	32 (309)	0.77	0.95 [0.69-1.32]
VEFG rs3025039				
CC	71 (75)	75 (368)	-	Ref.
CT	29 (30)	23 (110)	0.23	1.34 [0.82-2.15]
TT	0 (0)	2 (12)	-	-
C	86 (180)	86 (846)	-	Ref.
T	14 (30)	14 (134)	0.82	1.05 [0.69-1.61]
Haplotype*	**LVV-GCA pattern % (n)**	**Healthy controls % (n)**	**p**	**OR [95% CI]**
TGC	37 (76)	33 (326)	-	Ref.
CGC	27 (55)	29 (288)	0.31	0.82 [0.56-1.20]
TCC	12 (24)	13 (132)	0.33	0.78 [0.47-1.29]
CCC	10 (20)	10 (100)	0.58	0.86 [0.50-1.47]
CGT	4 (9)	5 (51)	0.47	0.76 [0.36-1.60]
TCT	4 (9)	4 (39)	0.98	0.99 [0.46-2.13]
CCT	5 (10)	3 (38)	0.75	1.13 [0.54-2.37]

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

*The polymorphism order was rs833061, rs2010963 and rs3025039.

4. DISCUSIÓN GLOBAL

4. DISCUSIÓN GLOBAL

A continuación, se pasan a discutir de manera conjunta los resultados obtenidos en las publicaciones que compendian este trabajo de tesis doctoral:

- **Artículo 1:** *Predictors of positive 18F-FDG PET/CT-scan for large vessel vasculitis in patients with persistent polymyalgia rheumatica.*
- **Artículo 2:** *Cranial and extracranial giant cell arteritis share similar HLA-DRB1 association.*
- **Artículo 3:** *The presence of both HLA-DRB1*04:01 and HLA-B*15:01 increases the susceptibility to cranial and extracranial giant cell arteritis.*
- **Artículo 4:** *Vascular Endothelial Growth Factor haplotypes are associated with severe ischemic complications in Giant Cell Arteritis regardless of the disease phenotype.*

4.1 Identificación de pacientes con ACG extracraneal y diferencias fenotípicas de la ACG craneal y la ACG extracraneal

El **artículo 1** nos permitió identificar una cohorte bien definida de pacientes con ACG extracraneal diagnosticada mediante ^{18}F-FDG PET/TAC. Este estudio confirmó que la ACG extracraneal a menudo se presenta en forma de polimialgia reumática refractaria [6,12,14]. Estudios previos habían reportado la presencia de ACG extracraneal en al menos un tercio de los pacientes con polimialgia reumática en los que se realizó ^{18}F-FDG PET/TAC[49,50]. En nuestra estudio la realización de ^{18}F-FDG PET/TAC en 84 pacientes con polimialgia reumática refractaria reveló la presencia de ACG extracraneal en el 60.7% de los pacientes [51]. Este estudio, además, permitió identificar rasgos clínicos predictivos de presencia de ACG extracraneal en pacientes con polimialgia reumática refractaria. La afectación predominante de cintura pelviana, la presencia de dolor lumbar inflamatorio y dolor difuso en miembros inferiores fueron factores predictivos para un resultado positivo en ^{18}F-FDG PET/TAC para ACG extracraneal[51]. Los

resultados obtenidos en este estudio contribuyen a mejorar la identificación de pacientes con ACG extracraneal y optimizar y rentabilizar el uso de ^{18}F-FDG PET/TAC pudiendo seleccionar aquellos pacientes que más se pueden beneficiar de esta técnica.

Este estudio asentó la base del presente trabajo de tesis doctoral para la identificación y descripción del espectro clínico de pacientes con ACG con fenotipo predominantemente extracraneal en ausencia de las manifestaciones craneales típicas de la ACG. La cohorte de pacientes obtenida inicialmente en este estudio (n=51) fue progresivamente ampliada con pacientes diagnosticados posteriormente en nuestro centro y, también, con pacientes procedentes de otros centros hospitalarios de España gracias a la colaboración desinteresada de profesionales del Hospital Universitario de Basurto (Bilbao), Hospital de León (León), Hospital Universitario de La Princesa (Madrid), Hospital Universitario y Politécnico La Fe (Valencia), Hospital Universitario Virgen del Rocío (Sevilla), Hospital Universitario de Pontevedra (Pontevedra), Hospital Universitario Lucus Augusti (Lugo), Hospital Universitario San Cecilio (Granada) y del Hospital San Agustín (Avilés).

A lo largo de la realización de esta tesis doctoral hemos conseguido reunir una cohorte de 105 pacientes con ACG con fenotipo predominantemente extracraneal identificada por ^{18}F-FDG PET/TAC o angio-RMN, 184 pacientes con ACG con fenotipo clásico craneal con biopsia y/o ecografía positiva y 486 controles sanos.

En los **artículos 2, 3 y 4** se recoge en la primera tabla los datos demográficos y clínicos de los pacientes con ACG de fenotipo clásico craneal y los pacientes con ACG de fenotipo extracraneal. El estudio descriptivo comparativo confirmó las diferencias observadas por otros autores entre estos dos subgrupos de pacientes [6,12,14].

Los pacientes con ACG con fenotipo predominantemente extracraneal fueron más jóvenes al diagnóstico que los pacientes con ACG craneal (65.5 ± 9.8 vs 74.0 ± 10.4 años; $p < 0.01$), existiendo un predominio de mujeres en ambos subgrupos sin diferencias significativas. La

presencia de polimialgia reumática (81.9% vs 40.2%; p < 0.01) y arteriopatía periférica (11.4% vs 0%; p < 0.01) fue más frecuente en pacientes con ACG extracraneal. Respecto a marcadores de laboratorio, la elevación de reactantes de fase aguda, PCR y VSG, fue menos llamativa en los pacientes con ACG con fenotipo extracraneal. Nuestros resultados confirmaron también la baja frecuencia de biopsia de arteria temporal positiva en pacientes con ACG con fenotipo extracraneal (8.1%) observada por otros autores [14]. Curiosamente, la frecuencia de biopsia positiva de nuestra cohorte de pacientes con ACG extracraneal fue idéntica a la observada en un estudio realizado hace décadas en pacientes con PMR del norte de España que se sometieron a una biopsia de la arteria temporal debido a PMR asociada con síntomas constitucionales o alta respuesta inflamatoria[52]. Posiblemente alguno de estos pacientes con PMR hubiesen sido diagnosticados con ACG extracraneal si hubiesen existido las técnicas de imagen adecuadas.

