PREVALENCE AND CLINICAL SIGNIFICANCE OF ANTIBODIES TO RIBONUCLEOPROTEINS IN SYSTEMIC LUPUS ERYTHEMATOSUS IN MALAYSIA

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SUMMARY

One hundred and seventy patients with systemic lupus erythematosus (SLE) were studied for the prevalence of antibodies to the small RNA-associated proteins Ro/SSA, La/SSB, Sm, U1RNP and Sm. The relationship of these autoantibodies to different races, sexes and clinical manifestations of SLE was evaluated. Passive immunodiffusion was employed using human spleen extract as antigen source for Ro and rabbit thymus extract for La, Sm and U1RNP. We found the prevalence of antibodies to be as follows: anti-Ro/SSA, 36%; anti-La/SSB, 8%; anti-Sm, 15%; anti-U1RNP, 21%. Except for a low prevalence of anti-La, the prevalence of these antibodies was similar to that in Western studies. The prevalence of anti-Ro/SSA is similar to that reported in the Western studies, but lower than that reported in other Oriental patients from Singapore and Hong Kong. Linkages of anti-Ro with anti-La antibodies were usual; however, although anti-Sm antibodies were usually associated with anti-U1RNP, they were more frequently associated with anti-Ro antibodies. The Malay patients had a high prevalence of anti-U1RNP compared to other races. No gender difference was detected. Anti-Sm antibody was associated with serositis and anti-U1RNP antibodies with Raynaud’s phenomenon. No association was found between the presence of skin, renal or cerebral manifestations and any specific antibodies or combination of antibodies.

KEY WORDS: Systemic lupus erythematosus, Racial comparison, Ro/SSA, La/SSB, Sm, U1RNP.

SYSTEMIC lupus erythematosus (SLE) is a multisystem disease with multiple autoantibody response, and the occurrence of autoantibodies directed against various nuclear and cytoplasmic components is common. Antibodies to small RNA-associated proteins are highly characteristic of connective tissue disease. There is a spectrum of antibodies to ribonucleoproteins that have been identified in patients with various rheumatic diseases. In SLE, the four ribonucleoproteins found in considerable frequency are those to Ro/SSA, La/SSB, Sm and U1RNP [1–3]. Various demographic factors have been shown to influence the prevalence of these antibodies and disease expression in SLE [4–6].

The objectives of this study were to determine the prevalence of antibodies to these ribonucleoproteins in a large and carefully evaluated group of SLE patients attending the SLE clinic at University Hospital, Kuala Lumpur, and to identify the demographic factors that may influence the prevalence of these antibodies; clinical correlation of these antibodies was examined. The data were compared with those published from Western and other Oriental countries.

PATIENTS AND METHODS

One hundred and seventy patients (155 women and 15 male) with a diagnosis of SLE were studied. There were 136 (80%) Chinese, 23 (14%) Malays and 11 (6%) Indians. All patients met the 1982 revised ARA criteria for SLE [7]. All patients had a detailed clinical and laboratory assessment, and were seen at least once by one of the two authors (CLW, FW). Clinical data were obtained by careful review of case records.

Immunoassays for anti-ribonucleoprotein antibodies

Antibodies to Sm, U1RNP, Ro/SSA and La/SSB were detected by passive immunodiffusion (Ouchterlony technique) using seven wells of 4 mm diameter and a centre well of 8 mm diameter, in 1% agarose gel. The volume of serum used was 12 μl. Human spleen extract was used as antigen source for Ro/SSA and buffered saline-soluble extract of rabbit thymus powder was used as a source of Sm, U1RNP and La/SSB. Serum samples were tested undiluted next to standard prototypes.

Statistical analysis

Conventional χ² test statistics were used to evaluate the relationship of antibodies to various clinical and demographic features. Fisher’s exact test was used when the expected frequency was smaller than five. Analysis of variance (ANOVA) was used where appropriate. Statistical significance was taken when P < 0.05.

RESULTS

The mean age of patients was 31.7 yr (range 12–64 yr). The mean duration of follow-up was 6.7 yr (range 0.5–20 yr). There was no statistically significant difference in the mean age or duration of disease among the different racial or gender groups. Seventy-seven (45%) patients tested positive for antibodies to the defined antigens. The frequency of antibodies in the study population is shown in Table I. Linkages of
autoantibodies were apparent. Anti-La/SSB antibodies were almost invariably associated with anti-Ro/SSA. Twelve out of 13 patients who had anti-La/SSB antibodies also had anti-Ro/SSA. Anti-Sm antibodies were often associated with either anti-Ro or anti-U1RNP. Of the 25 patients who had anti-Sm antibodies, 11 (44%) also had anti-U1RNP and 19 (76%) had anti-Ro/SSA.

The Chinese tended to have a higher prevalence of anti-Ro/SSA antibodies compared to other races, but this was not statistically significant \( (P = 0.07) \). Anti-U1RNP was higher, occurring in 36% of Malays compared to other races \( (P = 0.03) \).

The frequency of autoantibodies against different antigens among the male and female patients was as follows: anti-Ro, 27% vs 37%; anti-La, 7% vs 8%; anti-Sm, 20% vs 14%; anti-U1RNP, 27% vs 20%. There were no statistically significant differences in the prevalence of autoantibodies among the sexes.

