

Letters to the Editor

Observations on class II antigens and genetic susceptibility to primary antiphospholipid (Hughes) syndrome in Arab patients

Sirs,

Initial reports on HLA tissue typing on PAPS patients revealed an association with HLA DR 53 associated antigens, the DR7 (mainly in individuals of Hispanic origin), DR4 (mainly white individuals) and DQ3 (1, 2). Furthermore, the highest relative risk for PAPS is conferred by the DR 53 allele. This allele may play a direct role in mediating immune response to phospholipids (3). Subsequent reports on other populations indicated other HLA associations in addition to the former antigens suggesting further genetic heterogeneity of the condition. In this regard, associations with HLA antigens DR 5, DR6, DR 9, DQ6 and DR13-DQ6 haplotype have been identified (4). Despite the extensive research and publications in this line worldwide, the corresponding data on Arabs however, has remained unavailable. In this report we present the profile of the class II alleles in the first cohort of Arab patients with PAPS.

Eight Arab female patients with PAPS conformed to the established criteria of Alarcon-Segovia *et al.* of 1992 (5) and to Wilson *et al.* criteria for definite PAPS (6). Five were Arabian Peninsula Arabs (APA) and the other 3 were Southern Mediterranean Arabs (SMA). Their age ranged between 16-48 years (average 28.11±9.3 years) at the time of diagnosis.

They presented essentially, with venous/arterial thrombosis, often recurrent and/or repeated fetal loss and intra uterine death (IUD), and thrombocytopenia. They did not manifest any typical clinical or serological features of SLE (7) at the time of presentation. The exclusion of SLE included specifically, the absence of anti-native ds-DNA and ENAs antibodies, and negative to weakly positive ANF. All patients tested positive for anticardiolipin (aCL) antibodies and 4 were concurrently, positive for lupus anticoagulant (LAC). HLA-DR & DQ alleles were identified by microlymphocytotoxicity test and /or low resolution PCR-sequencing specific primers (PCR-SSP). Results were compared to those of geographically matched adult control subjects tissue typed by Valluri *et al.* (8). Appropriate statistical analysis of data was carried out by Fisher's exact test.

Table I shows the profile of HLA-DR and DQ of these patients and controls.

Obviously, there is a clustering of DR 4, followed by DR7 and DQ3 in this cohort of patients. The data, furthermore, indicate that the genetic susceptibility is likely to be related to HLA-DR 4 antigen as is evi-

Table I. Analysis of cumulative data of the DR & DQ antigens in PAPS patients.

Antigen	Patients 8 (%)	Rank	All controls 604 (%)	RR	95% CI	<i>p</i>
DR 3	2 25%	3	155 25.6%	0.974	0.291-3.261	0.966
DR 4	5 62.5%	1	153 25.3%	2.467	1.418 – 4.294	0.047
DR 5	2 25%	3	209 34.6%	0.722	0.216-2.41	0.846
DR 6	1 12.5%	4	143 23.6%	0.527	0.083-3.322	0.748
DR 7	3 37.5%	2	130 21.5%	1.742	0.702-4.318	0.511
DQ 1	1 12.5%	3	300 63%	0.198	0.031-1.245	0.010
DQ 2	3 37.5%	2	216 35.5%	1.048	0.425-2.582	0.918
DQ 3	5 62.5%	1	349 57.7%	1.081	0.629-1.858	0.788

dent by its significant frequency and high relative risk among the patients. The HLA DQ1, on the other hand, was the least likely antigen to have an association with the condition. Of note, in our recent work on 11 Arabs with classic SLE, the DR 4 was totally absent compared to the controls (0% vs. 25.5%, RR=0%, 95% CI=infinity) and the DR 2 was the antigen with significant association (63.5% vs. 30% RR= 3.94, 95% CI 1.944-13.32, *p*=0.04). These findings are suggestive of two separate disease entities within this population.

The increased susceptibility to PAPS or to antibodies has also been linked to other antigens in other populations. The DR3 was also found to predispose to the formation of anticardiolipin antibodies (aCL) Abs in Danish and Czech women with APS whereas the B8-DR3 haplotype was associated with significantly high levels of aCL Abs in young Italian women. The DR 5 was linked to Mexican patients with PAPS (9). The DQ3 was strongly correlated with anti-β2 GPI antibodies in some Mexicans and American whites and blacks, whereas it was frequently reported with secondary antiphospholipid syndrome (APS) in Brazilians (4).

In summary, the results here are in keeping with some important reports in other populations implying a shared susceptibility of these antigens across the ethnic line of predisposition. Nonetheless, larger number of patients need to be screened to substantiate the above conclusions. However, this report remains the first of its kind in documenting the HLA association in Arab patients with PAPS and it adds to the current understanding of the ethnic variations of the syndrome.

H.M. AL ATTIA¹, FRCP(I), FRCP(Glasg), FRCP (Lon)
A. SANTOSH², PhD

M.M. AL FARHAN³, BSc, M. Phil, MBA

Departments of ¹Internal Medicine and Rheumatology and ²Medical Research Laboratory, Mafraq Hospital, Abu Dhabi, UAE; ³Clinical Research Organization (Middle East), Sharjah, UAE.

Address correspondence to:

Haider M. Al Attia, Consultant Physician & Rheumatologist, Mafraq Hospital, P.O. Box 2951, Abu Dhabi, United Arab Emirates.

E-mail: haideralattia@hotmail.com

Competing interests: none declared.

References

- SEBASTIANI GD, GALEAZZI M, MOROZI G, MARCOLONGO R: The immunogenetics of the antiphospholipid syndrome, anticardiolipin, and lupus anticoagulant. *Semin Arthritis Rheum* 1996; 25: 414-20.
- CAMPS MT, CUADRADO MJ, ALONSO A *et al.*: Association between HLA class II antigens and primary antiphospholipid syndrome from the south of Spain. *Lupus* 1995; 4: 51-5.
- WILSON WA, GHARAVI AE: Genetic factors for aPL syndrome. *Lupus* 1996; 5: 398-403.
- UTHMAN I, KHAMASHTA M: Ethnic and geographical variation in antiphospholipid (Hughes) syndrome. *Ann Rheum Dis* 2005; 64: 1671-6.
- ALARCON-SEGOVIA D, PEREZ-VAZQUEZ ME, VILLA AR, DRENKARD C, CABIEDES J: Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. *Semin Arthritis Rheum* 1992; 21: 275-286.
- WILSON WA, GHARAVI AE, KOIKE T, LOCKSHIN MD, WARE BRANCH D, PIETTE JC: International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. *Arthritis Rheum* 1999; 42: 1309-11.
- HOCHBERG MC: Updating the American College of Rheumatology revisited criteria for classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
- VALURI V, MUSTAFA M, SANTOSH A *et al.*: Frequencies of HLA-A, HLA-B, HLA -DR and HLA-DQ phenotypes in the United Arab Emirates population. *Tissue Antigens* 2005; 66: 107-13.
- VARGAS-ALARCON G, GRANADOS J, BEKKER C, ALCOSER-VARELA J, ALARCON-SEGOVIA D: Association of HLA-DR 5 (possibly DRB1* 1201) with the primary antiphospholipid syndrome in Mexican patients. *Arthritis Rheum* 1995; 38: 1340-1.