4.2 Implicación de los genes HLA de clase I y II en la AGG craneal y la AGC extracraneal

El estudio de la influencia de los genes HLA de clase I y II en la susceptibilidad genética para el desarrollo del fenotipo clásico craneal y extracraneal de la ACG se realizó en el **artículo 2** y el **artículo 3**.

En el **artículo 2** se evaluó por primera vez si la reconocida asociación de la ACG craneal clásica con genes HLA de clase I, en concreto con *HLA DRB1*04*, se producía también en pacientes con ACG extracraneal.

Dado que la PMR se observa más frecuentemente asociada al fenotipo extracraneal de la ACG, y que previamente en población española se había observado que los pacientes con PMR sin clínica sugestiva de ACG craneal no presentaban asociación con *HLA-DRB1*04*, nosotros nos planteamos si la asociación con *HLA-DRB1*04* podía no estar presente en pacientes con ACG extracraneal.

La frecuencia del fenotipo *HLA-DRB1*04* fue significativamente mayor en los pacientes con ACG craneal clásica en comparación con controles (42.1% versus 23.5%, respectivamente; p < 0.01; odds ratio-OR [95% intervalo de confianza- IC] =2.38 [1.62-3.47]). Esta asociación se debió principalmente al alelo *HLA-DRB1*04:01* (20.8% versus 5.3%, respectivamente; p < 0.01; OR [95% IC] =4.64 [2.63-8.26]). La asociación con *HLA-DRB1*04* se observó también en pacientes con ACG extracraneal en comparación con controles (46.0% versus 23.5%, respectivamente; p < 0.01; OR [95% CI] =2.78 [1.73-4.44]). Como ocurrió con los pacientes con ACG clásica craneal, esta asociación también fue principalmente con el alelo *HLA-DRB1*04:01* (19.0% versus 5.3%, respectivamente; p < 0.01; OR [95% IC] =4.15 [2.06-8.19]). En el estudio comparativo entre el subgrupo de pacientes con ACG clásica craneal y el de pacientes con ACG extracraneal, se encontró una asociación similar con *HLA-DRB1*04:01.*

Hace más de dos décadas, ya se observó que los pacientes con PMR aislada que portaban el alelo *HLA-DRB1*04* presentaban recaídas de forma más frecuente que aquellos que no eran portadores de este alelo[53]. Teniendo en cuenta que en aquella época no existían técnicas de imágenes capaces de detectar la afectación extracraneal de la ACG, es posible que algunos de estos pacientes con PMR tuviesen en realidad una ACG de fenotipo extracraneal manifestándose como una PMR refractaria.

Los resultados del **artículo 2** permitieron llegar a la conclusión de que la ACG de fenotipo craneal y extracraneal comparten una misma asociación de susceptibilidad genética con *HLA-DRB1*04,* en especial con *HLA-DRB1*04:01*.

Dado que no pudimos encontrar diferencias en cuanto a susceptibilidad genética en genes HLA de clase II, y teniendo en cuenta las evidentes diferencias fenotípicas entre el patrón craneal y extracraneal de la ACG, en el **artículo 3** se trató de esclarecer si existían diferencias en susceptibilidad genética en genes HLA de clase I. Los genes HLA clase I han demostrado jugar también un papel en la susceptibilidad genética de las vasculitis de grandes vasos, especialmente

en la arteritis de Takayasu, que se asocia a *HLA-B52**[46,54]. La arteritis de Takayasu, al igual que la ACG de fenotipo extracraneal, suele afectar a pacientes más jóvenes que los pacientes con ACG clásica craneal, y se caracteriza por la inflamación de la pared vascular de arterias de gran calibre, como la aorta, pudiendo también conducir al desarrollo de estenosis, aneurismas y disección aórtica[55,56]. Teniendo en cuenta que la arteritis de Takayasu y la ACG craneal clásica presentan una asociación diferente con genes *HLA-B*, nosotros nos planteamos si los pacientes con ACG extracraneal podían presentar una asociación con genes *HLA-B* diferente a la de los pacientes con ACG clásica craneal. Además, evaluamos si la combinación de los alelos *HLA-B* y *HLA-DRB1* podía incrementar el riesgo de susceptibilidad de ACG tanto para el fenotipo craneal como extracraneal.

La frecuencia del fenotipo *HLA-B*15* fue significativamente mayor en pacientes con ACG clásica craneal en comparación con controles (14.7% versus 5.8%, respectivamente; p < 0.01; OR [95% IC] =2.81 [1.54-5.11]), principalmente debido al alelo *HLA-B*15:01* (12.5% versus 4.0%, respectivamente; p < 0.01; OR [95% IC] =3.51 [1.77-6.99]). En los pacientes con ACG extracraneal se observó una asociación similar con *HLA-B*15* (11.4% versus 5.8%, p= 0.04, OR [95% IC] =2.11 [1.04-4.30]). Esta asociación también fue principalmente con el alelo *HLA-B*15:01* (10.5% versus 4.0%, respectivamente; p = 0.0054; OR [95% IC] =2.88 [1.19-6.59]). Cuando se compararon los pacientes con ACG clásica craneal y los pacientes con ACG extracraneal, no se encontraron diferencias en cuanto a fenotipo *HLA-B*. Cabe destacar, que la presencia del alelo HLA-B15*01 junto con el alelo HLA-DRB1*04:01, aumentó significativamente tanto el riesgo de ACG clásica craneal (OR [95% IC] = 14.25 [3.82-78.67]) como de ACG extracraneal (OR [95% IC] = 7.49 [1.23-51.81]).

Por tanto, los resultados del **artículo 3** revelaron que los pacientes con ACG clásica craneal y ACG extracraneal presentan una asociación similar con *HLA-B*15*, principalmente con *HLA-B*15:01*. Además, observamos que la presencia de los alelos *HLA-DRB1*04:01* y *HLA-B*15:01*

tiene un efecto independiente y aditivo a la hora de aumentar el riesgo de ACG, independientemente del fenotipo clínico.

Un estudio previo realizado en 98 pacientes con ACG clásica craneal con biopsia probada había observado una asociación con *HLA-B15*01*[43]. El **artículo 3** confirmó la asociación con *HLA-B15*01* en 184 pacientes con ACG craneal, y además, reveló que esta asociación también se produce en pacientes con ACG con fenotipo extracraneal.