Anti-U1RNP was found to be highly associated with Raynaud’s phenomenon \( (P < 0.001) \). Fifty per cent of patients with Raynaud’s phenomenon had anti-U1RNP antibodies, whereas 17% of patients without Raynaud’s phenomenon had anti-U1RNP. Anti-Sm was associated with serositis, defined as the presence of pleuritis or pericarditis \( (P = 0.03) \). Thirty-six per cent of patients with serositis had anti-Sm, whereas 12% of patients without serositis had anti-Sm. No statistically significant association was found for the presence of skin, renal or cerebral disease and any particular antibody or combination of antibodies.

**DISCUSSION**

The presence of antibodies to small nuclear or cytoplasmic ribonucleoproteins is highly characteristic of connective tissue disorders [8]. These autoantibodies have also been found to identify certain subsets of patients within a disease entity [5, 9]. Various demographic factors have been shown to influence the prevalence of these autoantibodies and disease expression in SLE [6, 10].

We found that except for a low prevalence of anti-La antibodies, the prevalence of other antibodies was similar to that reported in Western patients. Linkages of certain autoantibodies have been described in several studies: anti-La antibodies were almost always accompanied by anti-Ro antibodies and anti-Sm antibodies by anti-U1RNP. Our data concurred with these findings. We found anti-La/SSB to be almost invariably accompanied by anti-Ro/SSA. However, anti-Sm antibodies were frequently associated with anti-Ro—occurring in 76% of patients with anti-Sm—than with anti-U1RNP, which were present in 44% of patients with anti-Sm antibodies.

The influence of a racial factor on the frequency of autoantibodies has been observed in several studies. Anti-Sm and anti-U1RNP antibodies are more common in peoples of African descent in comparison to those of European origin [10, 11]. We found a higher prevalence of anti-Ro among the Chinese patients compared to the non-Chinese, whereas the Malays had a higher prevalence of anti-RNP compared to the Chinese. Genetic factors have been associated with the production of autoantibodies. Among the White Caucasians, anti-Ro in the absence of anti-La have been associated with HLA-DR2 [6] as well as HLA-DQ1/DQ2 heterozygosity [12]. Anti-La antibodies, which were nearly always accompanied by anti-Ro antibodies, have been correlated with HLA-DR3 and heterozygosity at HLA-DQ1 and DQ2 loci; this association was weaker among the Black patients [15]. Wilson et al. [13] found an association of anti-Ro with HLA-DR7 in Black patients with SLE. The contribution of HLA phenotypes to the difference in antibody profiles observed in our patients requires further study.

It is of interest to note that the prevalence of anti-Ro/SSA is lower than that reported from other Oriental populations such as those from Singapore [14] and Hong Kong [15] using counterimmunoelectrophoresis, which reported prevalence of 60%. This difference from that in Singapore, a close neighbour of Malaysia with a similar ethnic composition, in the study population which consisted of a large proportion of Chinese is of particular interest as the Chinese populations from both countries are believed to derive from Southern Chinese extraction. The number of patients studied in the Singapore study was much smaller than in the current study. Otherwise, the reason for this difference is unclear at present and would merit further investigations. Technical reasons for this difference are unlikely as sera had been analysed for these antigens in two established laboratories in the UK: King’s College School of Medicine and Bath Institute of Rheumatic Diseases. Both yielded a similar prevalence rate for anti-Ro antibodies of 32–36%.

We found a low prevalence of anti-La/SSB antibodies compared to Western populations (18%)
[10, 16], but similar to other Oriental groups from Hong Kong (8.4%) and Singapore (12%).

Gender variation in disease expression and immunological features of SLE has been reported. The prevalence of anti-Ro has been found to be higher in female patients compared to male patients [17] and anti-La tended to be higher in White American males [18]. Our studies did not show a significant difference in the prevalence of autoantibodies between the sexes.

A number of studies have demonstrated associations of certain antibodies with a particular spectrum of clinical manifestations. Anti-Ro has been found to be especially prominent in SLE patients with cutaneous manifestations, including subacute cutaneous lupus syndrome and photosensitive skin rash in White as well as Black patients in the USA [19]. Wasieczk et al. [20] demonstrated that patients with SLE whose sera contained anti-Ro antibodies exhibited a high frequency of serious renal disease (53%), whereas those with anti-Ro and anti-La antibodies had a lower frequency of renal disease (9%). An association of anti-Ro antibodies with skin lesions or photosensitivity has not been shown among Oriental patients [14]. We found no relationship between anti-Ro antibodies and skin manifestations of SLE.

Several studies have suggested that patients with anti-Sm antibodies have milder renal and neurological disease [21]. We found anti-Sm to be associated with serositis, but could not demonstrate any correlation between anti-Sm antibodies and renal or neurological disease.

CONCLUSION

There are similarities in the prevalence of antibodies to small ribonucleoproteins among the SLE patients in different races and countries. We found a prevalence of anti-Ro antibodies similar to that of Western patients. This is in contrast to the high prevalence previously reported from other Oriental populations. The reason for this difference is unclear and would merit further investigations. We found the Malays had a higher prevalence of antibodies to U1RNP compared to other races. No gender difference in the prevalence of various antibodies was found. There was no specific antibody correlation with skin, renal or cerebral disease in SLE.

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