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Primary Sjögren's syndrome from the viewpoint of an internal physician

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Abstract

The characteristics of primary Sjögren's syndrome are described on the basis of the follow-up of 65 patients with extraglandular symptoms at the onset and during the disease. The mean age of the patients at onset was 41.8 years and at the time of definite diagnosis was 45.8 years. Articular (32 cases), lacrimal (30 cases) and salivary (30 cases) manifestations were the most frequent initial symptoms. In only 22 of the 65 patients could Sjögren's syndrome be diagnosed at the onset. In most cases, the articular symptoms observed observed in 56 patients during the course corresponded to true polyarthritis, as verified by joint scintigraphy. Most frequently the wrists and ankles were affected. Chronic atrophic gastritis was found in 35 patients. In the young patients (13 cases), both the antrum and the corpus were affected more frequently than in the controls. In middle-aged patients (21 cases), atrophy of the antrum, and in the elderly (10 cases) atrophy of the corpus was more frequent than in the controls. All three types of chronic atrophic gastritis occurred in the disease. The decreased gastric acid secretion was characteristic of types A and AB gastritis, but the hypergastrinaemia only of type A. It was verified that chronic duodenitis and jejunitis occur in the disease. The pancreatic lesions were mild. Renal involvement was detected in 15 patients, vascular symptoms in 22 and lower-airway changes in 21. The variety of the different symptoms proved that primary Sjögren's syndrome can involve many organs.

Sjögren's syndrome (SS) is an autoimmune disease characterized by a lymphoplasmacytic infiltration of exocrine glands [1–3]. It belongs among those illnesses which often cause diagnostic problems. As the disease can begin with a variety of symptoms, subjects with SS may turn to different specialists with their first complaints, e.g. the ophthalmologist, the stomatologist, the rheumatologist, the internal physician, the gynaecologist, the dermatologist or the phthisiologist. The length of the delay prior to diagnosis very often depends on the knowledge these specialists have of the clinical picture of SS.

We present here our observations on the clinical characteristics of the disease in our primary SS patients.

Patients and methods

Sixty-five patients with extraglandular symptoms (63 women and 2 men) were followed up from 1979 to 1989. All of them met the criteria of primary SS [4]. The mean age of the patients on the appearance of the first symptoms was 41.8 years (range 18–71), and at the time of the definite diagnosis of

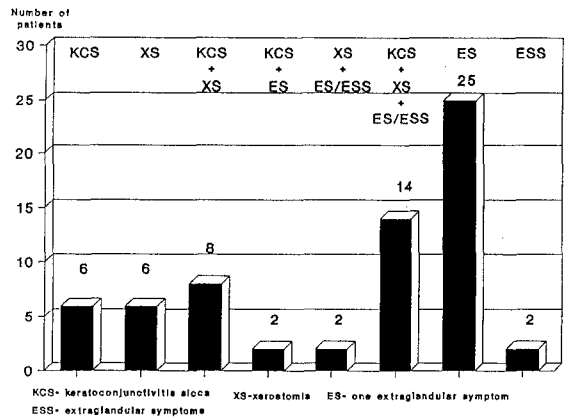

Fig. 1. First symptoms and combinations of symptoms in primary Sjögren's syndrome at the onset of the disease. (n = 65).

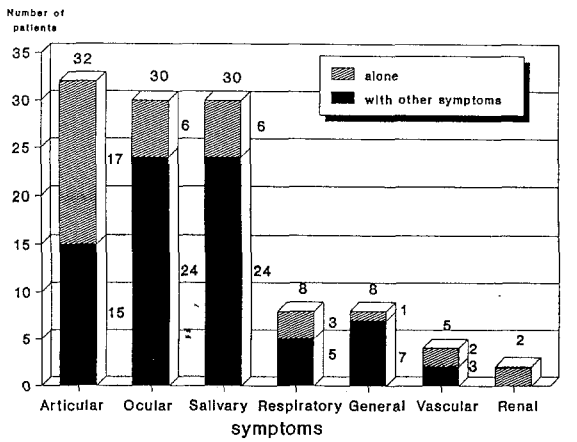

Fig. 2. Occurrence of the symptoms in primary Sjögren's syndrome at the onset of the disease. (n = 65).

SS it was 45.8 years (range 22–71). The mean time from the first symptoms of SS up to 1989 was 12.3 years (range 4–35).

Throughout the follow-up period, routine laboratory examinations, determination of serum immunoglobulins and different immunological parameters (rheumatoid factor, antinuclear antibody, anti-SSA, anti-SSB, and anti-native DNA antibodies, LE-cell phenomenon, complement C_3 concentration, circulating immune complexes and HLA typifying) were carried out on most of the patients.

