Case Report

# Familial Giant Cell Arteritis and Polymyalgia Rheumatica: Aggregation in 2 Families

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***ABSTRACT.*** The ethnic and geographic prevalence, the familial aggregation, and the reported association with some HLA class II antigens of both giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) strongly suggest the role of genetic factors in the pathogenesis of these diseases. We describe the familial aggregation of GCA and PMR in 2 unrelated families from Northern Italy. In the first family, 2 sisters developed GCA a few months apart. In the second, one sister had GCA, and 2 years later her siblings developed PMR nearly simultaneously. Patients with GCA in the first family shared the whole HLA genotype (A*24.*26, B*38.*55, DRB1*11.*14, DQB1*05.*07, DRB3*). In the second family, both PMR siblings carried the A*68, B*44, DRB1*11, DQB1*07, DRB3* alleles. Thus all patients of both families shared DRB1*11, DQB1*07, and DRB3*. Predisposing immunogenetic factors of both GCA and PMR are discussed. (J Rheumatol 2002;29:1551–5)

*Key Indexing Terms:*
GIANT CELL ARTERITIS
POLYMYALGIA RHEUMATICA
FAMILIAL AGGREGATION
HLA TYPING

Giant cell (temporal) arteritis (GCA) is a relatively common vasculitis of unknown etiology, almost exclusively affecting white people over 50 years of age, predominantly women, with a higher incidence in the northern hemisphere[1]. Although it may be generalized, GCA primarily involves the medium size and large arteries, with predilection for the cranial and extracranial branches of the proximal aorta. The main clinical features, such as headache, visual disturbances, scalp tenderness, and jaw claudication, are related to the vasculitic involvement of the arterial wall. In addition, signs and symptoms of systemic inflammation are present in almost all patients, usually preceding the development of vascular lesions[2]. Use of corticosteroids leads to prompt clinical improvement and prevents the most severe complications of the disease, such as blindness[2]. Nearly 30–50% of patients with GCA develop polymyalgia rheumatica (PMR), a clinical syndrome promptly responsive to low doses of corticosteroids, characterized by aching and stiffness of the neck, shoulder, and/or pelvic girdle[2]. Epidemiological observations, such as a regular cyclic pattern in incidence over time of GCA[3] and the seasonal pattern in the onset of PMR[4], suggest a possible infectious origin of these diseases. In addition, the occurrence of PMR and GCA in first-degree relatives (Table 1) indicates a genetic predisposition to both illnesses.

We describe the familial aggregation of GCA and PMR in 2 different and unrelated families from Northern Italy, as well as the results of the molecular HLA typing. In the first family, 2 sisters not living together developed GCA a few months apart. In the second family, a sister suffered from GCA and her siblings developed PMR 2 years later and nearly simultaneously.

*HLA typing (A, B, DRB, and DQB loci).* Polymerase chain reaction (PCR) based HLA typing of genomic DNA, extracted and purified from whole blood using a commercial kit (Qiagen, Hilden, Germany), was performed using commercial reagents (HLA-B SSP Kit, Biotest, Denville, NJ, USA; Micro SSP HLA-DR and DQ Typing, One Lambda, Canoga Park, CA, USA), using PCR sequence-specific primer (SSP) methodology[5], in an automated PCR thermal cycler (GeneAmp PCR system 9700, Applied Biosystems, Foster City, CA, USA).

## CASE REPORTS

*First family. Case 1.* Patient 1, a 79-year-old woman, was seen in May 1998 with a 3 mo history of aching and stiffness in the neck, shoulder, and hip girdle, worsening in the morning. In the last 4 weeks, she experienced severe frontal new onset headache, scalp tenderness, and jaw claudication, without visual disturbances. She reported asthenia, low grade fever, anorexia, and weight loss of 5 kg in the last 2 mo (at the first visit, her body weight was 49 kg). Her history was unremarkable. On examination, the temporal arteries were thickened and tender, with decreased pulse. The

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erythrocyte sedimentation rate (ESR, Westergren) was 98 mm/h, C-reactive protein (CRP) 6.5 mg/dl (normal < 0.5), fibrinogen 625 mg/dl (< 400). Autoantibodies and tumoral markers were negative. Color duplex high frequency ultrasonography showed a hypoechoic halo surrounding the lumen of both temporal arteries. Biopsy of the right temporal artery showed histological features consistent with a diagnosis of GCA. Treatment with 40 mg daily of 6-α-methylprednisolone (6-α-MP) for 1 mo was instituted, with prompt relief of symptoms. The corticosteroid dose was gradually tapered and stopped in July 2000. At the last followup in October 2000, she was free from symptoms and laboratory tests were normal (ESR 6 mm/h, CRP 0.4 mg/dl, fibrinogen 324 mg/dl).

