Ethnic and geographical variation in antiphospholipid (Hughes) syndrome

I Uthman, M Khamashta

Investigation of the clinical epidemiology of the antiphospholipid syndrome (APS) is in its early stages. During the past 20 years, studies of antiphospholipid antibodies (aPL) and APS have been made in many countries and ethno-geographical groups. aPL appear to occur in all populations studied, with some variations noted in their frequency and in the clinical complications. Environmental and genetic factors contribute to ethnic variation and susceptibility to APS and thus interethnic differences in disease patterns may be due to environmental or genetic factors, or both.

Antiphospholipid antibodies (aPL) are recognised as a group of antibodies whose specificity is directed not only towards phospholipids such as cardiolipin but also towards phospholipid binding proteins such as ((β2-glycoprotein I (β2-GPI) and prothrombin (PT)) or the complexes of phospholipids and phospholipid binding proteins.1 2 The presence of aPL is associated with arterial/venous thrombosis, recurrent fetal loss, neurological disorders, pulmonary hypertension, and thrombocytopenia. The term “antiphospholipid syndrome” (APS) or “Hughes syndrome” was coined to link these clinical manifestations with the persistence of aPL, which are now recognised as one of the most common causes of acquired thrombophilia.3 4

Investigation of the clinical epidemiology of APS is in its early stages. During the past 20 years, studies of aPL and APS have been made in many countries and ethno-geographical groups.5 17 aPL appear to occur in all populations studied, with some variations noted in their frequency and in the clinical complications.5 13 14 16 18 Environmental and genetic factors contribute to ethnic variation and susceptibility to APS and thus interethnic differences in disease patterns may be due to environmental or genetic factors, or both.5 18 In this review we examine the features of APS in various epidemiological studies.

Antiphospholipid Antibodies (aPL)

Routine screening for aPL now occurs in systemic lupus erythematosus (SLE) clinics because of the strong experimental and clinical evidence of the procoagulant nature of aPL and the demonstrations that anticoagulation provides effective secondary prophylaxis of thrombosis or pregnancy loss in patients with aPL.

Table 1 summarises the prevalence and isotype distribution of anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) in different populations of patients with primary APS and patients with SLE, mainly providing a point prevalence of these antibodies in various populations. It is evident from this that these antibodies occur in all populations of patients with SLE and primary APS studied, but with highly variable point prevalence.

A relative paucity of IgG (2%) and IgM (2%) aCL in Afro-Caribbean patients with SLE was noted and warrants further study.19 SLE in African-Americans and Afro-Caribbean patients with SLE is characterised by a generally worse outcome and a higher prevalence of autoantibodies than in other ethnic or geographical groups, and it would be of interest to determine if aPL are an exception to this pattern in SLE. In a largely Afro-American obstetric prenatal clinic population,20 the prevalence of IgG aCL was 1.25% which approximates the frequency of IgG aCL found in other unselected prenatal clinic populations.21 In general, most studies from various countries report a mixture of aCL isotypes in individual patients, with IgG aCL being the commonest and most closely associated with thromboses and fetal losses.

“IGG aCL are the commonest isotypes in most patients with SLE”

IgA aCL are rarely present alone, except in Afro-Caribbean patients with SLE. In African-American patients with SLE, IgA aCL are also common, but often coexist with other isotypes. The value of IgA aCL and their relationship with thrombotic events is still controversial.19 20 Some experimental work suggests that IgA aCL are prothrombotic as the IgG or IgM isotypes.20 Although some reports showed that testing for IgA aCL was of additional benefit in patients with APS, especially in certain ethnic groups,17 18 20 other authors could not support these data.24 25

Gharavi et al were the first to determine the distribution of immunoglobulin isotypes and phospholipid specificities of aCL in 40 patients with one or more of the following “aPL associated clinical complications”—namely, thrombosis, fetal loss, and thrombocytopenia.24 They found IgA aCL in 52% of their population.24

Abbreviations: aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; aPT, anti-prothrombin antibodies; β2-GPI, β2-glycoprotein I; LA, lupus anticoagulant; PT, prothrombin; SLE, systemic lupus erythematosus
Only one patient had IgA aCL as the sole aPL; thus it was concluded that this test is useful to identify occasional patients with APS. Molina et al studied 152 African-American, 136 Afro-Caribbean (Jamaican), and 163 Hispanic (Colombian) unselected patients with SLE. The major finding of their study was the higher prevalence of IgA aCL in the Afro-Caribbean population (21%), IgA aCL being the sole isotype, detected in 82% of these positive patients. This isotype was usually detected at low titres and did not co-occur with IgG or IgM isotype in four of them. In the same study they also found IgA anti-β2GPI in 4/8 patients, co-occurring with IgM isotype in three of them.

