CONCISE REPORT

Development of additional autoimmune diseases in a population of patients with primary Sjögren's syndrome

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Background: To investigate whether patients with primary Sjögren's syndrome (pSS) have an increased tendency to develop other autoimmune diseases.

Methods: A retrospective case note review was carried out on 114 patients in whom a diagnosis of pSS had been made in a department of rheumatology from 1979 onwards. The year of diagnosis of pSS was recorded, plus the diagnosis and year of diagnosis of any other identified autoimmune disease.

Results: Of the 114 patients with pSS, seven (6%) were male and 107 (94%) female. Mean age at diagnosis of pSS was 53 years (range 21 to 83). Patients were followed up for an average of 10.5 years (range 0 to 23). Thirty eight patients (33.3%) were diagnosed as having another autoimmune disease, while nine (7.9%) had two or more. Thirteen additional autoimmune diseases were identified. Twenty five diagnoses (51.0%) were made before the diagnosis of pSS, three (6.1%) within the same year, and 21 (42.9%) after the diagnosis. Hypothyroidism was the most common autoimmune disease (n = 16).

Conclusions: Although pSS is a relatively benign condition, affected individuals have an increased tendency to develop additional autoimmune diseases. Patients with pSS should be monitored on a regular basis for such diseases.

Primary Sjögren's syndrome (pSS) is an autoimmune rheumatic disease characterised by symptoms of dryness in the eyes and mouth. These symptoms are caused by destruction of the salivary and lachrymal glands by infiltrating lymphocytes. Patients can also develop systemic symptoms such as fatigue and arthralgia. The disease is strongly associated with the presence of the autoantibodies anti-Ro and anti-La. Patients positive for the anti-Ro autoantibody have been shown to have a greater risk of developing systemic complications.[1]

Sjögren's syndrome is closely linked with systemic lupus erythematosus (SLE). In a recent analysis of the long term follow up of 215 patients with SLE (from 1977 to 1998) we reported that 30% of these patients had developed an additional autoimmune disease.[2] In the present study we sought to determine how often patients with pSS developed other autoimmune diseases and what these diseases were, and to compare these findings with our group of patients with SLE. Both groups of patients have been followed up at University College Hospital/The Middlesex Hospital with the same ethos of trying to maintain contact with as many of them as possible—that is, to minimise loss to follow up.

METHODS

A retrospective case note review was carried out on 114 patients who had been attending our department between 1979 and 2003. Patients were diagnosed with pSS using the European classification criteria of 1993.[3] Ninety six (84%) had lip biopsies that showed histology consistent with the disease. Any other diagnosis that the patient was given was carefully verified and recorded. Those patients who met the ACR criteria for systemic sclerosis and the Bohan and Peter criteria for myositis were noted.[4 5] Autoimmune thyroid disease, autoimmune thrombocytopenia, autoimmune neutropenia, coeliac disease, pernicious anaemia, interstitial lung disease, autoimmune renal tubular acidosis, and glomerulonephritis were diagnosed on clinical, laboratory, and histological criteria. Note was taken about whether the additional autoimmune diseases developed before the diagnosis of pSS was made, at the same time (within the same year), or afterwards.

The antinuclear antibodies (ANA) were assessed by immunofluorescence using a rat liver substrate. Rheumatoid factor (RF) was assessed by a slide latex test. The anti-Ro and anti-La responses were assessed by enzyme linked immunosorbent assay (ELISA) (Sheild Diagnostics, Dundee, UK). The immunoglobulin levels were measured by laser nephelometry.

RESULTS

Of the 114 patients diagnosed with pSS, seven (6%) were male and 107 (94%) were female. Eighty seven per cent were white, 4% were of Afro-Caribbean origin, 4% were of south Asian origin, 2% were of Chinese origin, and 3% were of unknown origin. The mean age at diagnosis of pSS was 53 years (range 21 to 83). Patients were followed up for an average of 10.5 years (range 1 to 23).

Table 1 Serology of cohort of patients with primary Sjögren's syndrome (percentages in brackets)

ANA >1:80	84/114 (73.7)
Rheumatoid factor	76/113 (67.3)
Ro (SS-A)	63/113 (55.8)
La (SS-B)	45/113 (39.8)
Hypergammaglobulinaemia	67/114 (58.8)
Increased IgG	56/114 (49.1)
Increased IgA	25/114 (21.9)
Increased IgM	12/114 (10.5)
Hypogammaglobulinaemia	4/114 (3.5)
Decreased IgG	4/114 (3.5)
Decreased IgA	1/114 (0.9)
Decreased IgM	1/114 (0.9)

ANA, antinuclear antibodies.

