Tissue Antigens (1984) **23**, 107–111

Seronegative spondyloarthropathies and HLA antigens in a Mestizo population

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HLA-A and -B antigens incidence were investigated in 100 cases of Seronegative Spondyloarthropathies and in 303 control individuals of a Venezuelan Mestizo population. Significative increased incidence of B27 was found among 69% of patients with ankylosing spondylitis and 68% with Reiter syndrome being the incidence in the control group of 2.9%. The B27 negative patients showed 40.4% positivity for Bw35, with spondylitic lesion in 12 out of 17 cases. Our results question the applicability of B27 as diagnostic criteria in the Mestizo patients bearers of a Seronegative Spondyloarthropathy and suggest the need to investigate further the role of antigens of the B locus in the pathophysiology of these clinical entities.

Received for publication 15 November 1982, revised 7 April, accepted 27 May 1983

In Caucasians, the B27 antigen has been closely linked to susceptibility to Seronegative Spondyloarthropathies (SNSPA), particularly to Ankylosing Spondylitis (AS) and Reiter Syndrome (RS) (Bennet 1979, Brewerton 1976, Ford 1958). Furthermore, its usefulness as a diagnostic tool has been stressed by many authors. However, very little is known in relation to B27 and SNSPA in the Mestizo population which prevails as the most important ethnic group, not only in Venezuela but through many countries in Central and South America. We have investigated HLA-A and -B antigens incidence in 100 cases of SNSPA and assessed the B27 applicability as a diagnostic aid in these diseases among the Mestizo population.

Material and methods

Patients

One hundred untreated patients, diagnosed as having SNSPA, were studied and classified into the following categories: 36 Ankylosing Spondylitis (AS) according to the New York criteria (Bennet & Wood 1968); 16 Reiter's Syndrome (RS) following Ford's criteria (Ford 1958); 9 Psoriatic Arthropathy (PsA), including patients with symptoms indistinguishable from Rheumatoid Arthritis except for the absence of rheumatoid factor and the presence of sacro-iliitis (Bennet 1979); 8 Enteropathic Arthropathy (EA) including patients with Inflammatory Bowel Disease and joint involvement and finally 31 patients with

clinical overlap of the proceeding entities described as Seronegative Spondyloarthritis (SNSA) by Moll (Moll et al. 1974).

Controls

Three hundred and three healthy unrelated Venezuelan Mestizos were studied as the control group.

HLA typing and statistical analysis

HLA antigens were identified on peripheral blood lymphocytes separated from heparinized blood using Ficoll-Hypaque gradient, by microlymphocytotoxicity test following NIH technique (Terasaki & Park 1976). 31 antigens were studied for A and B loci: HLA-A1, 2, 3, 9, 10, 11, 28, w23, w24, w25, w26 and w19; HLA-B5, 7, 8, 12, 13, 14, 15, 17, 18, 27, 40, w16, w21, w22, w35. A minimum of two and in most cases three or more sera were used to define each specificity. Antigens and gene frequencies were compared with 303 controls. The statistical analysis was made by using Yates' corrected X^2 test. The corrected P values were obtained by multiplying the P values by the number of HLA antigenic specificities tested for (Svejgaard et al. 1974).

Results

The frequency distribution of the HLA-A and B loci specificities are shown in Table 1. Antigen frequency observed in SNSPA patients and controls were compared, and P values calculated and corrected as above. Only HLA-B27 was found increased in the SNSPA group (58%, $p < 0.015$). When the analysis was done by entities, HLA-B27 antigen frequency was increased in all groups except in EA (1/8). Table 2 shows these data, where the highest incidence of B27 corresponds to

Table 1.
HLA-A and B antigen frequency.

HLA	SNSPA[1] (n=100)	CONTROLS[1] (n=303)
A1	20	19
A2	47	41
A3	21	21
A9	23	28
A10	18	13.5
A11	16	6.2
A28	9	12
Aw19	20	35.3
B5	15	29
B7	13	23
B8	4	9
B12	11	25
B13	2	3
B14	5	10
B15	2	7
Bw16	5	3
B17	11	7
B18	4	0.7
Bw21	6	0.6
Bw22	0	0.3
B27*	58	2.9
Bw35	24	15
B40	11	17

[1] Antigen frequency expressed as percentage.
*: Corrected $p < 0.015$.

Table 2.
HLA-B27 antigen frequency in the clinical entities.

	n	B27+	F%	
SNSPA	100	58	58	*
AS	36	25	69.4	*
RS	16	11	68.7	*
PsA	9	5	55.5	
EA	8	1	12.5	
SNSA	31	16	51.6	*
Controls	303	9	2.9	

* Corrected $p < 0.015$.