When necessary because of the complaints of the patients, further examinations were performed (renal functional loading tests, gastric and intestinal functional investigations, histological evaluations of biopsy specimens, x-ray and isotope examinations of the joints, spirometry and radiography of the lungs and abdominal sonography).

Statistics

After one-way analysis of variance, the multiple range test (least significant difference procedure) was applied for statistical evaluation of the age of the patients, the duration of the disease, gastric acid secretion, concentrations of serum gastrin, immunoglobulins, complement C_3 levels, anti-native DNA and haematological parameters. The Exact Fischer test and McNemar test were used for statistical analysis of the incidence of antinuclear antibody, rheumatoid factor, LE-cell phenomenon, anti-SSA/SSB antibodies and the histological findings on the gastric and intestinal mucosa. The results of renal functional loading tests (verification of renal tubular acidosis by ammonium chloride loading and typifying of renal tubular acidosis by bicarbonate loading) were evaluated statistically with the two-tailed Student t-test. The disaccharidase activity in the mucosa of the small intestine was determined in the Mann-Whitney test. The chi-square test was applied for statistical evaluation of the serological parameters for the total patient material.

Results

On average, 4 years passed from the first symptoms of SS to the definite diagnosis of the disease. Figure 1 shows the symptoms and their combinations at the onset of the disease. In the 65 patients, SS could be diagnosed at the beginning of the disease in only 22, in 8 of the 22 on the basis of the two glandular symptoms and in 14 on the basis of the accompanying extraglandular manifestations too.

Articular involvement was the most common systemic symptom. It occurred in about half of the patients at the onset, similarly to the glandular symptoms (Fig. 2). Most symptoms were present in combinations.

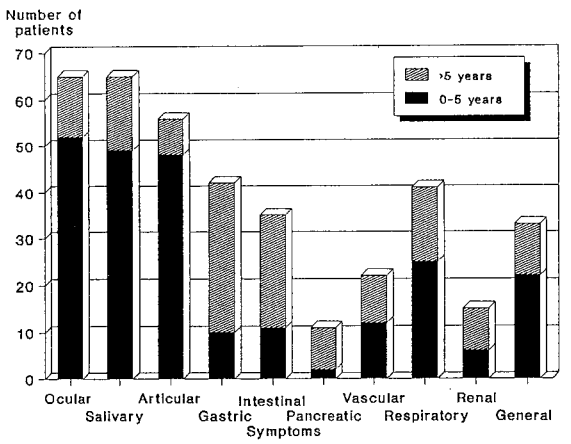

Fig. 3. Occurrence of the symptoms within the first five years and during the later course in primary Sjögren's syndrome (n = 65).

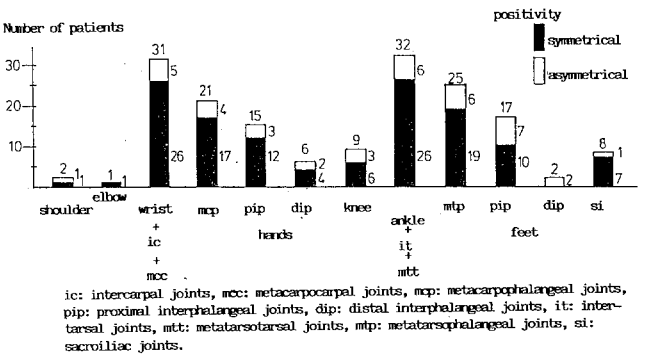

Fig. 4. Joint-scintigraphic distribution of symmetrical and asymmetrical articular changes in patients with primary Sjögren's syndrome. (n = 41).

During the later course of the disease, newer symptoms appeared in most cases. In 41 of the 65 patients, 3–5 extraglandular involvements were observed during the follow-up period, and in the other 24 there were 1, 2, 6, 7 or 8 systemic symptoms.

In most patients, the glandular, articular, respiratory and general symptoms, such as fatique, myalgia and tiredness, developed within the first five years of the illness (Fig. 3).

Swelling of the lacrimal glands occurred in 3 patients, in 2 of them at the onset. Salivary gland enlargement was seen in 20 patients (in 7 unilateral and in 13 bilateral); this symptom was present at the beginning of the disease in 8 cases.

Articular complaints were seen in 56 of the 65 patients. In 19 arthritis was evident clinically, while 37 had only arthralgia. In 41 patients (12 with evident arthritis and 29 with arthralgia), joint scintigraphy and x-ray examination were performed. Pathological isotope accumulations occurred most frequently in the wrist, ankle, metatarsophalangeal (MTP) and metacarpophalangeal (MCP) joints, most often symmetrically (Fig. 4). In all cases with clinically evident arthritis, the isotope examination confirmed the presence of the inflammation, and in 27 of the 29 patients with only arthralgia, true arthritis was proved by joint scintigraphy. Scintigraphy demonstrated monarthritis (1 joint) in 4 patients, oligoarthritis (2–5 joints) in 9 and polyarthritis (more than 5 joints) in 26.

