Precipitating antibodies to cellular antigens in Sjögren's syndrome, rheumatoid arthritis, and other organ and nonorgan-specific autoimmune diseases

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SUMMARY The prevalence of three precipitating antibodies, anti-SS-A, anti-SS-B, and rheumatoid arthritis precipitin (RAP), reacting with an extract of the human lymphoid cell line Wil₂, was studied in the sicca syndrome, Sjögren's syndrome with rheumatoid arthritis, rheumatoid arthritis, various seronegative spondyloarthritides, and organ and nonorgan-specific autoimmune diseases. Anti-SS-A and anti-SS-B occurred most frequently in the sera of patients with the sicca syndrome, whereas RAP occurred most frequently in seropositive rheumatoid arthritis sera. However, the data did not support previous studies where patients with sicca syndrome had a high incidence of anti-SS-A and/or -SS-B antibodies but had a low frequency of RAP, and patients with Sjögren's syndrome in association with rheumatoid arthritis had a high incidence of RAP but a low incidence of anti-SS-A and/or -SS-B. Instead the three antibodies were present in both forms of Sjögren's syndrome. This suggested a difference in the diseases in the UK compared to the USA, or that these antibodies do not have the more subtle diagnostic specificity that was originally suggested.

Sjögren's syndrome, like the other connective tissue diseases, is a multisystem disorder (Whaley *et al.*, 1973a) and is associated with a variety of immunological peculiarities including hypergammaglobulinaemia, a high incidence of serum autoantibodies (Whaley *et al.*, 1973b), impaired cell-mediated immunity (Levanthal *et al.*, 1967; Whaley *et al.*, 1971), and an unusual predisposition to develop malignant lymphoproliferation (Anderson and Talal, 1973; Whaley *et al.*, 1973b). Recently three new precipitating antigen-antibody systems in Sjögren's syndrome have been described, the antigens being contained in an extract of the Wil₂ human lymphoblastoid cell line (Alspaugh and Tan, 1975). Two antibodies, anti-SS-A and anti-SS-B, were found to occur almost exclusively in the sera of patients with the sicca complex of Sjögren's syndrome, while the third, the rheumatoid arthritis precipitin (RAP), was found almost exclusively in the sera of patients having rheumatoid arthritis with Sjögren's syndrome or seropositive rheumatoid arthritis alone (Alspaugh *et al.*, 1976). Since the prevalence of other auto-

antibodies in Sjögren's syndrome differs between patients from the UK and the USA, our Glasgow patients were examined for the prevalence of these precipitins. In addition, the sera of patients with various well-documented seronegative spondyloarthritides or organ-specific autoimmune diseases were also examined for these precipitating antibodies since most of these diseases had not been studied previously.

Materials and methods

Sjögren's syndrome was diagnosed by previously described criteria (Whaley *et al.*, 1973a). 23 patients had only the sicca syndrome, 39 had Sjögren's syndrome with rheumatoid arthritis, and 3 had the sicca syndrome associated with lymphoma: 1 reticulum cell sarcoma, 1 lymphosarcoma, and 1 Hodgkin's disease. Rheumatoid arthritis (Ropes *et al.*, 1958), Reiter's syndrome, ankylosing spondylitis, psoriatic arthritis, osteoarthritis, pernicious anaemia, Hashimoto's thyroiditis, thyrotoxicosis, simple goitre, and primary biliary cirrhosis were diagnosed using standard clinical, radiological, and laboratory criteria. 60 sera from geriatric patients

Accepted for publication August 10, 1977
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over 80 years of age were included in the study: none of these had rheumatoid arthritis, or other connective tissue diseases, although keratoconjunctivitis was a common finding (Whaley *et al.*, 1972). 71 sera from healthy US hospital personnel were included as controls. The number of patients in each group is shown in Tables 1-3.

The antigen used in the system was an extract of the Wil₂ human lymphoblastoid cell line, and precipitating antibodies to various antigens in this extract were detected by double diffusion in agarose as previously described (Alspaugh and Tan, 1975).

