Primary Sjögren's syndrome in children and adolescents: Proposal for diagnostic criteria

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Abstract

Objective

Primary Sjögren's syndrome (pSS) in childhood is a rare disease. Diagnostic criteria are available for adult patients only. In order to establish diagnostic criteria for juvenile pSS an analysis of 7 girls and one boy suffering from pSS with early onset is reported. Due to the rarity of the disease, data on patients with pSS reported in the literature are included in the proposal for modified diagnostic criteria.

Methods

The diagnosis of pSS was established according to the criteria for adulthood pSS, duly modified, which include clinical symptoms and laboratory immunological evaluation.

Results

The average age of our patients at clinical onset was 13.5 years (range: 10 - 17 yrs.). Clinical signs included systemic (fever, fatigue) as well as local (parotitis, vulvovaginitis, conjunctivitis) symptoms. Paralysis due to hypokalemia linked to renal tubular acidosis and central nervous system (CNS) involvement was seen in one patient. Asymptomatic renal tubular acidosis was diagnosed in another 2 patients. Autoimmune hepatitis was present in 2 patients. All patients had laboratory abnormalities: hyperimmunoglobulinemia IgG, high titers of antinuclear antibodies (anti-SS-A and/or anti-SS-B) and elevated serum amylases. Sicca syndrome was never seen during childhood, although it developed later in 3 patients, after 7 to 10 years of follow-up.

Conclusion

It has been stressed that the classical diagnostic criteria for adult Sjögren's syndrome, especially sicca syndrome, are not applicable to a pediatric onset of the disease. On the other hand, the presence of typical laboratory abnormalities can allow the diagnosis of these patients in the early stages. Both laboratory and clinical symptoms typical for childhood are included in our proposal for diagnostic criteria applicable to juvenile pSS. Life-threatening conditions such as hypokalemic paralysis, CNS involvement and hepatitis may also occur in children. Sicca syndrome tends to develop much later in pediatric patients.

Key words

Sjögren's syndrome, childhood onset, autoantibodies.

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Introduction

Sjögren's syndrome (SS) is an autoimmune disease of unknown etiology affecting predominantly the exocrine glands, with the possible involvement of many other organs such as the liver, lung, kidneys or nervous system. Lymphocytes and plasma cells infiltrate these affected organs. Chronic inflammation leads to the loss of the function of the main exocrine glands, characterized clinically by dry mouth (xerostomia) and dry eyes (xerophtalmia) (1, 2). The disease affects about 0.2% of adults and occurs approximately nine times more often in women then in men. The mean age at onset of the clinical symptoms is 40 - 45 years (3). A rare, but severe complication, is represented by the malignant proliferation of lymphocytes causing B-cell lymphoma (4).

Other important systemic manifestations include vasculitis, cryoglobulinaemia, autoimmune hepatitis, alveolitis or pulmonary fibrosis, neuropathy, and (rarely) CNS involvement. Renal tubular acidosis is the most common pathology affecting the kidneys in primary SS (5). Several forms of accompanying glomerulonephritis have also been reported. There are two forms of SS: primary (pSS), and secondary SS, which is associated with other systemic or organ-specific autoimmune diseases, chronic graft-versus-host reaction or HIV infection (6, 7). Diagnostic criteria are only available for adult patients with pSS (6).

The occurrence of SS is rare in childhood and in its primary form only single case reports or small groups of patients have been reported (7-9). No specific diagnostic criteria have been established for SS in childhood. In this article, we present 8 patients with primary SS in whom the disease manifested during childhood or adolescence. We summarize the initial clinical symptoms, laboratory findings, and the outcome over a long follow-up period. On the basis of the analysis of our group and other patients reported in the literature, we propose a set of diagnostic criteria for pediatric onset pSS.