*Case 2*. Patient 2, the 75-year-old sister of Patient 1, who had longstanding hypertension treated with enalapril 10 mg daily, was seen in September 1998 with a 2 mo history of fatigue, aching in neck and shoulder girdle, and new onset headache in the right temporal region. Thickening and tenderness of the right temporal artery was detected. Laboratory tests revealed increased inflammatory values — ESR 75 mm/h, CRP 4.9 mg/dl, fibrinogen 568 mg/dl. Biopsy of the right temporal artery showed histological features of GCA. Therapy with 40 mg daily of 6-α-MP was started, with prompt remission of her symptoms. The corticosteroid dose was tapered over the following months and stopped in January 2000. At the last examination in May 2000, she was in good health and the laboratory measures were normal (ESR 15 mm/h, CRP 0.4 mg/dl, fibrinogen 294 mg/dl).

*Family history.* These 2 sisters have no other siblings and do not live together. Patient 1 is living with her husband, who has Alzheimer's disease, in a hill town of the Piacenza area. Her 2 daughters are in good health. Patient 2 is a widow and lives alone in Piacenza city.

*HLA typing*. HLA genotype was identical in both sisters (A*24.*26, B*38.*55, DRB1*11.*14, DQB1*05.*07, DRB3*).

*Second family*. *Case 3*. Patient 3, a 73-year-old woman, had longstanding hypertension treated with combination triamterene and hydrochlorothiazide; she presented in April 1997 with a 4 mo history of general malaise, anorexia, depression, and severe pain and stiffness in the neck, shoulder, and hip areas, worsening over the last 3 weeks. At this time, she experienced new onset headache in the temporal regions and scalp tenderness. Examination revealed thickened and tender temporal arteries, with decreased pulse. Laboratory tests showed increased inflammatory values — ESR 92 mm/h, CRP 5.9 mg/dl, fibrinogen 578 mg/dl. Autoantibodies and tumoral markers were negative. Histological examination of the right temporal artery biopsy confirmed GCA. Therapy with 6-α-MP 40 mg daily for 1 mo was started, and shortly resulted in relief of her symptoms. The dose was tapered and then stopped in March 1999. At the last visit in August 1999, she was free from symptoms and the laboratory measures were normal. She died in October 1999 because of gastric bleeding following orthopedic surgery (hip replacement).

*Case 4*. Patient 4, the 69-year-old sister of Patient 3, with unremarkable clinical history, was first seen in December 1999 because of a 2 mo history of fatigue and marked pain in the neck and shoulder girdle, worsening during the night, and associated with morning stiffness lasting several hours. She denied systemic and cranial symptoms. Examination and color duplex high frequency ultrasonography revealed no abnormalities of the temporal arteries. Laboratory tests showed increased values of ESR (48 mm/h), CRP (2.8 mg/dl), and fibrinogen (492 mg/dl). A diagnosis of PMR was made[20] and therapy with 8 mg daily of 6-α-MP for 4 weeks was started, with prompt relief of symptoms. The corticosteroid dose was then tapered and ended in October 2000. At the last examination, in December 2000, she was in good health and the laboratory measures were normal (ESR 14 mm/h, CRP 0.3 mg/dl, fibrinogen 312 mg/dl).

*Case 5*. Patient 5, the 67-year-old brother of Patients 3 and 4, had longstanding hypertension treated with enalapril 10 mg daily; he presented in January 2000 with a 6 week history of pain in the neck and shoulder girdle, associated with morning stiffness lasting 2 h. He denied systemic and cranial symptoms. No abnormalities of his temporal arteries were found on examination or ultrasonography. Laboratory tests revealed increased ESR (46 mm/h), CRP (2.6 mg/dl), and fibrinogen (468 mg/dl). A diagnosis of PMR was made[20] and he was successfully treated with 8 mg daily of 6-α-MP for 1 mo. Then the corticosteroid was tapered and stopped in December 2000. In February 2001 he was free from symptoms and the laboratory measures were normal (ESR 12 mm/h, CRP 0.4 mg/dl, fibrinogen 311 mg/dl).