Table 3.
B27 negative patients and controls: HLA-Bw35 and B5-CREG antigen distribution.

	n	Bw35+ (F%)	B5-CREG (F%)
SNSPA	42	27 (40.4)*	25 (59.5)
AS	10	5 (50)	5 (50)
SNSA	16	7 (43.7)	16 (64)
Controls	294	46 (15.6)	181 (61.6)

* Corrected $p < 0.015$.

AS (69.4%) and RS (68.7%). It is important to note that in the PsA group, where 5/9 of the patients were B27+, none had any evidence of spondylitic involvement.

The B27 negative patients (42/100) were further analyzed. It was surprising to find that 17 out of 42 were Bw35 positive, corresponding to 40.4% antigen frequency and a corrected p value less than 0.015 as compared to B27 negative controls. Among this group of patients, spondylitic lesions were found in 12/17, and diagnosis of AS and SNSA was made in 5 and 7 cases, respectively (Table 3). If other antigens, known to cross-react with Bw35 and thus members of B5-CREG (B5, B15, B18 and B21) are included in the analysis of the B27 negative patients, no difference was found between patient groups and controls (Table 3).

Discussion

Seronegative Spondyloarthropathies represent a complex spectrum of clinical syndromes, in which the etiology and pathogenetic mechanism remain largely unknown. However, two major contributions have been made in recent years: the work of Moll and Wright in 1974 (Moll et al. 1974) emphasizing the tendency toward clinical overlap and familiar aggregation, and the striking association of HLA-B27 antigen with rheumatic disease characterized by axial (spondylitis) types of arthritis (Brewerton et al. 1973, Brewerton 1976, Schlosstein et al. 1973). In Caucasian populations, B27 has been reported in 84–95% of patients with ankylosing spondylitis and Reiter's disease (Brewerton 1976, Nicholls 1977).

In our Venezuelan Mestizo patients, B27 was present in 58% of 100 SNSPA cases. Furthermore, the incidence among the AS patients was 69.4% and 68.7% within the Reiter group. The only other report among the Latin American Mestizo population, of which we are aware, is that of Fraga et al. (1979), limited however to 51 AS cases (68.6% B27 positive). It is important to note that the B27 antigen in the Venezuelan population is rather low (2.9%) and could account for the somehow lower incidence among the disease group, where the presence of the antigen is close to 70%, while in Caucasians it is over 90% in most series. This finding suggests that typing for B27 as a diagnostic tool for AS and RS, among a Mestizo population might leave out one third of the patients who, having positive findings of the disease, will be B27 negative. Therefore we may use this genetic marker as a diagnostic aid but in no case as excluding diagnostic criteria, as would be the case in Caucasian patients. When SNSPA is analyzed as a whole group,

the incidence of B27 is even lower (58%) mainly due to the EA group, where only 1 out of 8 patients has the antigen (12.5%). Comparing different series, there appears to be general agreement that the association between spondylitis and B27 is less when chronic inflammatory bowel disease is also present. Brewerton et al. (1974, Brewerton 1976) found B27 in 21 out of 28 patients with chronic inflammatory bowel disease and AS, and in 2 out of 6 patients without clinical evidence of spinal involvement.

The group of B27 negative AS patients is of particular interest. In Caucasians, the presence of B7, Bw22 or Bw42 when B27 is absent has been reported, thus suggesting antigens of the B7-CREG (cross-reacting group) (Schwartz et al. 1980). B7 and Bw22 were typed for in our series and not found increased. Nevertheless, it was surprising to find Bw35 present in 17 our of 42 B27 negative SNSPA patients, and spondylitic lesions in 70.6% of them (12/17).

We have no evidence of cross-reactivity between Bw35 and B27 in normal Mestizos, either in our series or in Latin American Workshops. Moreover, when other antigens of the B5-CREG were analyzed, no difference with controls was found. Therefore, it seems to be an individual phenomenon confined to Bw35 and not to a common determinant shared by the cross-reacting antigens (Schwartz et al. 1980).

Antigens from the B locus of the MHC, different from B27, have been reported increased in AS; Kahn et al. (1978a, b) found B16 to be augmented and Espinoza et al. (1982) reported both B16 splits (Bw38 and 39) to be increased among the same group.

Our results suggest that among a Mestizo population, in the absence of the B27 antigen, Bw35 might play a role as a genetic marker in both AS and SNSA.

Acknowledgments

We would like to thank Mr. Jorge Bianco and Ms. Marina Palacios for excellent technical assistance. Also Ms. Amanda González for the typing of the manuscript.

This work was supported by a grant from CONICIT (ICC-3).

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