In most cases, the x-ray changes in the joints corresponded to osteoarthrosis or osteopenia. Erosive bone destructions developed in only 2 patients, in the MCP or MTP joints. In a further patient, the changes in the hand joints were characteristic of erosive osteoarthrosis. Mild changes in the sacroiliac joints (contour roughness, articular space changes and reactive sclerosis) were seen in 8 patients, and in 3 with positive joint scintigraphy.

Respiratory manifestations were present in 41 patients. Upper airway symptoms occurred alone in 20, and accompanied by lower airway involvement in 20. Lower airway symptoms alone were seen in 1 patient.

The gastrointestinal manifestations were the next most common changes in our patients. Chronic atrophic gastritis (CAG) was diagnosed histologically in 35 of 44 patients, examined because of abdominal complaints in 38 cases (epigastric pain in 15 and dyspepsia with or without nausea in 23), and because of other causes in 6 cases, such as anaemia, weight loss or lack of appetite. CAG occurred in the antrum mucosa in 22 patients with primary SS, and in the corpus in 17. The transitional zone between the antrum and corpus was affected with a similar incidence as for the antrum. In the 104 control patients, CAG of the antrum and of the corpus was found in 30 and 25 cases, respectively. When the findings on the SS patients were compared with those on the controls, the difference was

statistically significant only in the antrum ($p = 0.024$). The incidence of CAG displayed special characteristics depending on the age of the SS patients. In the young SS patients (≤ 44 years, 13 cases), atrophic mucosal lesions were 2.5 times more common in the antrum, and 4 times more common in the corpus, than in the control group. In middle-aged SS patients (range 45–59 years, 21 cases), only the antral atrophy was significantly more frequent than in the controls ($p = 0.016$). In contrast, in the elderly (≥ 60 years, 10 cases), the corpus was affected nearly twice as frequently in the SS patients as in the control subjects. Types of CAG were also determined in the patients [5]. In the 35 SS patients with CAG, gastritis of type A (only the corpus is affected) was present in 9, gastritis of type B (only the antrum is affected) in 14 and gastritis of type AB (both the corpus and antrum are affected) in 8 patients. In a further 4 cases, atrophic lesions developed only in the transitional zone between the antrum and the corpus. The basal gastric acid secretion (basal acid output) was decreased in most of the SS patients, mainly in gastritis of type A. The stimulated gastric acid secretion (calculated maximum acid output) was especially low in gastritis of types A and AB. Elevated serum gastrin concentrations were measured mainly in gastritis of type A, where the levels were significantly higher than in the other histological groups ($p < 0.05$).

Besides the atrophic lesions of the gastric mucosa, involvement of the small intestine was established in primary SS [6]. In 34 of 46 patients examined, chronic duodenitis was verified histologically, as was chronic jejunitis in 7 of 22. The results of the lactose loading test were abnormal in more than half of the cases, showing the functional disturbance of the intestinal mucosa due to the diminished mucosal disaccharidase activity.

As a pancreatic functional test, the Lundh test was performed in 12 SS patients. In 6 of them, the lipase concentration was moderately diminished, while in 5 the trypsin, in 3 the volume, in 1 the amylase and in 1 the bicarbonate level was reduced.

Liver biopsy was carried out in 3 SS patients because of liver functional disturbances. In all of them, the histologic picture involved chronic nonspecific reactive hepatitis with lymphoplasmacytic infiltrations.

Renal involvement was verified in 15 cases. Percutaneous renal biopsy was performed in 3 patients with SS. The histology showed mesangioproliferative glomerulonephritis (MSGN) in 1 case, and chronic tubulointerstitial nephritis (CTN) in the other 2. Renal tubular acidosis (RTA) was the most frequent tubular change in SS; it occurred in 12 patients (11 complete and 1 incomplete). Proximal RTA was seen in only 1 patient, in 5 cases the characteristics of the proximal and distal types were mixed, and the other cases corresponded to distal RTA. Hyposthenuria was present in 6 patients, proteinuria in 3 and aminoaciduria in 2.

Vascular manifestations were seen in 22 of the 65 patients with primary SS. The Raynaud phenomenon was the most frequent vascular symptom; it occurred in 16 of the 22 cases. Skin vasculitis was observed in 6 patients, and in 1 of them the vasculitis probably also affected the cerebral vessels; this presented clinically in epileptiform convulsions. Hyperglobulinaemic purpura was found in 6 cases, and in all but 1 renal lesions were verified.

Dryness of the skin and vulva caused complaints in 13 of the 65 patients. General symptoms such as fatique, tiredness and myalgia were observed in 33 cases; in 14 of them, anaemia was in the background of these symptoms.