Patients and methods

Patients were diagnosed and monitored at the Institute of Immunology, University Hospital Motol, Prague. Laboratory evaluations for each patient were performed regularly during follow-up visits. The following parameters were measured: the erythrocyte sedimentation rate (ESR), blood count, serum concentration of immunoglobulins (IgG, IgA, IgM), C3 and C4 complement components (nephelometry), antinuclear antibodies (indirect immunofluorescence on Hep-2 cells), anti-ds-DNA antibodies (indirect immunofluorescence using Crithidia), anti-ENA antibodies (counterimmunoelectrophoresis), anti-SS-A, anti-SS-B, anti-Scl70, anti-U1RNP, anti-Sm, anti-Jo1 antibodies [ELISA, Cogent Diagnostics Ltd, UK; confirmed by Western blotting on nuclear and cytoplasmic HeLa cell extracts (10)], rheumatoid factors of the IgG, IgA and IgM isotypes (ELISA, Cogent Diagnostics Ltd.), antineutrophil cytoplasmic antibodies (ANCA, indirect immunofluorescence on human neutrophils, Binding Site, UK). The blood chemistry work-up included ALT, AST, GMT, ALP and amylase (AMS) enzyme activity. Renal function was assessed by creatinine clearance. Latent distal renal tubular acidosis was diagnosed in patients whose urinary pH could not be lowered to below 5.5 in the presence of mild systemic acidosis induced by oral calcium chloride loading (0.1 g/kg) (11). In certain cases, other investigations were performed based on the clinical status of the child.

We used the diagnostic criteria for SS of Vitali *et al.* (6). However, subjective and objective symptoms documenting dryness were excluded owing to the fact that sicca syndrome is the result of irreversible damage to glands due to chronic inflammation that takes years before clinical symptoms of dryness evolve. The criterion of sicca syndrome was included only in those cases with a long-term follow up, as confirmation of the preliminary diagnosis established on the basis of other criteria. The absence of laboratory abnormalities typically associated with other autoimmune diseases (low C3 and C4 complement, positivity of anti-ds-DNA, anticardiolipin, and ANCA antibodies) were used as exclusion criteria for primary SS. The diagnostic criteria and their presence in individual patients are summarized in Tables I - II.

Table I. Diagnostic criteria for pSS. Diagnosis of SS: 4 out of 6 criteria positive; suspected SS: 3 out of 6 criteria positive.

Criteria of C. Vitali *et al.* for primary Sjögren's syndrome in adults (ref. 6)		Suggested modifications for pediatric pSS patients
I. Subjective symptoms		
1. Ocular symptoms (positivity = 1 positive sign out of a-c)	The feeling of: (a) dryness; (b) sand in the eyes; (c) use of artificial tears for > 3 mos.	These symptoms occurring at any time during the follow-up.
2. Oral symptoms (positivity = 1 positive sign out of a-c)	(a) feeling of dryness for > 3 mos.; (b) enlargement of parotid glands; (c) need to drink liquids frequently to aid in swallowing dry foods.	These symptoms occurring at any time during the follow-up.
II. Objective symptoms		
3. Ocular dryness	Schirmer test, Bengal red coloration	Documented at any time during the follow-up. To allow inclusion of ocular involvement at early stages, this criterion may be substituted for in children by recurrent conjunctivitis without obvious allergic or infectious etiology.
4. Infiltration of organs by lymphocytes	Biopsy	
5. Objective documentation of parotid gland involvement	Sialography, scintiscan	To enable early detection of inflammation before structural changes occur, this criterion may be substituted by laboratory findings documenting parotid gland inflammation or involvement of other glands with external secretion (i.e. pancreas) (elevation of amylases).
6. Laboratory abnormalities	Presence of one of the following autoantibodies: ANA, SS-A, SS-B or rheumatoid factor.	
		7. Distal renal tubular acidosis (manifest or latent).
		8. Signs of other mucosal surfaces involvement (i.e. vulvovaginitis).
Primary SS	The absence of any other systemic disease such as RA, DM/PM, SLE	

Results (Tables II, III and IV)

Patient 1. The patient presented at the age of 11 years with recurrent enlargement of the parotid glands accompanied by systemic symptoms - fatigue, arthralgias, myalgias and fever. The clinical signs slowly improved with immunosuppressive therapy. The disease course during the follow-up was complicated by repeated acute respiratory illnesses always accompanied by enlargement and inflammation of the parotid glands. A combination of immunosuppression and antibiotics showed beneficial effect at these times. Laboratory signs of the disease, characterized by extreme hyperimmunoglobulinemia (IgG as high as 50g/l), positive antinuclear antibodies and positive antibodies to SS-A, SS-B and rheumatoid factors, remained unchanged despite the treatment and good clinical status of the child.

