Seronegative Rheumatoid Arthritis in Elderly and Polymyalgia Rheumatica Have Similar Patterns of HLA Association

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ABSTRACT. ***Objective.*** To examine whether polymyalgia rheumatica (PMR) and late onset rheumatoid arthritis have identical or similar HLA-DRB1 genetic associations.

Methods. Seventy five PMR cases without evidence of giant cell arteritis were available for study. One hundred seven RA cases were investigated, of which 62 had disease onset after age 60 years. All cases were compared with 145 ethnically matched controls. All cases and controls originated from Lugo, NW Spain. HLA-DRB1 typing was performed on DNA samples using PCR based molecular methods.

Results. Early onset RA (≤ 40 yrs) was strongly associated with DRB1*04 (DRB1*0401 and *0404). In contrast late onset RA (≥ 60 yrs) was not associated with DRB1*04 but was associated with DRB1*01. Stratification of late onset RA cases by rheumatoid factor status revealed that DRB1*01 was only increased in seropositive RA cases. Late onset seronegative RA cases exhibited increased frequency of DRB1*13/*14; this was also observed in PMR cases where coexistence of GCA had been excluded.

Conclusion. These data indicate that (1) HLA associations with RA differ with respect to age at disease onset; and (2) seronegative late onset RA and "isolated" PMR have a similar HLA-DRB1 association and may have an identical etiological basis. (J Rheumatol 2001;28:122–5)

Key Indexing Terms:
POLYMYALGIA RHEUMATICA HLA RHEUMATOID ARTHRITIS GENETICS

Rheumatoid arthritis (RA) is classically considered to be a chronic disease with onset in middle age. However, disease onset is variable and RA may start in childhood or in patients in their 8th decade of life or even later. Cases with disease beginning above the age of 60 are defined as having a late or elderly onset[1]. A subset of patients with late onset RA may present with polymyalgic symptoms that are sometimes difficult to differentiate from polymyalgia rheumatica (PMR). Furthermore, some patients initially presenting with PMR may later develop features more clearly consistent with seronegative RA[2-4] and thus meet the 1987 American College of Rheumatology (ACR) criteria for RA[5]. In addition, peripheral synovitis may be present in up to 25% of patients with PMR[6]. In these cases synovitis is frequently asymmetrical and nonerosive. As in some patients with symmetrical seronegative late onset RA, synovitis and polymyalgia manifestations in PMR are very responsive to low dose steroid treatment[4,6,7]. Thus the relationship between late onset RA in the elderly and PMR remains unclear. One approach to this problem is to examine the genetic associations observed with both conditions. If they have an identical or a similar etiology, a shared genetic basis would be predicted.

A strong and reproducible association between RA and HLA-DR4 (DRB1*04) has been described[8]. Other DRB1 alleles (DRB1*0101, DRB1*1001, DRB1*1402) have also been associated with RA in southern European Caucasoid and non-Caucasoid RA populations[9]. A molecular basis for these associations has been suggested in that all DRB1 alleles associated with RA share a highly conserved sequence of amino acids in the third hypervariable region of their DRß1 chain. This has been referred to as the RA shared epitope (SE) hypothesis[10]. This has remained a working hypothesis explaining the heterogeneity of HLA-DRB1 associations with RA, although some problems remain[11].

Similarly, HLA associations have been reported for PMR and the closely allied condition of giant cell arteritis (GCA). A number of HLA associations have been reported for PMR in different populations; these include HLA-DRB1*04, *01, and *13/*14[12-14]. The range of associations may be explained by the underlying variation between population groups or by the clinical heterogeneity that exists within

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PMR. A significant proportion of PMR patients develop GCA, which is strongly and reproducibly associated with DRB1*04[14]. Recently we have examined PMR patients in whom GCA comorbidity was carefully excluded based on clinical and histological assessment. Underlying associations between "isolated PMR" and DRB1*13/*14 (DR6)[14] and tumor necrosis factor b3[15] were identified. These associations were not seen in patients who coexpressed both PMR and GCA symptoms. This suggested to us that "isolated PMR" and "PMR with GCA" may represent similar phenocopies but with different underlying etiologies.

Few studies have examined the relationship between HLA and age of onset in RA, although some differences have been reported[16,17]. We addressed this issue in a group of RA patients from NW Spain, in whom early and late onset cases have been identified. To understand the overlapping clinical manifestations observed in elderly patients with rheumatic disease we also examined the immunogenetic similarity between late onset RA and PMR patients without GCA.