Drug allergy was present in 35 of the 65 patients, in 18 of the 35 only to one drug and in 17 to two or more drugs. Penicillin allergy was the most frequent, in 13 cases, with allergy to sulfonamides in 11 patients and to amidazophen in 9.

Malignant lymphoproliferative disorders did not develop in any patient during the follow-up period. 2 patients were operated on successfully for gynaecological tumour, 2 for skin basalioma and 2 for colonic malignancy.

Rheumatoid factor positivity was the most frequent immunological change, in 43 of the 65 SS patients. Hypergammaglobulinaemia was present in 34 cases. Antinuclear antibody positivity and an elevated serum IgG concentration were each found in 28 patients. The anti-SSA and/or anti-SSB anti-

body was detected in 31 of the 61 SS patients where these examinations were performed. Circulating immune complexes were determined in 57 patients. Their levels were elevated in 25 of them. HLA typifying was carried out in 36 cases. B 8 antigen positivity was found in 18 patients, DR 3 positivity in 20, DR 5 positivity in 11 and DR 2 positivity in 10.

Discussion

Primary SS is predominantly a disease of females. Of the 47 patients described by Pavlidis, 42 were women [7]. In our own 65 patients, there were only 2 men. In primary SS, the length of the delay before diagnosis can be very long. Pavlidis observed an average latent period of 8 years between the onset of symptoms and diagnosis of the disease [7]. For our patients, its duration was on average 4 years. A firm diagnosis of SS could be made at the onset in only one-third of the patients. Swelling of the lacrimal glands was very rare, and enlargement of the parotid glands was observed in only 30% of our patients with SS.

Articular manifestations were the most common systemic symptoms both at the onset of the disease and later. Joint scintigraphy confirmed that most of the cases with only arthralgia corresponded to true polyarthritis. The wrist and ankle were affected most frequently and the inflammation of the joints was very often symmetrical. This observation contradicts the opinion that the knees and elbows are most frequently involved in SS [8], and also contradicts the view that the incidences of affection of the small and large joints are similar in this disease [9]. Sacroileitis was also observed in our patients. This may be connected with repeated infections caused by the vaginal dryness. Fortunately, destructive bone changes were very rare in our patients.

Respiratory involvement was present in two-thirds of the patients, but the lower airways were affected in only half of these cases.

Among the gastrointestinal manifestations, CAG and chronic duodenitis were the most common changes. The incidence of CAG in SS patients has been reported to be extremely high: more than 80% of the cases. However, the relevant studies involved a small number of relatively old patients, and only the corpus mucosa was evaluated histologically [10, 11]. In our patients, CAG was found in the antrum and in the transitional zone between the antrum and the corpus in half of the primary SS patients, and in the corpus in two-fifths of the cases. The occurrence of CAG involving either the antrum or the corpus was more frequent in young SS patients than in the controls. In the middle-aged SS patients, antral CAG alone was significantly more frequent than in the controls; in the elderly, the corpus mucosa was more commonly affected in SS patients than in the controls. In such an autoimmune disease as SS, the AB type of CAG would have been expected to be the dominating form. However, all three types of CAG occurred separately in primary SS, and the duration of the disease was similar in all types. Hence, it is unlikely that the AB type develops from of type A or B in the course of the disease. Decreased gastric acid secretion was associated mainly with atrophic gastritis of types A and AB, and hypergastrinaemia with type A [12].

Chronic duodenitis occurred in three-quarters, and chronic jejunitis in one-third of our patients. The pancreatic functional changes were not severe, and liver involvement was very rare.

Like Siamopoulos, we have found primarily tubular renal changes in primary SS [13]. Clinically, the renal changes were not severe in most of our patients. However, in 2 cases the disease started with a nephrolithiac attack, and in one of them with severe muscular weakness due to hypopotassaemia [4]. In a different SS patient with severe renal and intestinal involvement, secondary hyperparathyroidism and acquired vitamin D deficiency developed, which caused multiple bone fractures [14]. Of the vascular symptoms, hyperglobulinaemic purpura showed a close correlation with the renal involvement [4]. As concerns the immunological changes, hyperproteinaemia, hypergamma-globulinaemia and an elevated serum IgA concentration were significantly more frequent in cases of renal involvement than without renal lesions ($p < 0.05$).

In patients with vasculitis, anti-SSA antibody positivity was more frequent than in those without vasculitis ($p < 0.05$), as were elevated circulating immune complex concentrations in cases with the Raynaud phenomenon.

Our experience on primary SS shows that the systemic symptoms can occur in variable combinations in the disease. This is connected with the fact that the autoimmune process can damage any of the organs with exocrine functions. Patients with primary SS need not only ophthalmological and stomatological care, but also a careful follow-up by an internal physician.

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