Patient 2. The second patient, now 29 years old, has been followed since the age of 14 due to a high ESR accidentally discovered after tonsillitis and for intermittently elevated serum transaminases. Liver biopsy showed lymphocytic infiltration. Elevation of serum and urine amylases was repeatedly found. This fact led finally to the suspicion of Sjögren's syndrome, supported by laboratory immunological examination and nephrological examination which established the diagnosis of asymptomatic latent distal renal tubular acidosis. In the absence of any clinical problems, no therapy was introduced. Sicca syndrome appeared at the age of 19 and manifested as dry eyes, dry mouth, and dyspareunia. All of these symptoms improved with local treatment. The patient's first pregnancy was normal and she delivered a healthy child. Therapy with prednisone was then introduced due to a marked elevation of serum transaminases. The maintenance dose was kept during the patient's second pregnancy, which successfully terminated with the delivery of a healthy child. During both pregnancies a prenatal cardiologic follow-up was performed, but no signs of A-V heart block were detected despite the high levels of anti-SS-A and anti-SS-B antibodies in the mother's serum. In spite of maintenance therapy with prednisone, parotid inflammation occurred approximately twice a year, necessitating antibiotic treatment and an increase in the corticosteroid dose.

Patient 3. This patient has been followed for recurrent conjunctivitis, headache, fatigue, upper respiratory tract infections and neutropenia since the age of 10. Recurrent vulvovaginitis appeared beginning at the age of 12. She was treated in

Table II. The presence of diagnostic criteria in patients.

	Patient no. 1	2	3	4	5	6	7	8
I. Subjective symptoms								
1. Ocular symptoms (positivity = 1 positive sign out of a-c)	-	+	+ (b)	+	+	-	-	-
2. Oral symptoms (positivity = 1 positive sign out of a-c)	+ (c)	+	-	+	+	+	+ (c)	-
II. Objective								
3. Ocular dryness or recurrent inflammation	-	+	+	+	+	-	-	-
4. Infiltration of organs by lymphocytes (by biopsy)	+	+	n.d.	n.d.	n.d.	+	n.d.	+
5. Objective signs of parotid gland inflamm. (enlargement or elevated amylases)	+	+	+	+	+	+	+	+
6. Laboratory abnormalities (anti- SS-A, SS-B, ANA, RF autoantibodies)	+	+	+	+	+	+	+	+
7. Renal tubular acidosis	-	+	n.d.	n.d.	+	n.d.	-	+
8. Other mucosa involv. (vulvovaginitis)	+	+	+	-	+	+	-	-
Primary SS (the absence of any other systemic disease such as RA, DM/PM, SLE)	+	+	+	+	+	+	+	+

(+) symptom present; (-) symptom absent; n.d. not done

Table III. Clinical symptoms, organ involvement (other than diagnostic criteria) and therapy in our 8 pediatric patients with pSS.

Pt.	Born	Sex	First clinical symptoms (age)	Sicca symptoms (age)	Hepatic involvement	CNS involvement	Current treatment
1	1984	f	11	-	-	-	Intermmitently Prednison, antibiotics
2	1968	f	14	+(20)	+	-	Prednison
3	1981	f	10	-	-	-	Prednison
4	1972	m	14	+(24)	-	-	Prednison
5	1974	f	16	+(23)	-	-	Prednison
6	1979	f	17	-	-	-	Intermitently Prednison
7	1976	f	16	-	-	-	Without th.
8	1986	f	10	-	+	+	CyA, corticosteroid (Deflazacort), correction of RTA

Table IV. Results of laboratory investigations in our series of pediatric patients with pSS.

Pt.	ESR	IgG	C3, C4	ANA	ENA SS-A	ENA SS-B	ANCA, ds-DNA, anti-cardiolipin	RF IgM	EBV VCA, IgM	AMS
1	n. or ↑	↑↑↑	normal	+++	+	+	-	++	++	+
2	↑↑ - ↑↑↑	↑↑	normal	+++	+	+	-	+++	+	+
3	↑ - ↑↑	↑↑	normal	+++	+	-	-	+	++	+
4	↑	↑↑	normal	+++	+	+/-	-	-	+	+
5	↑↑ - ↑↑↑	↑↑	normal	+++	+/-	+	-	+++	+	+
6	↑↑ - ↑↑↑	↑↑	normal	+++	+	-	-	+	-	+
7	↑	↑↑	normal	++	+	+	-	+++	-	+
8	↑↑	↑↑↑	normal	+++	+	+	-	+	-	+

