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Pancreatic Ductal Morphology and Function in Primary Sjögren's Syndrome

*Eva Lindström,**[,1] *Folke Lindström,*[2] *Henning von Schenck,*[3] *and Ingemar Ihse*[1]

Departments of [1]*Surgery,* [2]*Medicine, and* [3]*Clinical Chemistry, University Hospital, 581 85 Linköping, Sweden*

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Summary

In six patients with primary Sjögren's syndrome defined with HLA-antigens and no clinical signs of pancreatitis, the pancreatic ductal morphology (as described by endoscopic retrograde pancreatography), serum pancreatic enzymes, and fecal fat excretion were examined and secretin test was carried out. Further, oral glucose tolerance test with concomitant determination of serum insulin and C-peptide were done. All patients had at least two pathological signs of exocrine function and/or ductal morphology. There was no evidence of endocrine malfunction. The findings are suggestive of the existence of a clinically silent pancreatitis, perhaps of autoimmune etiology.

Key Words: Autoimmunity; pancreatic function; pancreatitis; pancreatography (ERP); primary Sjögren's syndrome.

INTRODUCTION

Dryness of the mucous membranes in the mouth (xerostomia, XS) and eyes (keratoconjunctivitis sicca, KCS) in association with rheumatoid arthritis (RA) was described by the Swedish ophthalmologist Henrik Sjögren in 1933 (*1*). Since then, the triad has been known as a clinical entity, usually referred to as Sjögren's syndrome (SS). It is caused by lymphocyte-mediated destruction of exocrine glands leading to diminished or absent glandular secretions and mucosal dryness. The lymphocyte infiltration is the result of an autoimmune process, and the disease is thus an autoimmune exocrinopathy (*2*).

During the last decade, several reports have indicated that XS and KCS may occur without RA; this has been named primary Sjögren's syndrome (PSS) (*3*). Recent developments in immunology and immunogenetics have

*Author to whom all correspondence and reprint requests should be addressed.

made it clear that PSS is an entity separate from SS serologically and genetically, as well as clinically (*4*). PSS is characterized by, apart from sicca symptoms, B-cell hyperreactivity resulting in hypergammaglobulinemia and autoantibody production, and is also associated with various immunologically mediated diseases like thyroiditis, vasculitis, and lymphoma (*4*). Dryness of the mucous membranes in SS and PSS may also involve the upper and lower respiratory tract leading to dry throat, hoarseness, improductive cough, and otitis (*4*). Involvement of the gastrointestinal tract leads to esophageal mucosal atrophy, dysphagia (*5*), and atrophic gastritis (*6*). It may also extend to the genital tract, causing dyspareunia and pruritus.

HLA antigens (HLA-A,B,C, and DR) are controlled by genes in the major histocompatibility complex (MHC) on the sixth chromosome. During the last two decades, it has become obvious that HLA antigens may be markers for certain diseases, which means, that they may play an important role in disease pathogenesis. PSS is one of the autoimmune diseases associated with the histocompatibility antigens HLA-DR3,B8, whereas RA and SS is associated with DR4, indicating genetic differences between primary Sjögren's syndrome and secondary Sjögren's syndrome.

Some authors have suggested that pancreatic involvement may be present in Sjögren's syndrome (*7–9*). However, these authors have not distinguished between PSS and SS, that might influence their conclusions. A study of serum pancreatic isoamylase in 53 patients with Sjögren's syndrome (both PSS and SS) showed normal levels in most cases, but abnormally high or low values were seen more frequently in patients than in controls (*10*).

The aim of our study was to investigate pancreatic exocrine and endocrine function, and ductal morphology in a well defined group of PSS patients without clinical suspicion of pancreatic disease.

MATERIALS AND METHODS

One male and five female patients with PSS, mean age 57 yr (range 45–70), were studied. Patient data are shown in Table 1. The mean duration of disease was 12 yr (range 8–16), and the sicca diagnosis was confirmed by lip salivary gland biopsy (*11,12*). Focus score (Table 1) denotes the degree of infiltration of lymphoid cells in the small salivary glands; a score of two is the upper limit of normal and a score of ten represents maximum lymphoid cell infiltration. In all patients, HLA-antigens were determined. The six patients were all DR3 positive, and four had also the B8 antigen (Table 1), that indicates the genetic homogeneity of the group and their belonging to the primary variant of Sjögren's syndrome. Other disease manifestations in our PSS patients were: lymphadenopathy (1/6), autoimmune thyroditis with hypothyrosis (1/6), renal tubular acidosis (3/6), all autoimmune disturbances known to occur in PSS. Abnormalities in routine laboratory measurements included high sedimentation rate (secondary to elevated levels of immunoglobulins), and various autoantibodies (rheumatoid factor, antinuclear antibodies-ANA, antibodies to thyroid antigens). Serum creatinine was normal in all.