Abbreviations: ACR, American College of Rheumatology; ANA, antinuclear antibodies; pSS, primary Sjögren's syndrome; RF, rheumatoid factor

Table 2 Additional autoimmune diseases diagnosed in a cohort of patients with primary Sjögren's syndrome

	Before diagnosis of pSS (%)	At diagnosis of pSS (%)	After diagnosis of pSS (%)	Total (%)
Hypothyroidism	12 (10.5)	1 (0.9)	3 (2.6)	16 (14.0)
Graves disease/thyrotoxicosis	1 (0.9)	0 (0)	1 (0.9)	2 (1.8)
Scleroderma	0 (0)	1 (0.9)	4 (3.5)	5 (4.4)
Pulmonary fibrosis	0 (0)	0 (0)	3 (2.6)	3 (2.6)
Chronic active hepatitis	2 (1.8)	0 (0)	1 (0.9)	3 (2.6)
Primary biliary cirrhosis	0 (0)	0 (0)	2 (1.8)	2 (1.8)
Discoid lupus	4 (3.5)	0 (0)	1 (0.9)	5 (4.4)
Myositis	0 (0)	0 (0)	2 (1.8)	2 (1.8)
Renal tubular acidosis	2 (1.8)	1 (0.9)	0 (0)	3 (2.6)
Glomerulonephritis	1 (0.9)	0 (0)	2 (1.8)	3 (2.6)
Idiopathic thrombocytopenia	0 (0)	0 (0)	2 (1.8)	2 (1.8)
Coeliac disease	1 (0.9)	0 (0)	0 (0)	1 (0.9)
Pernicious anaemia	2 (1.8)	0 (0)	0 (0)	2 (1.8)
Total	25	3	21	49

pSS, primary Sjögren's syndrome.

Serologically these patients were characterised by a positive ANA and RF in over 60% of cases (table 1). Fifty six per cent were anti-Ro positive and 40% anti-La positive.

Among our 114 patients a range of 13 other autoimmune diseases were noted. Thirty eight (33%) were diagnosed as having one additional autoimmune disease, seven (6%) had two, and two (2%) had three. The mean age at diagnosis of the first additional autoimmune disease was 51 years.

Forty nine diagnoses were made in all (table 2). Twenty five (51%) of these diagnoses were made before the diagnosis of pSS, three (6%) within the same year, and 21 (43%) after the diagnosis of pSS. Hypothyroidism was the most common autoimmune disease, with 16 patients diagnosed (14%). Of these 16 patients, 12 (75%) had been diagnosed with hypothyroidism before the diagnosis of pSS. The mean age at diagnosis of hypothyroidism was 52 years.

DISCUSSION

Our cohort of patients with pSS all met the standard criteria of Vitali and colleagues.[3] Serologically, with respect to the ANA, RF, anti-Ro, and anti-La, our patients were similar to other published cohorts.[6]

Our study confirms that patients with pSS are also at risk of developing additional autoimmune diseases, with approximately one third of patients developing another autoimmune disorder either before or after being diagnosed with pSS.

The most common autoimmune disease developed by patients in our cohort was hypothyroidism. This is consistent with other prospective studies.[1] However, there were differences in the frequencies with which our patients developed other autoimmune diseases. In our study 16% of our patients developed autoimmune thyroid disease, compared with frequencies ranging between 10% and 30% in other studies.[7 8] Four per cent of our patients developed autoimmune liver disease compared with 13% in another study,[9] and 3% developed interstitial lung disease compared with 25% in a small prospective study.[10] However, the frequency with which our patients developed clinical renal disease was similar to a large prospective study[11] (5% *v* 4%). Discrepancies between this study and those of others are most likely to reflect differences in the methods used.

Patients appeared equally likely to develop the additional autoimmune disease before or after pSS was diagnosed, with 51% being diagnosed before developing pSS and 43% after. There may be differences within certain subgroups; for example, 72% of those patients with autoimmune thyroid disease were later diagnosed with pSS. The average ages at which patients developed the additional autoimmune disease were also similar to the age at which they were diagnosed with pSS, suggesting that there may be a common aetiology and pathogenesis.

A similar study looking at the incidence of additional autoimmune diseases in a group of patients with SLE over a similar period of time showed that a similar percentage (30% *v* 33% of patients with pSS) also developed another autoimmune disorder. However, there were differences in the types of disorder developed. In the group with SLE, the most common autoimmune disease was secondary Sjögren's syndrome (13%) followed by rheumatoid arthritis (6%). Only 4% developed hypothyroidism. No patients developed scleroderma or primary biliary cirrhosis.[2] There were no patients with pSS in our cohort who subsequently developed the criteria sufficient for a diagnosis of SLE, although several developed suggestive clinical manifestations, for example glomerulonephritis and discoid rashes. It is worth noting that there is an ongoing debate about the overlap of SLE and pSS which includes concerns about their current classification criteria.[12] There were also no patients with pSS and antiphospholipid syndrome, although two patients were found to be positive for anticardiolipin antibodies. No patients from our cohort with pSS developed rheumatoid arthritis, although one was noted to have erosive changes of articular surfaces on *x* ray imaging.

As well as the antibody mediated autoimmune diseases, the patients in this cohort were also found to have other immune mediated clinical manifestations, such as cutaneous vasculitides (9%), peripheral neuropathies (7%), vitiligo, and psoriasis. There were also two cases of coexistent sarcoid. These conditions have all been reported previously in patients with pSS, which illustrates the multiple immunological abnormalities involved in the pathogenesis of this condition, as characterised by Oxholm and Asmussen.[13]

Primary Sjögren's syndrome remains a relatively benign condition, but this study reinforces the need for extra vigilance and monitoring—as for all patients with an autoimmune disease—because those affected are at greater risk of developing additional autoimmune diseases. This clustering of autoimmune diseases also increases the likelihood of a common aetiological factor or factors. Such factors may be genetic, environmental, viral, or hormonal. Further work needs to be carried out to identify these factors in order that appropriate treatments can be developed.

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