ESR (erytrocyte sedimentation rate): ↑ 20 - 40 /hr; ↑↑ 40 - 70/hr; ↑↑↑ ≥70/hr.
Immunoglobulin G: ↑↑ 20 - 30 g/l; ↑↑↑ ≥ 30 g/l.
C3, C4: serum complement concentration (normal C3 = 0.6 - 1.1 g/l, normal C4 = 0.2 - 0.4 g/l).
ANA: antinuclear autoantibodies, speckled type on immunofluorescence, (++) titer 1:320 - 640, (+++) titer > 1:640.
ANCA: antineutrophil cytoplasmic antibodies; RF-IgM: rheumatoid factor isotype IgM.
EBV-VCA: viral capsid antigen of Epstein-Barr virus, IgM isotype.
AMS: serum amylase (+) above normal range, (-) within the normal range.

the allergology department with antihistamines without improvement of her clinical status. She was referred to our department at the age of 13 by the hematologist investigating the cause of her neutropenia. High titers of ANA (1:2000) and anti-SS-A were found. Low dose prednisone normalized all of her clinical symptoms. Before the initiation of this therapy she was frequently absent from school due to respiratory infections and prolonged low-grade fever. During 2 years of therapy with prednisone (average dose of 2.5 - 5 mg daily) she was free of infections, the number of leukocytes normalized and the ANA titer dropped to 1:100. No side effects of corticosteroid treatment were seen. She has no sicca syndrome at present.

Patient 4. This patient, now 25 years old and the only male in our group, has been followed at the pediatric gastroenterology department since the age of 14 years for elevated serum amylase levels. The diagnosis of SS was established at the age of 18 during an investigation of proteinuria. Laboratory findings were typical for SS. A non-functioning kidney had been removed early in childhood, so the patient had only one kidney. Such patients often suffer from mild proteinuria due to long-term glomerular hypertension, but clearly the possibility of interstitial nephritis or mild glomerulonephritis related to Sjögren's syndrome cannot be excluded. Therapy with prednisone was introduced (maintenance dose of 2.5 - 5 mg daily). At the age of 24, the patient developed mild xerostomia and dry eyes. No side effects of corticosteroid therapy were observed.

Patient 5. The patient, now 24 years old, presented at the age of 16 with symptoms of systemic vasculitis-Kawasaki-like syndrome. Hypergamaglobulinemia and high titers of ANA and RF were found. She was lost to follow-up for several years, but then returned at the age of 23 with sicca syndrome accompanied by recurrent vulvovaginitis, conjunctivitis and dental caries. Laboratory investigations continued to show ANA positivity at 1:2000, anti-SS-A, RF IgM and hyperimmunoglobulinaemia.

Patient 6. The sixth patient was referred to our department at the age of 17 for recurrent upper respiratory tract infections, arthralgias and fatigue. Laboratory investigation showed leukopenia and high titers of ANA (1:1000) and anti-SS-A antibodies. A small salivary gland biopsy showed lymphocytic infiltration. When low dose prednisone therapy was introduced, all of the patient's clinical symptoms disappeared, including her frequent respiratory tract infections, and her leukocyte count normalized. Therapy with prednisone was withdrawn after 2 years. Antinuclear antibodies and anti-SS-A were still detectable; the ANA titer dropped transiently to 1:100, but slowly rose again after withdrawal of the corticosteroids. She has not yet shown any clinical signs of sicca syndrome.

Patient 7. Symptoms in this patient started at the age of 16 in the form of recurrent abdominal pain and aphthous stomatitis, once she had parotitis. Elevated levels of serum and urine amylases were repeatedly detected. She was referred to our department at the age of 20. Laboratory markers were compatible with the diagnosis of pSS (hyperimmunoglobulinemia, ANA speckled type 1:500, anti-SS-A and SS-B positive, RF IgA and IgM positive). A short course of prednisone therapy was introduced due to severe aphthous stomatitis. Her clinical problems resolved with this therapy, which was withdrawn after 3 months. After a one-year follow-up no clinical problems have appeared, although laboratory abnormalities are still detectable.