Teniendo en cuenta en conjunto los resultados del **artículo 2** y el **artículo 3**, podemos llegar a la conclusión de que la susceptibilidad genética de la ACG está fuertemente relacionada con genes de la región HLA, independientemente de la expresión fenotípica de la enfermedad. Por tanto, es posible que genes que se localicen fuera de esta región puedan explicar las diferencias fenotípicas de la ACG.

4.3 Potencial papel de otras variantes genéticas implicadas en la ACG clásica craneal y la ACG extracraneal

En la fisiopatología de la ACG participan múltiples vías de inflamación y citocinas. Variantes genéticas en estas vías podrían explicar las diferencias entre el fenotipo craneal clásico y el fenotipo extracraneal de la ACG. El factor de crecimiento endotelial (VEGF) es un mediador pivotal de la angiogénesis que ha demostrado estar implicado en la patogenia de la ACG[57–59]. En este sentido, se han encontrado niveles altos de VEGF circulante en pacientes con ACG y PMR activa, que disminuyen en respuesta a corticoides[60,61]. VEGF modula la formación de nuevos vasos sanguíneos y, por tanto, podría compensar los fenómenos isquémicos que se producen en la ACG[62]. Por otro lado, VEGF también tiene un papel proinflamatorio al inducir la expresión de moléculas de adhesión leucocitaria en las células endoteliales[63]. Se ha observado que algunos polimorfismos funcionantes de *VEGF* están asociados con la susceptibilidad para el desarrollo de varias enfermedades sistémicas inflamatorias, entre ellas la ACG[64–66]. En concreto, un estudio previo encontró que el polimorfismo *VEGF* rs2010963 (-634G/C) estaba

asociado con el desarrollo de manifestaciones isquémicas severas en pacientes con ACG clásica craneal con biopsia probada[64]. Teniendo en cuenta estos hallazgos, en el **artículo 4** evaluamos por primera vez si polimorfismos funcionantes de *VEGF* (rs833061 T/C, rs2010963 G/C y rs3025039 C/T) podrían asociarse con los dos diferentes fenotipos clínicos de la ACG. Además, tratamos de evaluar la influencia de polimorfismos funcionantes de VEGF en el desarrollo de manifestaciones isquémicas severas tanto en pacientes con ACG con fenotipo clásico craneal y fenotipo extracraneal.

La frecuencia de alelos, genotipos y haplotipos de *VEGF* fue similar en pacientes con ACG en comparación con controles y también entre pacientes con ACG craneal clásica y ACG extracraneal. Sin embargo, observamos que el haplotipo CGC de *VEGF* (OR= 1.63 [1.05-2.53]) y el haplotipo CGT de *VEGF* (OR= 2.55 [1.10-5.91]) fueron significativamente más frecuentes en pacientes con ACG con manifestaciones isquémicas severas en comparación con pacientes sin estas complicaciones.

Por tanto, los resultados obtenidos en el **artículo 4** revelaron que los polimorfismos funcionantes de VEGF (rs833061 T/C, rs2010963 G/C y rs3025039 C/T) no parecen tener influencia en el desarrollo del fenotipo craneal o extracraneal de la ACG. Sin embargo, observamos que dos haplotipos de *VEGF* (CGC y CGT) se asociaron con el desarrollo de manifestaciones isquémicas severas, independientemente del fenotipo clínico de la ACG. Curiosamente estos dos haplotipos portan el alelo G del polimorfismo rs2010963. Un estudio previo que incluyó 103 pacientes con ACG craneal clásica encontró que el alelo G de rs2010963 estaba sobrerrepresentado en pacientes con ACG craneal con manifestaciones isquémicas severas[64]. En el **artículo 4**, confirmamos la posible implicación de VEGF en el desarrollo de manifestaciones isquémicas severas tanto en pacientes con ACG craneal clásica como en pacientes con ACG extracraneal. En este sentido, un estudio previo observó que el alelo G de rs2010963 estaba asociado con una transcripción disminuida de *VEGF* y, por tanto, con una

menor producción de VEGF y menor angiogénesis[67], lo que podría explicar el aumento de riesgo de complicaciones isquémicas.

4.4 Futuras líneas de investigación

A pesar del esfuerzo realizado por determinar si existen diferentes patrones de susceptibilidad genética que influyan en el desarrollo de los distintos fenotipos clínicos de ACG, esta cuestión continúa siendo desconocida, por lo que es preciso seguir estudiando potenciales factores genéticos que expliquen las diferencias fenotípicas de la ACG craneal clásica y la ACG extracraneal.

A lo largo de esta tesis doctoral se han estudiado los principales genes candidatos implicados en la susceptibilidad genética de la ACG que pudieran explicar estas diferencias clínicas. Sin embargo, la inmunopatogenia de la ACG es muy compleja y existen otras vías de inflamación que podrían estar potencialmente implicadas. Hipotéticamente la vía inflamatoria mediada por IL-17/IL-6 podría estar más implicada en la ACG de fenotipo extracraneal debido al predominio de manifestaciones sistémicas inflamatorias, mientras que la vía IL-1/IFN-γ podría estar más relacionada con el fenotipo craneal clásico de la ACG en el cual las manifestaciones isquémicas son más frecuentes. Como línea de trabajo para el futuro, se planteará el estudio sobre el papel de genes relacionados con IFN-γ/IFN-γ receptor, IL-1, IL-6, IL-17, endotelina 1, intracelular adhesion mollecule-1 (ICAM-1) y pentraxina 3 que podrían ejercer una influencia sobre el desarrollo de los distintos fenotipos de la ACG.

Para completar el trabajo de esta línea de investigación se realizarán estudios a nivel de expresión genética y/o proteica. La descripción de diferentes patrones y marcadores genéticos entre la ACG craneal y la ACG extracraneal podría contribuir al diseño de nuevas dianas terapéuticas en función de los distintos fenotipos de ACG. Como consecuencia de lo expuesto,

estos avances se podrían traducir en un manejo clínico y terapéutico más eficaz e individualizado para los pacientes con ACG.

5. CONCLUSIONES

5. CONCLUSIONES

Primera. La ACG de fenotipo extracraneal a menudo se manifiesta como un cuadro polimiálgico refractario al tratamiento convencional con corticoides. A menudo se asocia con síntomas constitucionales (pérdida de peso, fiebre, astenia) y síntomas atípicos, como predominio de clínica polimiálgica a nivel de cintura pelviana, dolor lumbar inflamatorio y dolor difuso en extremidades.