*Family history.* Patient 3 was a widow with one healthy daughter and lived in the same town near Piacenza where her siblings lived. Patient 4 is married and lives with her husband, who has Parkinson's disease; her 2 sons are in good health. Patient 5 lives with his wife; his 2 sons are in good health.

*HLA typing*. HLA genotype was determined in the 2 living siblings, as follows: Patient 4: A*02.*68, B*44.*51, DRB1*01.*11, DQB1*05.*07, DRB3*; and Patient 5: A*01.*68, B*15.*44, DRB1*04.*11, DQB1*07.*08, DRB3*, DRB4*.

## DISCUSSION

GCA and PMR are relatively common diseases among Caucasian elderly people, particularly in the northern countries and in populations of Anglo-Saxon or Scandinavian origin, but are unusual in non-Caucasians[1,21]. The role of genetic factors in predisposing to these diseases is suggested by reports of familial aggregation and HLA typing studies.

The most common form of familial aggregation of GCA and PMR is between siblings. However, mother-daughter or father-daughter familial recurrence has also been reported (Table 1). We provide another example of familial clustering of these diseases among the members of 2 unrelated families: in the first, 2 sisters had GCA; in the second, one sister had GCA and her siblings had PMR.

The predisposing role of genetic factors is also suggested by the association of GCA and PMR with either the HLA-DR4 class II serological antigen or the DRB1 alleles, although discordant results have been found, likely owing to the different ethnic background of the populations studied. Indeed, some studies report the association of HLA-DR4 with PMR[22] and GCA[23,24]. In this latter disease, however, the association with HLA-DR4 is due to the concomitant PMR, since the prevalence of DR4 in patients with GCA alone does not differ from that of controls[23,24]. In contrast, in other studies of patients with PMR[25,26] and GCA[25] the frequency of DR4 is not significantly increased compared with healthy controls[25,26]. Similar discordant results have been reported by HLA molecular analysis, since PMR and GCA are reported as HLA-DRB1 associated diseases in some studies[27-31], but not others[26,32,33].

Besides the HLA genes, others may predispose to PMR and GCA. A recent study on the biallelic polymorphism (A or G) occurring within the promoter region of the RANTES gene (position-403) showed that the A allele may be a genetic risk for PMR, but not of GCA, in patients from Northwestern Spain[34]. Further, in the same population different tumor necrosis factor (TNF) gene polymorphisms (endowed in HLA region) were observed, providing further evidence of the immunogenetic heterogeneity of such

*Table 1*. Reported cases of familial GCA and PMR.