Table 1
Patient Data

Patient	Age/sex	Duration of symptom (years)	Sicca symptom (+ -+++)	Focus score (normal ≤2)	HLA
1	51/F	13	+	7.6	DR3,B8
2	45/F	16	++	3.0	DR3,B8
3	67/F	12	+++	6.4	DR3,-
4	60/F	15	+++	7.0	DR3,B8
5	67/F	8	+++	9.4	DR3,-
6	70/M	9	(+)	4.0	DR3,B8

None of the patients had abdominal discomfort, or any suspicion of pancreatic disorder. There were no signs of concomitant primary bilary cirrhosis or other hepatobiliary diseases, and none of the patients were known to overconsume alcohol. There were no known intestinal diseases or previous surgical procedures that could explain the presence of increased fecal fat excretion. At the time of the study, no patient was on corticosteroid medication.

Classification of Antigens

HLA-A, B, and C antigens were defined by serological methods on peripheral lymphocytes, and the DR locus antigens on T-cell depleted B-cells according to previously described methods (*13*).

Pancreatic Exocrine Function

Serum total amylase and pancreatic serum isoamylase were analysed using the Phadebas® Amylase and Isoamylase Test kits (Pharmacia AB, Uppsala, Sweden) (*14*) and serum lipase by Monotest lipase (Boehringer, Mannheim, FRG) (*15*). Fat absorption was assessed with estimation of fecal fat (*16*).

A standard secretin test was performed after an overnight fast (*17*). Two Salem tubes were passed, one through each nostril. One tube was placed in the third part of the duodenum and the other one in the stomach for separate aspirations. After a 10 min basal period, 1 CU/kg bw of secretin (Ferring AB, Malmö, Sweden) was administered iv and the sampling continued for three 15 min portions. Duodenogastric regurgitation was considered if the gastric aspirate volume exceeded 15 mL/15 min period and/or bile-stained discoloration of it was obvious. The vol of the duodenal juice aliquots were measured and its bicarbonate content determined titrimetrically. In our laboratory, normal values for maximal bicarbonate concentration is ≥ 80 mmol/L, bicarbonate output $\geq 0{,}30$ mmol/kg bw/h, and duodenal aspirate vol $\geq$ mL/kg/h.

Table 2
Exocrine Pancreatic Function Tests
in Six Patients with Primary Sjögren's Syndrome

Patient	Amylase (1.2-5.0) µkat/l	Pancreatic amylase (0.6-3.3) µkat/l	Lipase (<2,7) µkat/l	Fecal fat (<20) mmol/day	Secretin test HCO3 (> 80) mmol/l	MaxHCO3 (>0.25) mmol/kg/h	volume (>2) ml/kg/h
1	14.2*	8.1*	3.44*	13	89.7	0.48	4.6
2	5.6*	5.1*	2.66	16	56*	0.08*	2.1
3	4.8	3.0	2.93*	44*	109.6	0.31	2.4
4	5.6*	4.3*	3.01*	23*	88.4	0.39	3.0
5	2.1	2.0	2.56	11	56*	0.13*	2.5
6	3.7	2.8	1.33	26*	94.4	0.29	2.9

Figures within brackets denote normal values. * = abnormal test result. Amylase, pancreatic amylase, and lipase are serum values.

Pancreatic Endocrine Function

Oral glucose tolerance test (OGTT) was performed in fasting patients, using 75 g of anhydrous glucose according to the WHO recommendations (*18*). Blood samples were, drawn at −10, 0, 10, 20, 30, 60, 120, and 180 min, respectively, for determination of blood glucose. At 0, 60, and 120 min, serum samples were obtained for insulin and C-peptide measurements. Insulin was assayed according to Arnquist et al. (*19*), and C-peptide according to Nilsson et al. (*20*). Twenty healthy blood donors were used as reference group, when evaluating blood glucose, insulin and C-peptide values obtained during the oral glucose tolerance test.

Endoscopy

Endoscopic retrograde pancreatography (ERP) was done in a routine manner using Olympus duodenoscope JF-1T 10 (*21,22*).

The study had been approved by the local Ethics committee.

STATISTICAL ANALYSIS

Student's *t*-test was used when comparing serum insulin and C-peptide values with those of the reference group.

RESULTS

Pancreatic Exocrine Function

Four of the six patients had abnormal serum levels of pancreatic enzymes. Three patients had increased pancreatic isoamylase levels and lipase levels were increased in three of the six patients (Table 2). Fecal fat excretion was

Table 3
Results of Endoscopic Retrograde Pancreatography (ERP) and Secretin Test in Six Patients with Primary Sjögren's Syndrome

	Secretin test		
	normal	pathological	total number
normal ducts	2/6	0/6	2/6
pancreatitis	2/6	2/6	4/6
total number	4/6	2/6	6/6

above normal in three of the six patients (Table 2). The secretin test was consistent with pancreatic insufficiency in two of the patients (Table 2); the vol of the duodenal aspirates were in all above 2 mL/kg/h, which, in our opinion, is required for a reliable test result. In four patients, the vol of the duodenal aspirates were bordering to subnormal values (2,0–2,9 mL/kg bw/h).

Pancreatic Endocrine Function

All patients had normal oral glucose tolerance tests. Further, the serum insulin and C-peptide values, and the calculated insulin/glucose ratio were similar to those of the normal reference group at any time interval studied.