MATERIALS AND METHODS

Patients and controls. Patients and controls originated from the area of Lugo, Northwestern Spain. Controls were ethnically matched to cases and judged to be healthy at time of venopuncture. Patients were either recruited from the outpatient rheumatology clinic by general practitioners or were self-referred to the emergency unit of the Hospital Xeral-Calde of Lugo. Seventy-five patients diagnosed with PMR were available for study. The main characteristics of this group are summarized in Table 1. All patients met the following criteria: (1) severe and bilateral pain associated with morning stiffness (≥ 30 min) for more than 1 month in at least 2 of the 3 areas: neck, shoulder, and/or pelvic girdles; (2) an erythrocyte sedimentation rate (ESR) at time of diagnosis ≥ 40 mm/h; (3) resolution of the syndrome in less than 7 days after treatment with 10–20 mg/day of prednisone; (4) exclusion of other diseases that may present with polymyalgic manifestations or that mimic PMR. Care was taken to exclude patients who had other diseases presenting with polymyalgic manifestations or mimicking PMR[18]. The majority of such patients were those with neoplasms or rheumatic conditions.

Patients with PMR associated with GCA were not included in this study. The possibility of GCA was excluded by either a negative temporal artery biopsy or by a resolution of the syndrome following low dose prednisone therapy, and absence of GCA manifestations after followup of at least 24 months. A temporal artery biopsy was performed on all patients with clinical manifestations of GCA. In these cases the biopsies were performed before corticosteriod treatment or within the first 3 days after start of corticosteroid therapy. The side with predominant local temporal, neck, or shoulder symptoms was selected for biopsy[4,19]. As the arterial involvement in GCA is segmental and may be missed, segments of artery longer than 2.5 cm were generally obtained for histological analysis. Also, in patients with cranial manifestations suggestive of GCA, contralateral temporal biopsies were considered if the first biopsy was normal[20]. Moreover, in patients with PMR without cranial or ischemic manifestations of GCA, a temporal artery biopsy was usually considered if there was a constitutional syndrome and/or ESR was > 80 mm/h[21]. Patients who at any time during the course of the disease fulfilled the 1987 ACR criteria for RA[5] were also excluded. It is generally considered that age ≥ 50 years is appropriate for diagnosis of PMR[7,22]. However, to establish a more precise comparison with elderly patients with RA we considered an age at onset of symptoms ≥ 60 years as another inclusion criterion. Finally, patients fulfilling the above criteria but with a positive rheumatoid factor (RF; by nephelometry) were also excluded.

One hundred seven patients with RA were also available for study and key clinical details are summarized in Table 1. Patients were diagnosed as having RA if they fulfilled at least 4 of the 7 1987 ACR criteria for RA[5]. These patients were selected on the basis of age at disease onset. Late onset RA was defined in patients whose arthritis began after age 60[1]. To best discriminate between late onset RA and the remaining patients with RA, we arbitrarily included a subgroup of patients with RA named early onset RA whose age at disease onset was between 16 and 40 years. The main clinical features of patients with PMR and RA are also shown in Table 1.

HLA typing. HLA-DRB1 typing of patients was performed as reported[14]. Briefly, EDTA anticoagulated blood samples were used. DNA was extracted by an automated phenol chloroform procedure. HLA-DRB1 phenotypes were determined using a semi-automated reverse dot-blot method (Innolipa, Innogenetics, Ghent, Belgium). Phenotypes were assigned by computer aided analyses of reaction patterns. Phenotype frequencies were compared between patient groups and controls using chi-squared analysis. The strength of association was assessed by the calculation of odds ratios with 95% confidence intervals (CI).

RESULTS

Stratification of RA patients by age of onset showed that HLA-DRB1 phenotype frequencies were different between those with early and late disease onset (Table 2). Compared with controls, a high frequency of DRB1*04 was observed in those patients with disease onset starting before the age of 40 years (77.8% vs 26.2% OR 9.9, 95% CI 4.5–21.4) and this was largely accounted for by an increase in DRB1*0401 (40% vs 10.3%, OR 6.0, 95% CI 2.7–13.2) and DRB1*0404 (13% vs 4.1%, OR 3.5, 95% CI 1.1–11.1). No increase was observed in the frequency of the SE bearing alleles DRB1*01 and *10 in patients with early onset RA.

In contrast, DRB1*04 and *0401 were only at a marginally increased frequency in RA patients with a late age at disease onset, although a significantly increased frequency of DRB1*01 was observed (30.6% vs 15.8%, OR 2.3, 95% CI 1.2–4.7).

To allow comparison with PMR patients, the late onset RA patients were further stratified by RF status (Table 3). Interestingly, the increase in DRB1*01 frequency in late onset RA patients was largely accounted for by RF positive patients. Although the increase in DRB1*04 was again not

Table 1. Clinical features of patients with RA and PMR.

	F:M Ratio	Age at Onset (yrs), mean ± SD	Rheumatoid Factor Positive	Erosions*
RA onset ≤ 40 yrs (n = 45)	35:10	30.9 ± 6.5	33/45	39/45
RA onset ≥ 60 yrs (n = 62)	43:19	69.2 ± 6.0	39/62	24/62**
PMR (n = 75)	42:33	71.6 ± 6.1	0	0

*Observed on plain radiographs of hands and/or feet. **Erosive status was based on radiological assessment after a minimum of 2 years' disease duration.

Table 2. HLA-DRB1 phenotype frequencies (%) in patients with early and late age of onset RA.