Segunda. La ACG de fenotipo extracraneal, en comparación con la ACG de fenotipo craneal clásico, debuta a edades más jóvenes. La presencia de polimialgia reumática y arteriopatía periférica es más frecuente en pacientes con ACG extracraneal. La elevación de reactantes de fase aguda (PCR y VSG) es menos llamativa en los pacientes con ACG con fenotipo extracraneal. La frecuencia de biopsia positiva es menor que en los pacientes con ACG de fenotipo craneal.

Tercera. La susceptibilidad genética de la ACG está fuertemente relacionada con genes HLA de clase II, independientemente del fenotipo clínico. La ACG de fenotipo craneal y extracraneal comparten una misma asociación de susceptibilidad genética con *HLA-DRB1*04,* en especial con *HLA-DRB1*04:01*.

Cuarta. Los genes HLA de clase I también están implicados en la susceptibilidad genética de la ACG. Los pacientes con ACG clásica craneal y ACG extracraneal presentan una asociación similar con *HLA-B*15*, principalmente con *HLA-B*15:01*.

Quinta.La presencia de los alelos HLA-DRB1*04:01 y HLA-B*15:01 tiene un efecto independiente y aditivo a la hora de aumentar el riesgo de ACG, independientemente del fenotipo clínico.

Sexta. Los polimorfismos funcionantes de VEGF (rs833061 T/C, rs2010963 G/C y rs3025039 C/T) no tienen influencia en el desarrollo del fenotipo craneal o extracraneal de la ACG. Los haplotipos de VEGF (CGC y CGT) se asocian con el desarrollo de manifestaciones isquémicas severas, independientemente del fenotipo clínico de la ACG.

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ANEXOS

ANEXO I: PRODUCCIÓN CIENTÍFICA RELACIONADA CON LA LÍNEA DE INVESTIGACIÓN Y METODOLOGÍA DE LA TESIS DOCTORAL

PUBLICACIONES EN REVISTAS

1. **Prieto-Peña D**, Remuzgo-Martínez S, Genre F, Ocejo-Vinyals JG, Atienza-Mateo B, Muñoz-Jiménez A, Ortiz-Sanjuán F, Romero-Yuste S, Moriano C, Galíndez-Agirregoikoa E, Calvo I, Ortego-Centeno N, Álvarez-Rivas N, Miranda-Filloy JA, Llorente I, Blanco R, Gualillo O, Martín J, Márquez A, Castañeda S, Ferraz-Amaro I, López-Mejías R, González-Gay MA. Vascular Endothelial Growth Factor haplotypes are associated with severe ischemic complications in Giant Cell Arteritis regardless of the disease phenotype. Clin Exp Rheumatol. 2021 [Ahead of print]
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8. **Prieto-Peña D**, Bernabeu P, Vela P, Narváez J, Fernández-López JC, Freire-González M, González-Álvarez B, Solans-Laqué R, Callejas Rubio JL, Ortego N, Fernández-Díaz C, Rubio E, García-Morillo S, Minguez M, Fernández-Carballido C, de Miguel E, Melchor S, Salgado E, Bravo B, Romero-Yuste S, Salvatierra J, Hidalgo C, Manrique S, Romero-Gómez C, Moya P, Álvarez-Rivas N, Mendizabal J, Ortiz-Sanjuán F, Pérez de Pedro I, Alonso-Valdivielso JL, Perez-Sanchez L, Roldán R, Fernandez-Llanio N, Gómez de la Torre R, Suarez S, Montesa Cabrera MJ, Delgado Sánchez M, Loricera J, Atienza-Mateo B, Castañeda S, González-Gay MA, Blanco R. Tocilizumab in refractory Caucasian Takayasu's arteritis: a multicenter study of 54 patients and literature review. Ther Adv Musculoskelet Dis. 2021;13: 1759720X211020917. doi: 10.1177/1759720X211020917. PMID: 34211589; PMCID: PMC8216399.

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Agirregoikoa E, Arca B, Solans-Laqué R, Conesa A, Hidalgo C, Vázquez C, Román-Ivorra JA, Lluch P, Manrique-Arija S, Vela P, De Miguel E, Torres-Martín C, Nieto JC, Ordas-Calvo C, Salgado-Pérez E, Luna-Gomez C, Toyos-Sáenz de Miera FJ, Fernández-Llanio N, García A, Larena C, Palmou-Fontana N, Calvo-Río V, **Prieto-Peña D**, González-Vela C, Corrales A, Varela-García M, Aurrecoechea E, Dos Santos R, García-Manzanares Á, Ortego N, Fernández S, Ortiz-Sanjuán F, Corteguera M, Hernández JL, González-Gay MÁ, Blanco R. Tocilizumab in giant cell arteritis. Observational, open-label multicenter study of 134 patients in clinical practice. Semin Arthritis Rheum. 2019;49:126-135. doi: 10.1016/j.semarthrit.2019.01.003. PMID: 30655091.

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COMUNICACIONES A CONGRESOS

American College of Rheumatology (ACR/ARHP) Annual Meeting 2021 (Online November 2021)

1. POSTER: **D. Prieto-Peña**, I Martínez-Rodríguez, B. Atienza-Mateo, O. Cuenva-Vera, FJ Gómez de la Fuente, A. Sánchez-Salmón, MA González-Gay, R. Blanco. *Clinical, laboratory and Imaging outcomes in Tocilizumab-treated patients with large-vessel giant cell arteritis according to early onset therapy.*

2. POSTER: **D. Prieto-Peña**, Pilar Bernabéu, Paloma Vela-Casasempere, J.Narváez, Carlos Fernández-López, Mercedes Freire González, Beatriz, González-Alvarez,Roser Solans-Laqué, Jose Luis Callejas-Rubio, Norberto Ortego, Carlos Fernández-Díaz, Esteban Rubio Romero, Salvador García Morillo, Mauricio Minguez, Cristina Fernández-Carballido, Eugenio De Miguel, Sheila Melchor, Eva Salgado-Pérez, Beatriz Bravo,Susana Romero-Yuste, J Salvatierra, Cristina Hidalgo, Sara Manrique Arija, C. Romero-Gómez, Patricia Moya, Noelia Alvarez-Rivas, Javier Mendizabal, Francisco Miguel Ortiz Sanjuan, I. Pérez de Pedro, Javier Loricera, Santos Castañeda, Miguel A González-Gay, Ricardo Blanco. *Tocilizumab in Caucasian Patients with Takayasu Arteritis: Multicenter Study of 54 Patients.*

XLVII Congreso Nacional de la Sociedad Española de Reumatología SER 2021 (Palma de Mallorca 19-22 Octubre 2021)