Results

SJÖGREN'S SYNDROME (TABLE 1)

Five of 23 (22%) sera from patients with the sicca syndrome were found to contain anti-SS-A, 9 of 23 (40%) contained anti-SS-B, and 7 of 23 (30%) RAP. None of the 7 with RAP had clinical or radiological evidence of rheumatoid arthritis. Of the sera from patients with Sjögren's syndrome with rheumatoid arthritis, 6 of 39 (15%) contained anti-SS-A, 3 of 39 (8%) contained anti-SS-B, and 15 of 39 (38%) contained RAP. 2 of 3 sera (67%) from patients with the sicca syndrome complicated by lymphoma contained both anti-SS-A and anti-SS-B; RAP was not detected. Anti-SS-A and anti-SS-B were not found in any of the normal control sera, but RAP was found in 6 of 71 (8%). In the geriatric group, 1 of 60 (2%) had anti-SS-A, and 5 of 60 (8%) had RAP, whereas none had anti-SS-B. The patient with anti-SS-A had keratoconjunctivitis sicca but not xerostomia.

INFLAMMATORY ARTHRITIDES (TABLE 2)

RAP was found in 19 of 29 (65%) sera from patients with seropositive, but only in 5 of 30 (17%) patients with seronegative rheumatoid arthritis. Anti-SS-A and anti-SS-B were not detected in any of the seronegative spondyloarthritic sera. RAP was found in only a low variable prevalence, ranging from 10% in the psoriatic arthritis or osteoarthritis patients

to 18% in Reiter's syndrome. Since there was an incidence of 8% in the normal population, 10% in psoriatic or osteoarthritis is not significant.

OTHER AUTOIMMUNE DISEASES (TABLE 3)

Simple goitre was the only one of the organ-specific autoimmune diseases with a significant prevalence of any of the antibodies, RAP being found in 7 of 20 (35%) sera. The sera of 2 of these patients contained rheumatoid factor in titres greater than 1/80, using the RA latex test. In primary biliary cirrhosis associated with keratoconjunctivitis sicca there was a low prevalence of anti-SS-A of 1 of 9 (11%), and RAP of 2 of 9 (22%), whereas no antibodies were detected in any sera from primary biliary cirrhosis without associated keratoconjunctivitis sicca.

Discussion

The prevalence of three precipitating autoantibodies found in the sera of patients with Sjögren's syndrome was investigated. As in previous studies (Alspaugh *et al.*, 1976), anti-SS-A and anti-SS-B were found most commonly in the sera of patients with the sicca syndrome, although the prevalence of these two antibodies in this disease was lower in the present study. This finding is not unexpected as previous studies have shown that patients with the

Table 2 Prevalence of precipitating antibodies in various arthritides

Disease	No. of sera tested	anti-SS-A	anti-SS-B	RAP
RA, seropositive	29	1 (3%)	0	19 (65%)
RA, seronegative	30	0	0	5 (17%)
Psoriatic arthritis	10	0	0	1 (10%)
Ankylosing spondylitis	24	0	0	4 (16%)
Reiter's syndrome	11	0	0	2 (18%)
Osteoarthritis	29	0	0	3 (10%)
Normal controls (USA)	71	0	0	6 (8%)

Table 3 Prevalence of precipitating antibodies in organ specific autoimmune diseases

Disease	No. of sera tested	anti-SS-A	anti-SS-B	RAP
Hashimoto's thyroiditis	17	0	0	2
Thyroiditis	20	0	0	1 (5%)
Simple goitre	20	0	0	7 (35%)
Pernicious anaemia	20	0	0	0
Primary biliary cirrhosis with keratoconjunctivitis sicca	9	1 (11%)	0	2 (22%)
Primary biliary cirrhosis without keratoconjunctivitis sicca	10	0	0	0
Normal controls (USA)	71	0	0	6 (8%)