In a cross-sectional study to determine the prevalence of IgA aCL and anti-β2GPI and study their clinical significance in a cohort of 114 SLE patients with SLE, we found a low prevalence (13%) of IgA aCL in patients with SLE. It is not clear whether the African origin or ancestry of these populations correlates with the autoantibody profile. It would seem likely that methodological, and possibly, environmental factors underlie the variations that occur in the aCL isotypes among these populations. Whether IgA aCL might contribute to a more comprehensive identification of APS in some SLE populations is still controversial.

### Table 1: Prevalence and isotype distribution of aCL and LA in different populations of patients with primary APS and SLE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ethnicity or country</th>
<th>Any aCL isotype</th>
<th>IgG aCL (%)</th>
<th>IgM aCL (%)</th>
<th>IgA aCL (%)</th>
<th>LA (%)</th>
<th>Correlation with thrombosis and/or fetal loss</th>
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<tr>
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<td></td>
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<td></td>
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<td>44</td>
<td>9</td>
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<td>14</td>
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<td>43.6</td>
<td>12.2</td>
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<td>13</td>
<td>2.5</td>
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<td>44</td>
<td>1</td>
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<tr>
<td>Malaviya et al (1996)</td>
<td>Kuwait, Middle-Eastern and North-African Arabs (29)</td>
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<td>NA</td>
<td>NA</td>
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<td></td>
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<tr>
<td>Al Maini et al (2002)</td>
<td>Gulf Arabs and Arabs of Persian descent (83)</td>
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<td>17.3</td>
<td>14.2</td>
<td>NA</td>
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<td></td>
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* IgG and IgM aCL or LA, or both; †patients from seven European countries: 97.7% white, 2.3% other races; ‡in-house ELISA test done at Louisiana State University Health Sciences Center in New Orleans; ††IPLIBA Study Group: Lupus in African-American populations: NA=ture v nurture. From University of Alabama at Birmingham, University of Texas-Houston Health Sciences Center, and University of Texas Medical Branch at Galveston; §two studies from All India Institute of Medical Sciences, New Delhi; ¶population comprised 164 Chinese, 26 Malay, and 10 Indian. No differences were found in the prevalence of raised aCL between the three ethnic groups. NA, data not available.
group; its frequency was increased more in primary APS than in secondary APS, the association being even stronger in anti-
\( \beta_2 \)GPI positive primary APS.67 Accordingly, it is suggested that this (DQB1*0604/5/6/7/9-DQA1*0102-DRB1*1302) haplotype predisposes to anti-
\( \beta_2 \)GPI, which is one of the most specific markers of APS.68–70 HLA-DR and DQ molecules function by binding specific peptides with subsequent presentation by antigen presenting cells to regulatory or effector T cells.71–73 Our data may be viewed in this context and suggest that a molecule encoded by the DQB1*0604/5/6/7/9-DQA1*0102-DRB1*1302 haplotype may preferentially present peptides derived from \( \beta_2 \)GPI or associated molecules.74 Consequently, people bearing this haplotype may be prone to generate anti-
\( \beta_2 \)GPI after taking other genetic and environmental variables into account.75

In addition to these classic class II molecules, it has recently been shown that HLA-DM molecules have crucial roles in HLA class II restricted antigen presentation, by studies of cell lines lacking HLA-DM, which are defective in class II restricted antigen processing.76–78 The presence of polymorphisms in DM genes79–81 raised the possibility of their involvement in the development of HLA class II associated diseases, although the relation between these polymorphisms and the function of DM molecules has not yet been clarified. A study of SLE in a Japanese population did not find any significant association between the HLA-DM polymorphisms and the function of DM molecules has not yet been clarified. A study of SLE in a Japanese population did not find any significant association between the HLA-DM polymorphisms and the function of DM molecules has not yet been clarified. A study of SLE in a Japanese population did not find any significant association between the HLA-DM polymorphisms and the function of DM molecules has not yet been clarified. A study of SLE in a Japanese population did not find any significant association between the HLA-DM polymorphisms and the function of DM molecules has not yet been clarified.
“Different HLA polymorphisms associated with APS may lead to development of different aspects of the disease.”