1. POSTER: **D. Prieto-Peña**, I Martínez-Rodríguez, B. Atienza-Mateo, O. Cuenca-Vera, FJ Gómez de la Fuente, A. Sánchez-Salmón, MA González-Gay, R. Blanco. *Respuesta clinica, analítica y en pruebas de imagen en pacientes con arteritis de células gigantes extracraneal de acuerdo con el inicio temprano o tardío de Tocilizumab.*

2. POSTER: **D. Prieto-Peña**, Pilar Bernabéu, Paloma Vela-Casasempere, J.Narváez, Carlos Fernández-López, Mercedes Freire González, Beatriz, González-Alvarez,Roser Solans-Laqué, Jose Luis Callejas-Rubio, Norberto Ortego, Carlos Fernández-Díaz, Esteban Rubio Romero, Salvador García Morillo, Mauricio Minguez, Cristina Fernández-Carballido, Eugenio De Miguel, Sheila Melchor, Eva Salgado-Pérez, Beatriz Bravo,Susana Romero-Yuste, J Salvatierra, Cristina Hidalgo, Sara Manrique Arija, C. Romero-Gómez, Patricia Moya, Noelia Alvarez-Rivas, Javier Mendizabal, Francisco Miguel Ortiz Sanjuan, I. Pérez de Pedro, Javier Loricera, Santos Castañeda, Miguel A González-Gay, Ricardo Blanco. *Tocilizumab en arteritis de Takayasu en caucásicos: Estudio multicéntrico de 54 pacientes.*

European Association of Nuclear Medicine Congress 2021 (April 2021)

1. POSTER: I Martínez-Rodríguez, D. Prieto-Peña, A. Gutierrez-González, M de Arcocha-Torres, O. Cuenca-Vera, J Andrés-Pacheco, F. Gómez de la Fuente, N. Martínez-Amador, A. Sánchez-Salmón, J. Jimenez-Bonilla, S. Ruiz-Llama, M. Pombo-López, A. Bota-Bota, MA González-Gay, R. Quirce. *Influence of Tocilizumab therapy on osteoarticular inflammatory activity assessed by 18F-FDG PET/CT in patients with refractory polymyalgia rheumatica.*

Annual European Congress of Rheumatology EULAR 2021 Virtual Congress (3-6 June 2021)

1. POSTER: **D. Prieto-Peña**, I Martínez-Rodríguez, B. Atienza-Mateo, O. Cuenva-Vera, FJ Gómez de la Fuente, A. Sánchez-Salmón, MA González-Gay, R. Blanco. *Clinical, laboratory and Imaging outcomes in Tocilizumab-treated patients with large-vessel giant cell arteritis according to early onset therapy.*

American College of Rheumatology (ACR/ARHP) Annual Meeting 2020 (Online November 2020)

1. POSTER: L. Sánchez-Bilbao, **D. Prieto-Peña**, I Martínez-Rodríguez, B. Atienza-Mateo, O. Cuenva-Vera, FJ Gómez de la Fuente, A. Sánchez-Salmón, MA González-Gay, R. Blanco. *Response to Tocilizumab in Large Vessel Vasculitis According to the Extent of Baseline 18F-FDG Vascular Uptake.*
2. POSTER: L. Sánchez-Bilbao, **D. Prieto-Peña**, I Martínez-Rodríguez, B. Atienza-Mateo, O. Cuenva-Vera, FJ Gómez de la Fuente, A. Sánchez-Salmón, MA González-Gay, R. Blanco. *Ongoing vascular 18F-FDG uptake despite clinical remission in patients receiving tocilizumab for large vessel vasculitis giant cell arteritis: Single University Center Experience of 30 patients*

3. POSTER: A. Sebastian, Kayani A, **Prieto-Pena D**, Tomelleri A, Whitlock M, Mo J, van der Geest N, Dasgupta B. *Efficacy and safety of tocilizumab in giant cell arteritis: a single centre NHS experience using imaging (ultrasound and PET-CT) as a diagnostic and monitoring tool.*

European Association of Nuclear Medicine Congress 2020 (October 2020)

1. POSTER: Martinez-Rodriguez I, **Prieto-Peña D**, Quirce R, Jimenez-Bonilla J, Arcocha-Torres M, Sánchez-Salmón A, Martínez-Amador N, Molina-Mendoza G, Cuenca-Vera O, Andrés-Pacheco J, Gutierrez-Gonzalez A, Ruiz-Llama S, Gomez-de la Fuente FJ, Calderón-Goercke M, Blanco R, González-Gay MA, Banzo I. One-year follow-up with 18F-FDG PET/CT of large vessel vasculitis treated with tocilizumab. e-Poster.
2. POSTER: Martinez-Rodriguez I, **Prieto-Peña D**, Quirce R, Jimenez-Bonilla J, Arcocha-Torres M, Sánchez-Salmón A, Martínez-Amador N, Molina-Mendoza G, Cuenca-Vera O, Andrés-Pacheco J, Gutierrez-Gonzalez A, Ruiz-Llama S, Gomez-de la Fuente FJ, Calderón-Goercke M, Blanco R, González-Gay MA, Banzo I. Correlation of clinical and biochemical parameters with 18F-FDG PET/CT in patients with large vessel vasculitis under biological therapy with tocilizumab.

Annual European Congress of Rheumatology EULAR 2020 E-Congress (3-6 June 2020)

1. COMUNICACIÓN ORAL: Calderón-Goercke, M., **Prieto-Peña, D**., Castañeda, S., Fernández-Díaz, C., Moriano, C., Becerra-Fernández, Revenga, M., E., Álvarez-Rivas, N., Galisteo, C., Prior, A., Galindez-Agirregoikoa, E., Hidalgo, C., Manrique-Arija, S., De Miguel, E., Salgado-Pérez, E., Aldasoro, V., Villa, I., Humbría, A., Romero-Yuste, S., Narváez, J., Gómez-Arango, C., Pérez-Pampín, E., Melero, R., Sivera, F., Olivé-Marqués, A., Álvarez del Buergo, M., Marena-Rojas, L., Fernández-López, C., Navarro, F., Raya, E., Arca, B., Solans-Laqué, R., Conesa, A., Vázquez, C., Román-Ivorra, JA., Lluch, P., Vela, P., Torres-Martín, C., Nieto, JC., Ordas-Calvo, C., Luna-Gómez, C., Toyos-Sáenz de Miera, FJ., Fernández-Llanio, N., García, A., Loricera, J., González-Vela, C., García Casteñedo, N.,