| Study | Relationship | Diagnosis | HLA Typing |
|---|---|---|---|
| Barber[5] | Sister | PMR | — |
| | Sister | PMR | — |
| Hamrin[6] | Sister | GCA | — |
| | Sister | GCA | — |
| Wadman[7] | Sister | GCA | — |
| | Brother | GCA | — |
| Liang[8] | Daughter | GCA | — |
| | Mother | GCA | — |
| | Sister | GCA | — |
| | Sister | GCA | — |
| | Mother | GCA | — |
| | Daughter | PMR | — |
| | Sister | PMR | — |
| | Sister | PMR | — |
| Kemp[9] | Sister* | GCA | A9.w26; B12.27; Cw3.w5 |
| | Sister* | GCA | idem |
| Kvernebo[10] | Sister | PMR | A1.3; B8.27; Cw4 |
| | Sister | PMR | A1.2; B8.27; Cw2 |
| | Sister | PMR | — |
| Granato[11] | Father | GCA | — |
| | Daughter | GCA | — |
| Ninet[12] | Brother | GCA | A28.x; B15.x; B15.x; DR4.x |
| | Sister | GCA | A28.2; B15.8; Cw3.x; DR4.3 |
| | Sister | GCA | A28.2; B15.12; Cw3.x; DR4.5 |
| Tanenbaum[13] | Sister | GCA | — |
| | Sister | GCA | — |
| Mathewson[14] | Brother | GCA | A1.2; B8.w62.26; Cw3.w7; DR3.4.w52.w53 |
| | Brother | GCA | A2.28; Bw44.w62.w4.w6; Cw3.w7; DR4.w53 |
| Wernick[15] | Sister | GCA | A1.24; B8.62; DR3.4 |
| | Brother | GCA | idem |
| Schwizer[16] | Sister | GCA | A3.28; B55.60; Cw3; DR4.13.52.53, DQ1.3 |
| | Sister | GCA | idem |
| | Sister | GCA | A2.24; B35.39; Cw4; DR1.4; DQ1.3 |
| | Brother | GCA | A2.Ax; B13.39; Cw6; DR7; DRx; DR53; DQ2 |
| Zauber[17] | Father | GCA | — |
| | Daughter | GCA | DR3; DR4 |
| Gros[18] | Sister | GCA | A1.26; B8.18; DR15.17 |
| | Sister | GCA | A1.29; B8.27; DR1 (DRB1*0103); DR17 |
| Bartolome[19] | Sister | GCA | DRB1*04 (DRB1*0401)/DRB1*12 |
| | Brother | GCA | DRB1*07/DRB1*12 |
| Our cases | Sister | GCA | A*24.*26; B*38.*55; DRB1*11.*14; DQB1* 05.07 |
| | Sister | GCA | idem |
| | Sister | GCA | — |
| | Sister | PMR | A*02.*68; B*44.*51; DRB1*01.*11; DQB1*05.*07 DRB3* |
| | Brother | PMR | A*01.*68; B*15.*44; DRB1*04.*11; DQB1*07.*08; DRB3*; DRB4* |

*Monozygotic twins.

diseases. Indeed, GCA was associated with TNF-A2 and PMR with TNF-B3 alleles, independent of any HLA-DRB1 association[35]. Finally, another genetic factor implicated in PMR/GCA susceptibility may be represented by the IL-1RN*2 polymorphism of the IL-1Ra gene[36], whereas the G/R 241 polymorphism of the intercellular adhesion molecule-1 gene may be a genetic risk factor in some[37] but not in other[38] populations.

HLA typing has been performed in some cases of familial GCA and PMR and molecular analysis in the most recent reports, including ours (Table 1). In our first family, the GCA sisters carried the same HLA genotype and, in particular, the DRB1*11.*14, DQB1*05.*07, and DRB3* alleles. In the second family, the PMR patients shared the DRB1*11, DQB1*07, and DRB3* alleles. It is noteworthy that the patients in both families shared DRB1*11,

DQB1*07, and DRB3*. Interestingly, HLA-DRB1*11 is one of the DRB1 alleles, as well as DRB1*0401 and DRB1*15/16, carrying the associated sequence polymorphism (DRYF 28-31), encoded by the second hypervariable region[27]. In North America, the DRYF 28-31 motif is strongly associated with GCA/PMR and, among the DRB1 alleles carrying this tetrapeptide, DRB1*0401 appears to be the strongest risk factor for GCA[27]. In the same geographical area, the frequency of DRB1*11 in GCA/PMR patients is low, while the frequency of DRB1*04 is significantly higher, compared to controls[28]. On the other hand, in GCA patients from Northern Italy the frequency of DRB1*11 is higher and DRB1*04 is lower, although both are not significantly different from controls[32]. In our local population sample of 183 healthy subjects, the frequency of DRB1*11 was 34.4%; thus the random probability of sampling 2 individuals identical for DRB1*11 is 11.8%. Since all our patients with GCA and PMR shared the DRB1*11 allele, it is unlikely that such genetic concordance occurred by chance. Further studies of familial GCA and PMR with similar ethnic backgrounds are needed for conclusive information; however, our cases show a strong inter- and intrafamily genetic concordance.

In the second family, in addition to the role of the genetic background, the intervention of environmental factors should be considered, owing to the nearly simultaneous onset of PMR in both siblings. By contrast, the influence of exogenous factors seems less likely in the sisters with GCA of the first family, in whom the disease began several months apart.

The interaction of multiple variables, such as age, genetic predisposition, and environmental influences, is likely involved in the pathogenesis of GCA and PMR. In this complex scenario, we describe the interesting occurrence of familial cases of GCA and PMR with a strong genetic concordance, confirming the role of genetic factors in the development of such diseases.

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