We conclude that several HLA class II gene polymorphisms are associated with APS, probably along with other genetic factors, and may determine the development of different aspects of the disease.” These polymorphisms may be correlated with the immune response against thrombosis related autoantigens, such as phospholipid binding proteins and phospholipids. It is also possible that some undefined polymorphisms in linkage disequilibrium with the HLA region are responsible for the induction of anti-β2GPI antibodies.

### POLYMORPHISMS OF TARGET ANTIGENS AND COAGULATION FACTORS

Polymorphisms of target antigens and coagulation factors are reported (table 3) to be associated with aPL induction and the development of thrombosis.

The human β2GPI gene is located on chromosome 17 and so far four common single nucleotide polymorphisms in protein coding region have been identified. The polymorphisms Ser/Asn 88, Val/Leu 247, Cys/Gly 306, and Trp/Ser 316 are located in exons 3, 7, 7, and 8 of the β2GPI gene, respectively. The Val/Leu polymorphism at codon 247 has been extensively studied among these polymorphisms. Hirose et al reported that Val 247 alleles were found more frequently in Asian patients with APS than among controls matched for ethnicity, and Val 247 was significantly associated with the presence of anti-β2GPI. They found no significant differences in allele frequencies in comparisons of the white or the black patients with APS with appropriate controls, although Val 247 alleles were more common in these ethnic groups than in Asians. Atsumi et al analysed the Val/Leu 247 polymorphism in a cohort of 88 British patients with APS and found that Val 247 correlated with anti-β2GPI production in patients with primary APS, and Val 247 might be important in the formation of β2GPI antigenicity. Prieto et al suggested that the Val/Val genotype at codon 247 played a part in the generation of anti-β2GPI and in the expression of arterial thrombosis in primary APS in Mexican patients. More recently, Yasuda et al in a study of 65 Japanese patients with APS and/or SLE compared with 61 controls found that the Val 247 β2GPI allele, compared with the Leu 247 β2GPI allele, was associated with both a high frequency of anti-β2GPI antibodies and stronger reactivity with anti-β2GPI antibodies. This suggests that the Val(247) β2GPI allele may be one of the genetic risk factors for development of APS. On the other hand, Camilleri et al found no association Val/Leu 247 polymorphism and the presence of anti-β2GPI in a white population.

### LIMITATIONS OF GENETIC STUDIES IN APS

Interpretation of epidemiological studies in various ethnic groups is quite difficult for the following reasons:

- Although the enzyme linked immunosorbent assay (ELISA) for aCL antibodies and LA testing has been extensively standardised, significant variation between laboratories in the results of testing still remains. The precise cut off points for positive/negative results vary among laboratories.
- Clinical heterogeneity: the clinical definition of APS has varied among studies. Some patients with APS also manifest SLE, and constitute a heterogeneous population, making it difficult to analyse the role of a single factor. With the publication of the Sapporo criteria for the preliminary classification criteria for definite APS this problem will be solved with studies done on more uniform patient groups.
- Interethic variation in the associations of aPL with thrombosis or pregnancy loss must also take into account the multiple risk factors that exist in most populations for these complications. Possibly, variation in such collateral risk factors—for example, drug use or genetic risk factors for thrombosis, may influence complication rates associated with aPL in various populations. For instance, in Lebanon, a high prevalence of prothrombin G20210A and factor V Leiden mutations exists. These factors will increase the thrombotic risk, especially in patients with aPL.
- Disease activity: The level of disease activity is an important factor to control for in future studies. In early studies in the African-American clinic population in New
Orleans it was found that IgG aCL were present in 27% of patients with SLE during periods of disease activity, compared with only 5% of patients with SLE during periods of less active SLE.

- Geographical migration: with the current increasing geographical migration and intermingling across geographical and ethnic groups, it is important to consider these variables in the interpretation of future studies.

CONCLUSIONS
Genetic susceptibility related to aPL and APS has been extensively examined in past years. However, it has been difficult to determine genetic risk factors for aPL and APS because of the heterogeneity in the antigen specificity, and pathogenesis of the clinical manifestations of APS. It is clear from the above that the study of the clinical epidemiology of APS is still in its infancy. Most studies have reported data on only one ethnic and/or geographical group, and comparisons between these studies are confounded by methodological variations or patient selection. The publication in 1999 of international consensus criteria for APS should facilitate a better understanding of the genetic predisposition which produces aPL and leads to the development of the clinical features of APS.

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