García-Manzanares, A., Ortego, N., Ortiz-Sanjuán, F., Corteguera, M., Hernández, JL., González-Gay, MA., Blanco, R. *Optimization of tocilizumab therapy in giant cell arteritis. A multicenter real-life study of 134 patients*

2. POSTER: **D. Prieto-Peña**, Monica Calderón-Goercke, Isabel Martínez-Rodríguez, Jose Ignacio Banzo, Patricia Vicente-Gómez, Javier García-Fernández, Miguel A González-Gay, Ricardo Blanco. *Response to Tocilizumab in large vessel vasculitis according to the extent of baseline 18F-FDG vascular uptake.*

3. POSTER: **D. Prieto-Peña**, Monica Calderón-Goercke, Pilar Bernabéu, Paloma Vela-Casasempere, J.Narváez, Carlos Fernández-López, Mercedes Freire González, Beatriz, González-Alvarez,Roser Solans-Laqué, Jose Luis Callejas-Rubio, Norberto Ortego, Carlos Fernández-Díaz, Esteban Rubio Romero, Salvador García Morillo, Mauricio Minguez, Cristina Fernández-Carballido, Eugenio De Miguel, Sheila Melchor, Eva Salgado-Pérez, Beatriz Bravo,Susana Romero-Yuste, J Salvatierra, Cristina Hidalgo, Sara Manrique Arija, C. Romero-Gómez, Patricia Moya, Noelia Alvarez-Rivas, Javier Mendizabal, Francisco Miguel Ortiz Sanjuan, I. Pérez de Pedro, Javier Loricera, Santos Castañeda, Miguel A González-Gay, Ricardo Blanco. *Tocilizumab in refractory Takayasu arteritis. Open-label national multicenter study of 53 patients of clinical practice.*

4. POSTER: **D. Prieto-Peña**, Monica Calderón-Goercke, Isabel Martínez-Rodríguez, Jose Ignacio Banzo, Javier García-Fernández, Patricia Vicente-Gómez, Miguel A González-Gay, Ricardo Blanco. *Persistent vascular 18f-fdg uptake despite clinical-analytical remission in patients with large vessel vasculitis under tocilizumab therapy. Single universitary center experience of 30 patients*

5. POSTER: Calderón-Goercke, M., **Prieto-Peña, D.,** Castañeda, S., Fernández-Díaz, C., Moriano, C., Becerra-Fernández, Revenga, M., E., Álvarez-Rivas, N., Galisteo, C., Prior, A., Galindez-Agirregoikoa, E., Hidalgo, C., Manrique-Arija, S., De Miguel, E., Salgado-Pérez, E., Aldasoro, V., Villa, I., Humbría, A., Romero-Yuste, S., Narváez, J., Gómez-

Arango, C., Pérez-Pampín, E., Melero, R., Sivera, F., Olivé-Marqués, A., Álvarez del Buergo, M., Marena-Rojas, L., Fernández-López, C., Navarro, F., Raya, E., Arca, B., Solans-Laqué, R., Conesa, A., Vázquez, C., Román-Ivorra, JA., Lluch, P., Vela, P., Torres-Martín, C., Nieto, JC., Ordas-Calvo, C., Luna-Gómez, C., Toyos-Sáenz de Miera, FJ., Fernández-Llanio, N., García, A., Loricera, J., González-Vela, C., García Casteñedo, N., García-Manzanares, A., Ortego, N., Ortiz-Sanjuán, F., Corteguera, M., Hernández, JL., González-Gay, MA., Blanco, R. *Serious infections in 134 patients with giant cell arteritis with tocilizumab in clinical practice. Frequency, type and clinical associations.*

American College of Rheumatology (ACR/ARHP) Annual Meeting 2019 (Atlanta 8-13 Noviembre 2019)

1. POSTER: **Prieto-Peña D**, Calderón-Goercke M, Loricera J, Narváez J, Aurrecoechea E, Villa I, Castañeda S, Gómez-Arango C, Mera A, Perez Pampín E, Aldasoro Caceres V, Alvarez Rivas N, Fernandez Llanio N, Álvarez del buergo M, Marena-Rojas L, Sivera F, Galindez-Agirregoikoa E, Solans-Laqué R, Romero-Yuste S, Sanchez-Bilbao L, Gonzalez-Mazon I, Martínez Rodríguez I, Banzo I, González-Gay M, Blanco R. *Real-world Comparative Study of Methotrexate vs Tocilizumab in Patients with Giant Cell Arteritis with Large Vessel Involvement [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10).*
2. POSTER: **Prieto- Peña D**, Calderón-Goercke M, Martínez Rodríguez I, Banzo I, Sanchez-Bilbao L, Gonzalez-Mazon I, Atienza-Mateo B, González-Gay M, Blanco R. *Influence of Steroid Treatment on 18F-FDG PET/CT Accuracy to Detect Vascular and Musculoeskeletal Involvement in Patients with Polymyalgia Reumatica [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10).*
3. POSTER: Calderón-Goercke M, Loricera J, **Prieto-Peña D**, Aldasoro Caceres V, Castañeda S, Villa I, Humbría A, Moriano C, Romero-Yuste S, Narváez J, Gómez-Arango C, Perez

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4. POSTER: **Prieto- Peña D**, Calderón-Goercke M, Gonzalez-Mazon I, Martín-Varillas J, Sanchez-Bilbao L, Atienza-Mateo B, González-Gay M, Blanco R. Application of Different Sets of Classification/diagnostic *Criteria for Polymyalgia Rheumatica: Single Center Study of 100 Patients [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10).*

5. POSTER: Calderón-Goercke M, Loricera J, **PRIETO- PENA D**, Castañeda S, Aldasoro Caceres V, Villa I, Humbría A, Moriano C, Romero-Yuste S, Narváez J, Gómez-Arango C, Perez Pampín E, Melero R, Becerra-Fernández E, Revenga M, Álvarez-Rivas N, Galisteo C, Sivera F, Olivé-Marqués A, Álvarez del buergo M, Marena-Rojas L, Fernández-López C, Navarro F, Raya E, Galindez-Agirregoikoa E, Arca B, Solans-Laqué R, Conesa A, Hidalgo C, Vazquez C, Román-Ivorra J, Lluch P, Manrique S, Vela P, de Miguel E, Torres-Martín C, Nieto J, Ordas-Calvo C, salgado-Pérez E, Luna-Gómez C, Toyos-Sáenz De Miera F, Fernández-Llanio N, García A, Larena C, Varela-García M, Dos Santos R, Ortego N, Hernández J, González-Gay M, Blanco R. *Response to Tocilizumab in Patients with Giant Cell Arteritis, According to Ischemic vs Systemic Symptoms [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10).*