Patient 8. The youngest patient in our group was admitted to the emergency clinic at the age of 10 years in a metabolic crisis. Severe hypokalemia led to intestinal paralysis and ileus. Central and peripheral nervous system involvement was manifested by polyradiculoneuritis and meningoencephalitis, which quickly resulted in quadruparesis. The diagnosis of SS syndrome was suspected because of hyperimmunoglobulinemia, positive serum ANA, anti-SS-A, and anti-SS-B antibodies, and cerebrospinal fluid anti-SS-A positivity. The severe hypokalemia could be explained by the presence of renal tubular acidosis, as the urine pH was high. HLA typing showed A1 and B8 alleles.

Therapy was initiated with pulse methylprednisolone and was continued thereafter with a combination of corticosteroids and cyclosporin A. Despite this aggressive treatment, the course of the disease was twice complicated by severe attacks of retrobulbar neuritis. Although the metabolic changes were successfully corrected, recovery was slow. Demyelinating changes in the CNS were detected by nuclear magnetic resonance. The paresis improved slowly, as did the initially observed marked hepatosplenomegaly. Severe osteoporosis developed as a consequence of the corticosteroid treatment. Renal tubular acidosis persists, requiring daily correction. The current clinical status of this patient is stable, although laboratory investigation shows persistent abnormalities.

Taking into the account the clinical and laboratory symptoms seen in our group of patients, as well as these reported in the literature, we have formulated a proposal for diagnostic criteria applicable to pediatric onset pSS (Table V).

Discussion

In our experience the diagnosis of childhood Sjögren's syndrome may be difficult. The clinical symptoms in children do not fulfill the classical diagnostic criteria which are successfully used for adults.

The onset of the disease is characterized by non-specific symptoms and the only typical clinical presentation is salivary gland enlargement or recurrent parotitis. On the other hand, laboratory signs of continuing disease are present early in the disease course. Laboratory immunological abnormalities are quite uniform and include hypergammaglobulinemia, positivity of anti-SS-A and/or anti-SS-B antibodies, high titer of antinuclear antibodies of the speckled type, and/or positivity of rheumatoid factors.

None of these markers is specific only for Sjögren's syndrome; however, the absence of anti-ds-DNA, anti-cardiolipin or antineutrophil cytoplasmic autoantibodies and normal complement serum level make the diagnosis of other systemic autoimmune diseases, such as lupus erythematosus, unlikely. Furthermore, elevated levels of amylases (parotic and/or pancreatic) were present in all of our pediatric patients. These represent laboratory signs of the parotid gland or pancreas inflammation which are typical of

Table V. Proposal for diagnostic criteria for juvenile pSS.

I. Clinical symptoms:
   1. Oral: recurrent parotitis or enlargement of parotis gland
   2. Ocular: recurrent conjunctivitis without obvious allergic or infectious etiology, keratokonjunctivitis sicca
   3. Other mucosal: recurrent vaginitis
   4. Systemic: a) fever of unknown origin; b) non-inflammatory arthralgias; c) hypokalemic paralysis; d) abdominal pain

II. Immunological abnormalities: presence of at least one of the following antibodies: anti-SS-A, anti-SS-B, high titer of ANA (speckled type), rheumatoid factor.

III. Other laboratory abnormalities or additional investigations
   1. Biochemical: elevated serum amylases (parotic isoenzyme, pancreatic isoenzyme or both)
   2. Hematological: leukopenia, high ESR
   3. Immunological: polyclonal hyperimmunoglobulinemia
   4. Nephrological: renal tubular acidosis (incapacity of spontaneous or challenged acidification of urine)
   5. Histological proof of lymphocytic infiltration of salivary glands or other organs (i.e. liver biopsy)
   6. Objective documentation of ocular dryness (Bengal red staining or Schirmer test)
   7. Objective documentation of parotis gland affection (sialography)

IV. Exclusion of all other autoimmune diseases

pSS, but which do not form part of the current validated diagnostic criteria.

Severe metabolic collapse due to RTA as well as the CNS involvement may also occur in children (12-14). RTA is associated very specifically with primary Sjögren's syndrome and does not occur in other autoimmune diseases, which provides a strong reason for including this particular criterion in our proposed diagnostic criteria set for children.