Table 1 Prevalence of precipitating antibodies in Sjögren's syndrome

Disease	No. of sera tested	anti-SS-A	anti-SS-B	RAP
Sicca syndrome	23	5 (22%)	9 (40%)	7 (30%)
Sicca syndrome with lymphoma	3	2 (67%)	2 (67%)	0
Sjögren's syndrome with rheumatoid arthritis	39	6 (15%)	3 (8%)	15 (38%)
Normal controls (USA)	71	0	0	6 (8%)
Geriatric sera	60	1 (2%)	0	5 (8%)

RAP=rheumatoid arthritis precipitin.

sicca syndrome in the USA have a higher prevalence of most autoantibodies, with the exception of gastric parietal cell antibody, than sicca syndrome patients in the West of Scotland. This is thought to reflect milder disease in the Glasgow patients (Whaley *et al.*, 1973b). Apart from the sicca syndrome, anti-SS-A and anti-SS-B were found in patients with keratoconjunctivitis sicca (Sjögren's syndrome with rheumatoid arthritis, 1 geriatric patient with keratoconjunctivitis sicca; 1 patient with primary biliary cirrhosis and keratoconjunctivitis sicca), except in one instance, a patient with seropositive rheumatoid arthritis who had no clinical evidence of Sjögren's syndrome.

RAP was present in the sera of 65% of patients with seropositive rheumatoid arthritis, and was found in 10% to 18% of sera from patients with seronegative rheumatoid arthritis, osteoarthritis, or spondyloarthritis. Unexpectedly, RAP was detected in the sera of 30% of patients with the sicca syndrome, which is in marked contrast to previous results (Alspaugh *et al.*, 1976). None of the latter patients had evidence of arthritis. Of the remaining organ and nonorgan-specific autoimmune disease studies, there were two findings of interest. First, the prevalence of RAP in simple goitre was 35%. This observation at present is unexplained, although there is an increased prevalence of thyroid autoantibodies in this condition (Doniach *et al.*, 1960), which shows that simple goitre is associated with autoimmune phenomena. The sera of 2 of these patients contained rheumatoid factor which, of course, occurs in diseases other than rheumatoid arthritis. Secondly, 22% of patients with the combination of primary biliary cirrhosis and keratoconjunctivitis sicca had RAP in their sera, whereas RAP was absent in the sera from patients with primary biliary cirrhosis without evidence of Sjögren's syndrome. The low prevalence of these precipitins in the sera from geriatric patients is somewhat unexpected as most other autoantibodies increase with age (Whaley *et al.*, 1971).

In summary, the presence of anti-SS-A and/or -SS-B precipitins in serum supports a diagnosis of Sjögren's syndrome. RAP was generally confined to the inflammatory arthritides and occurred most frequently in seropositive rheumatoid arthritis. Previous studies have shown that the incidence of RAP was very low in other connective tissue diseases (Alspaugh *et al.*, 1976); and in this study, with the exception of simple goitre, the incidence in organ-specific diseases was less than in the normal population suggesting that RAP is most likely an antibody related to seropositive rheumatoid arthritis. However, in contrast to previous studies on Sjögren's syndrome (Alspaugh *et al.*, 1976) where

anti-SS-A and/or -SS-B were found primarily in sicca syndrome and RAP was found in rheumatoid arthritis or Sjögren's syndrome with associated rheumatoid arthritis, these three antibodies did not segregate patients into two types of Sjögren's syndrome. Instead all three antibodies were found in both types of Sjögren's syndrome. This difference may be due to variations in patient population and severity of the disease in the UK compared to the USA, or these antibodies may not have the more subtle diagnostic specificity originally suggested.

The pathogenetic significance of these antigen-antibody systems is currently unknown. The identification of the antigens is important, as the antigen preparation we used was obtained from a continuous cell line. If any of these antigens are restricted to certain cell lines, *in vitro*, then the demonstration of these antibodies in the sera of patients with Sjögren's syndrome or rheumatoid arthritis will have opened an important line of research into the aetiology of these diseases.

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