6. POSTER: Calderón-Goercke M, Loricera J, **PRIETO- PENA D**, Castañeda S, Aldasoro Caceres V, Villa I, Humbría A, Moriano C, Romero-Yuste S, Narváez J, Gómez-Arango C, Perez Pampín E, Melero R, Becerra-Fernández E, Revenga M, Álvarez-Rivas N, Galisteo C, Sivera F, Olivé-Marqués A, Álvarez del buergo M, Marena-Rojas L, Fernández-López C,

Navarro F, Raya E, Galindez-Agirregoikoa E, Arca B, Solans-Laqué R, Conesa A, Hidalgo C, Vazquez C, Román-Ivorra J, Lluch P, Manrique S, Vela P, de Miguel E, Torres-Martín C, Nieto J, Ordas-Calvo C, salgado-Pérez E, Luna-Gómez C, Toyos-Sáenz De Miera F, Fernández-Llanio N, García A, Larena C, Varela-García M, Aurrecoechea E, Ortiz-Sanjuán F, Hernández J, González-Gay M, Blanco R. *Tocilizumab in Giant Cell Arteritis: Route of Administration: Intravenous or Subcutaneous [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10).*

7. POSTER: Calderón-Goercke M, Loricera J, **PRIETO- PENA D**, Castañeda S, Aldasoro Caceres V, Villa I, Humbría A, Moriano C, Romero-Yuste S, Narváez J, Gómez-Arango C, Perez Pampín E, Melero R, Becerra-Fernández E, Revenga M, Álvarez-Rivas N, Galisteo C, Sivera F, Olivé-Marqués A, Álvarez del buergo M, Marena-Rojas L, Fernández-López C, Navarro F, Raya E, Galindez-Agirregoikoa E, Arca B, Solans-Laqué R, Conesa A, Hidalgo C, Vazquez C, Román-Ivorra J, Lluch P, Manrique S, Vela P, de Miguel E, Torres-Martín C, Nieto J, Ordas-Calvo C, salgado-Pérez E, Luna-Gómez C, Toyos-Sáenz De Miera F, Fernández-Llanio N, García A, Larena C, Varela-García M, Aurrecoechea E, Ortiz-Sanjuán F, Hernández J, González-Gay M, Blanco R. *Optimization of Tocilizumab Therapy in Giant Cell Arteritis: A Multicenter Real Life Study of 134 Patients [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10).*

8. POSTER: Calderón-Goercke M, Loricera J, **PRIETO- PENA D**, Castañeda S, Aldasoro Caceres V, Villa I, Humbría A, Moriano C, Romero-Yuste S, Narváez J, Gómez-Arango C, Perez Pampín E, Melero R, Becerra-Fernández E, Revenga M, Álvarez-Rivas N, Galisteo C, Sivera F, Olivé-Marqués A, Álvarez del buergo M, Marena-Rojas L, Fernández-López C, Navarro F, Raya E, Galindez-Agirregoikoa E, Arca B, Solans-Laqué R, Conesa A, Hidalgo C, Vazquez C, Román-Ivorra J, Lluch P, Manrique S, Vela P, de Miguel E, Torres-Martín C, Nieto J, Ordas-Calvo C, salgado-Pérez E, Luna-Gómez C, Toyos-Sáenz De Miera F, Fernández-Llanio N, García A, Aurrecoechea E, Ortego N, Ortiz-Sanjuán F, Corteguera M,

Hernández J, González-Gay M, Blanco R. *Tocilizumab in Giant Cell Arteritis: The Safest and Most Effective Initial Dose of Prednisone [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10).*

9. POSTER: Calderón-Goercke M, Loricera J, **PRIETO- PENA D**, Castañeda S, Aldasoro Caceres V, Villa I, Humbría A, Moriano C, Romero-Yuste S, Narváez J, Gómez-Arango C, Perez Pampín E, Melero R, Becerra-Fernández E, Revenga M, Álvarez-Rivas N, Galisteo C, Sivera F, Olivé-Marqués A, Álvarez del buergo M, Marena-Rojas L, Fernández-López C, Navarro F, Raya E, Galindez-Agirregoikoa E, Arca B, Solans-Laqué R, Conesa A, Hidalgo C, Vazquez C, Román-Ivorra J, Lluch P, Manrique S, Vela P, de Miguel E, Torres-Martín C, Nieto J, Ordas-Calvo C, salgado-Pérez E, Luna-Gómez C, Toyos-Sáenz De Miera F, Fernández-Llanio N, García A, Larena C, Aurrecoechea E, Ortiz-Sanjuán F, Corteguera M, Hernández J, González-Gay M, Blanco R. *Efficacy of Tocilizumab in Giant Cell Arteritis, Independent of the Time of Disease Evolution [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10).*

Annual European Congress of Rheumatology EULAR 2019 (Madrid 12-16 Junio 2019)

1. COMUNICACIÓN ORAL: Calderón-Goercke M, Loricera J, **Prieto-Peña D**, Aldasoro V, Castañeda S, Villa-Blanco I, Humbría A, Moriano C, Romero-Yuste S, Narváez J, Gomez-Arango C, Pérez-Pampín E, Melero R, Becerra-Fernández E, Revenga M, Alvarez-Rivas N, Galisteo C, Sivera F, Olive A, Alvarez de Buergo M, Marena Rojas L, Fernadez-Lopez C, Navarro F, Raya E, Galindez E, Arca B, Sonlans-Laqué R, Conesa A, Hidalgo C, Vázquez C, Román-Ivorra A, Lluch P, Manrique-Arija S, Vela-Casasampere P, de Miguel E, Torres-Martín C, Nieto JC, Ordas-Calvo C, Salgado-Pérez E, Luna-Gomez C, Francisco J, Saenz de Miera T, Fernandez-Llanio N, Garcia N, Larena C, Palmou-Fontana N, Calvo-Río V, González-Vela C, Corrales A, Varela-García M, Aurrecoechea E, Dos-Santos R, García-Manzanares A, Ortego N, Fernandez S, Ortiz-Sanjuán R, Corteguera M, Hernández JL,

González-Gay MA, Blanco R. Tocilizumab in giant cell arteritis. *Monotherapy versus combined with conventional immunosuppressive drugs. Ann Rheum Dis. 2019; 78 (Supp 2): A252.*