Endoscopy

In all patients, the ERP was technically adequate. Four of the six patients had unequivocal signs of pancreatitis as defined (*23*); in all four the changes were of moderate degree, but confined to the main duct as well as the side branches. The ductal pancreatitis was affecting the whole ductal system of the gland. As shown in Table 3, two of the patients with pancreatitis changes at ERP also had pathological secretin test.

All patients had at least two abnormal tests of exocrine function and ductographic morphology and half of them had the combination of three abnormal signs (Table 4).

DISCUSSION

Up to a third of all patients with RA may have Sjögren's syndrome, but the frequency of primary Sjögren's syndrome is unknown, and available figures depend largely on diagnostic criteria used. Our impression is that PSS is relatively uncommon, only 29 patients being identified at our institution during a 5-yr period (the hospital serving a primary population of 150,000 inhabitants). From these 29 PSS-patients, a selection was made; the patient should have no gastrointestinal and/or pancreatitis symptoms. After informed consent, six appropriate patients were willing to participate in the study including ERP.

Table 4
Summary Showing That All Six Patients Had At Least Two Abnormal Tests

Patient	pancreatic amylase	lipase	fecal fat	secretin test	ERP
1	+	+			
2	+			+	+
3		+	+		+
4	+	+	+		
5				+	+
6			+		+

The results suggest that exocrine pancreatic pathology may be present in PSS patients without clinical signs of acute or chronic pancreatitis. In fact, all our patients had at least two positive signs for pancreatic involvement and half of our patients had even three positive signs. Although the sensitivity of pancreatic serum enzyme determinations is low in chronic pancreatic disease, the tests are more useful in active disease (*24*). In our patients, there were no subnormal enzyme values but four patients with raised values. This might point to a slow subclinical inflammatory process of the gland in some patients with Sjögren's syndrome as previously suggested by Tsianos et al. (*25*). However, Magid et al. (*10*) found both low and elevated pancreatic amylase values among their patients. Apart from the abnormal serum enzyme levels, four of our patients had pancreatitis changes at ERP in combination with abnormal results of either the secretin test or fecal fat excretion. Three patients had increased fecal fat content but normal secretin tests. In two of them, the fecal fat values, however, were bordering to the normal range. The third had undisputed raised fat contents although the secretin test was normal. It is, however, known that secretin test may occasionally yield false-negative results in patients with chronic pancreatitis (*26*). Contrary to these findings of exocrine pancreatic affection, none of the patients displayed any signs of endocrine pancreatic malfunction.

Previous reports on exocrine pancreatic insufficiency do not separate PSS patients from those with SS (*7–10,27*). Therefore, it is not possible to compare the findings of a high frequency of exocrine pancreatic involvement in our small study with previously published data; the wide variation from a 27% frequency in the study of Lankisch et al. (*27*) to 90% as reported by Hradsky et al. (*9*), and our findings suggesting a 100% involvement may possibly reflect different proportions of PSS cases in their series.

As the specific immunological features of PSS increase the risk of autoimmune manifestations, it might tentatively be assumed, that there is an increased risk of autoimmune pancreatitis as well. Obviously, proof of autoimmune

etiology or pathogenesis of pancreatitis must rest on histopathologic evidence and/or the demonstration of autoantibodies directed against specific ductal antigens. Actually, serum antibodies to pancreatic duct cells in four of 12 patients with Sjögren's syndrome (PSS and SS not separated) (*28*), as well as sporadic reports about mononuclear cell infiltration of exocrine pancreas (*29, 30*) indicate possible autoimmune damage to pancreas in this disease. Also, the more recent observations of Bovo et al. (*31*) on biopsy material from 12 patients with chronic pancreatitis (10 of which were addicted to alcohol) with lymphocyte infiltration and increased expression of HLA-DR antigens, indicate an autoimmune mechanism in this variety of chronic pancreatitis. The same phenomenon has recently been observed in lip salivary gland biopsy from patients with Sjögren's syndrome (*32*), that suggests a similar pathogenetic process of autoimmune exocrinopathy in salivary glands and pancreas.

To our knowledge, this is the first time ERP-findings are reported in patients with Sjögren's syndrome without clinical signs of pancreatitis. The high frequency of ductal changes suggesting pancreatitis in our patients is surprising. One objection could be that they represent ductal alteration seen by increasing age (*33,34*). The studies by Kreel (*33*) and Schmitz-Moormann (*34*), often cited in this respect, are however, done on necrosy material. Therefore, the results should be interpreted with caution when compared to pancreatographic morphology by ERP in live patients. Sahel (*35*) found in a ERP-series that above the age of 50, half of the population exhibited ductal enlargement. However, the changes in our series were too advanced in all four cases to be regarded simply as normal age related atrophy.

In summary, this paper described a surprisingly high frequency of exocrine functional and morphological pancreatic changes in a small series of patients with primary Sjögren's syndrome without clinical signs of pancreatitis, suggestive of a silent pancreatitis, perhaps of autoimmune origin. There were no signs of endocrine pancreatic insufficiency.

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