HLA-DRB1*	Controls, n = 145	RA Onset < 40 yrs, n = 45	RA Onset ≥ 60 yrs, n = 62
01	15.8	17.8	30.6[1]
15/16	26.2	26.7	35.5
03	20.0	11.1	4.8
04	26.2	77.8[2]	37.1
0401	10.3	40.0[3]	19.4
0404	4.1	13.0[4]	9.7
0405	3.4	6.7	3.2
11/12	22.8	17.8	14.5
13/14	35.2	24.4	29.0
07	26.9	15.6	30.6
08	7.6	4.4	3.2
09	3.4	0.0	1.6
10	4.1	0.0	3.2

All comparisons versus controls.

	OR	95% CI	p
1	2.3	1.2–4.7	0.02
2	9.9	4.5–21.4	< 0.00011
3	6.0	2.7–13.2	< 0.0001
4	3.5	1.1–11.1	0.03

Table 3. HLA-DRB1 phenotype frequencies (%) in patients with PMR and patients with late onset RA stratified by RF status.

HLA-DRB1*	RA Onset ≥ 60 yrs RF+ n = 39	RA Onset ≥ 60 yrs RF– n = 23	PMR n = 75
01	38.5[1]	17.4	13.3
15/16	33.3	39.1	20.0
03	7.7	4.3	18.6
04	41.0[2]	30.4	32.0
0401	23.1[3]	13.0	16.0
0404	12.8[4]	4.3	9.3
0405	2.6	4.3	2.7
11/12	10.3	21.7	24.0
13/14	20.5	43.5	50.7[5]
07	33.3	26.1	14.7
08	0.0	8.7	4.0
09	2.6	0.0	1.3
10	5.1	0.0	1.3

All comparisons versus control frequencies.

	OR	95% CI	p
1	3.3	1.5–7.2	0.002
2	2.0	0.9–4.1	0.07
3	2.7	1.1–6.6	0.03
4	3.4	1.0–11.2	0.04
5	1.9	1.0–3.5	0.03

significant in this group, this was not the case for DRB1*0401 and *0404, which were weakly associated. No increase in frequency of DRB1*01, *04, or SE bearing alleles was observed in the RF negative RA group. HLA-DRB1 *13/*14 (previously defined serologically as DR6) was observed at marginally increased frequency in these patients versus controls, although this did not achieve statistical significance. However, when seronegative RA was compared with late onset seropositive cases, a significant increase in DRB1*13/*14 frequency was observed (43.5% vs 20.5%, OR 2.9, 95% CI 1.0-9.1, p = 0.05). The only HLA-DRB1 allele significantly increased in isolated PMR patients compared with controls was DRB1*13/*14 (50.7% vs 35.2%, OR 1.9, 95% CI 1.0-3.5, p = 0.03).

DISCUSSION

While well defined clinical features and clearly established HLA-DR genetic associations have been observed in RA patients in most populations, controversy still exists regarding the relationship between late onset RA and PMR. We describe different HLA-DRB1 associations in RA patients according to age at disease onset and a further clear differentiation between RF positive and negative RA patients with a late onset. Seronegative late onset RA and "isolated PMR" patients do not appear to be associated with DRB1*04 or 01. However, a weak association is observed between DRB1*13/*14 and isolated PMR and a similar association, although not significant versus controls, is also suggested for late onset seronegative RA.

The relationship between HLA-DR status and age at disease onset in RA has been examined in a small number of studies. A decreasing association of DR4 with increasing age at disease onset has been described in UK patients with RA, although this was observed in female and not in male patients[16]. More recently it was reported that SE homozygosity and the DRB1*0401/*0404 genotype was strongly associated with risk of early disease onset in UK patients with RA[23]. Similar associations may exist in other populations, although in a recent study of Japanese patients with RA, different trends in HLA-DRB1 frequencies were observed for late onset RA[17]. However, significant differences between early and late onset RA were only observed in the frequency of DRB1*1502, which was more frequent in early onset RA cases.

In our study stratification of patients with late onset RA by RF status revealed further heterogeneity. RA patients with a late onset but who are RF seropositive appear to display the "characteristic RA pattern" of DRB1 association, although DRB1*01 is the strongest risk factor. In contrast, patients with late onset RA who are seronegative differ significantly and may exhibit DRB1 associations similar to PMR patients in whom coexistent GCA has been excluded. This suggests that these 2 groups of patients may have an identical or similar immune based etiopathogenesis. Such findings lend support to Healey's proposal[1] of a discrete condition within RA identified in the elderly that is seronegative, has a polymyalgic-like onset, is largely nonerosive and responsive to low dose steroids, and has a good prognosis.

If “isolated” PMR and seronegative elderly onset “RA” are the same condition, this should be taken into account in classification criteria and their application in epidemiological and clinical trials where appropriate nosological definition is required. Further, it is of importance to both patients and physicians to fully appreciate the explanation why “late onset seronegative RA” has a good prognosis and why early treatment with disease modifying antirheumatic drugs may not be necessary.

It is important to confirm our observation and determine whether it holds true in other population groups.

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