2. POSTER: **Prieto-Peña D**, Martínez-Rodríguez I, Calderón-Goercke M, Loricera J, Banzo J, González-Gay MA, Blanco R*. Effect of long-term medium-dose steroid treatment on 18F-FDG PET/CT finding to assess vascular and musculoskeletal involvement in patients with polymyalgia rheumatica. Ann Rheum Dis. 2019; 78 (Supp 2): A1020.*

3. POSTER: **Prieto-Peña D**, Calderón-Goercke M, González-Gay MA, Blanco R. *Comparison of the performance of classification/diagnostic criteria for polymyalgia rheumatica. Single center study of 100 patients. Ann Rheum Dis. 2019; 78 (Supp 2): A2012.*

4. POSTER: **Prieto-Pena D**, Calderón-Goercke M, Loricera J, Nárvaez J, Aurrecoechea E, Villa I, Castañeda S , Gómez-Arango C, Mera A, E. Pérez-Pampín E , V. Aldasoro V, N. Álvarez-Rivas N, Fernández-Llanio N, Álvarez-Buergo M, Marena-Rojas L, Sivera F , Galíndez-Agirregoikoa E , Solans-Laqué R , Romero-Yuste S, Martínez- Rodríguez I, Banzo I, Martín-Varillas I, Atienza-Mateo B, Sánchez Bilbao L, González-Mazón I, González-Gay M, Blanco R. *Comparative study of clinical, analytical and vascular 18F-FDG uptake evolution in patients with giant cell arteritis treated with methotrexate vs tocilizumab. Ann Rheum Dis. 2019; 78 (Supp 2): A435.*

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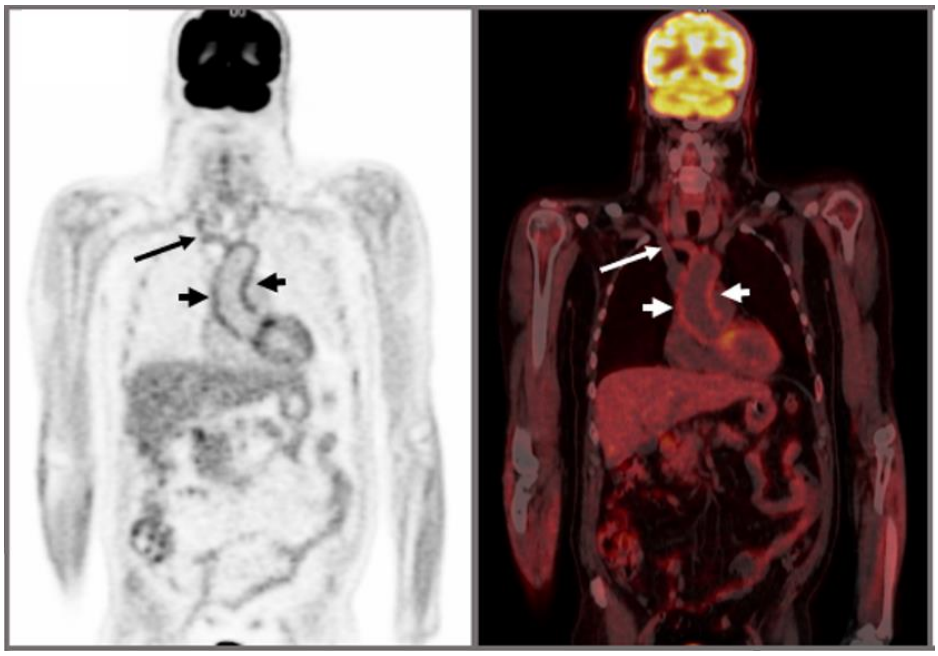
CONTRATO

Dña. Diana Prieto Peña obtuvo un **Contrato Río Hortega (CM20/00006)** del Instituto de Salud Carlos III durante los años 2021-2022. El objetivo del contrato es continuar trabajando en su línea de investigación que se basa en la identificación de biomarcadores genéticos de la Arteritis de Células Gigantes craneal y extracraneal. Y además, de forma simultánea, continuar realizando la actividad asistencial correspondiente a su especialidad, especializándose en la creación y puesta en marcha de una Unidad de diagnóstico rápido y tratamiento integral de las Vasculitis de Grandes Vasos en el Hospital Universitario Marqués de Valdecilla (Cantabria, España)



La arteritis de células gigantes (ACG) es la vasculitis más frecuente en pacientes mayores de 50 años en nuestro medio. Actualmente se describen dos patrones clínicos: el fenotipo craneal clásico y el fenotipo extracraneal. La ACG extracraneal, en comparación con la ACG craneal clásica, habitualmente debuta a edades más jóvenes y se caracteriza por un cuadro polimiálgico refractario que, a menudo, se asocia con síndrome general y síntomas atípicos como predominio de clínica a nivel de cintura pelviana, dolor lumbar inflamatorio y claudicación en miembros. Estas diferencias plantean si la susceptibilidad genética en pacientes con ACG extracraneal es diferente a la de los pacientes con ACG craneal clásica. El estudio realizado revela que la ACG craneal y la ACG extracraneal comparten una misma asociación de susceptibilidad genética con *HLA-DRB1*04:01* y *HLA-B*15:01*. Estos alelos tiene un efecto aditivo a la hora de aumentar el riesgo de ACG, independientemente del fenotipo clínico. Los haplotipos de *VEGF* (CGC y CGT) se asocian a mayor riesgo de manifestaciones isquémicas tanto en la ACG craneal como en la ACG extracraneal, pero no tienen influencia en el desarrollo de los dos diferentes fenotipos clínicos.

Giant cell arteritis (GCA) is the most common vasculitis among patients over 50 years of age in our setting. Two different clinical patterns of GCA have been described: the classic cranial phenotype and the extracranial phenotype. Compared with cranial GCA, patients with the extracranial GCA phenotype are often younger and more commonly present with refractory polymyalgic symptoms associated with constitutional syndrome and atypical manifestations such as predominant pelvic girdle involement, inflammatory low back pain and limb claudication. These differences suggest that a different genetic susceptibily may exist in cranial and extracranial GCA. We found that cranial and extracranial GCA share a similar *HLA-DRB1*04:01* and *HLA-B*15:01* association. These alleles additively increase the risk of GCA, regardless of the clinical phenotype. *VEGF* haplotypes (CGC and CGT) are related to an increased risk of severe ischemic complications in both cranial and extracranial GCA, but have no effect on the clinical phenotype expression of GCA.

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