Initial symptoms may sometimes mimic immune deficiency or allergy (respiratory tract infections, vaginitis, and conjunctivitis). This could be the result of diminished local resistance due to the loss of exocrine gland secretion capacity or a phagocytic dysfunction (15).

The treatment of Sjögren's syndrome remains controversial. Immunosuppressive therapy in adults is recommended only in the presence of organ involvement. In children and adolescents, we consider this therapy to be justified only in the presence of laboratory signs of organ damage, significant leukopenia or severe clinical symptoms. Local treatment of sicca syndrome is useful in preventing local infectious complications. New therapeutic modalities such as α-interferon which have been used in adults with SS (16), or specific immunotherapy with possible candidate autoantigens (17) await appropriate testing. Clinical follow-up is important even in the absence of any treatment to prevent the complications which are typical of this disease, such as atrioventricular block in the newborn babies of female patients with SS or malignant lymphoproliferation. Careful follow-up is also needed in order to prevent systemic complications such as organ involvement or vasculitis. Diagnostic criteria enabling the early diagnosis of pSS are therefore required. With this preliminary proposal we would like to initiate the establishment of official criteria for pSS in pediatric patients.

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References

1. BLOCH KJ, BUCHANAN WW, WOHL MJ, BUNIN JJ: Sjögren's syndrome. A clinical, pathological and serological studies of 62 cases. *Medicine* 1965; 44: 187-231.
2. TALAL N: Clinical and pathogenetic aspects of Sjögren's syndrome. *Semin Clin Immunol* 1993; 6: 11-20.
3. KAPLAN G: Syndrome de Gougerot-Sjögren. *In* KAHN MF, PELTIER AP, MEYER O, PIETTE JC (Eds.): *Les Maladies Systémiques.* Paris, Flammarion 1991; 499-544.
4. PARIENTE D, ANAYA JM, COMBE B: Non-Hodgkin's lymphoma associated with primary Sjögren's syndrome. *Eur J Med* 1992; 1: 337-42.
5. TALAL N, ZISMAN E, SCHUR PH: Renal tubular acidosis and immunologic factors in Sjögren's syndrome. *Arthritis Rheum* 1970; 11: 774-86.
6. VITALI C, BOMBARDIERI S, MOUTSOPOULOS HM *et al*.: Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European community. *Arthritis Rheum* 1993; 36: 340-7.
7. ANAYA JM, OGAWA N, TALAL N: Sjögren's syndrome in childhood. J Rheumatol 1995; 22: 1152-8.
8. CHUDWIN DS, DANIELS TE, WARA DW *et al*.: Spectrum of Sjögren syndrome in children. *J Pediatr* 1981; 98: 213-7.
9. OSTUNI PA, IANNIELLO A, SFRISO P, MAZZOLA G, ANDRETTA M, GAMBARI PF: Juvenile onset of primary Sjögren's syndrome: Report of 10 cases. *Clin Exp Rheumatol* 1996; 14: 689-93.
10. VERHEIJEN R, SALDEN M, VAN VENROOIJ WJ: Protein blotting. *In* VAN VENROOIJ WJ and MAINI RN (Eds.): *Manual of Biological Markers of Disease.* Dordrecht, Kluwer Academic Publishers, 1993; A4: 1-25.
11. OSTER JR: A short duration renal acidification test using calcium chloride. *Nephron* 1975; 14: 216-30.
12. CHANG YC: Renal tubular acidosis complicated with hypokalemic periodic paralysis. *Pediatr Neurol* 1995; 13: 52-4.
13. KOBAYASHI I, FURUTA H, TAME A *et al*.: Complications of childhood Sjögren syndrome. *Eur J Pediatr* 1996; 155: 890-4.
14. ALEXANDER GE, PROVOST TT, STEVENS MB, ALEXANDER ES: Sjögren syndrome: central nervous system manifestations. *Neurology* 1981; 31: 1391-6.
15. BARTUNKOVÁ J, ARAUJO A, HRUSÁK O, SEDIVÁ A: Autoimmunity to polymorphonuclears: Functional consequences of the binding of antibodies to membrane and cytoplasmic target antigens of polymorphonuclear leukocytes. *J Clin Immunol* 1997; 17:455-61.
16. SHIOZAWA S, MORIMOTO I, TANAKA Y, SHIOZAWA K: A preliminary study on the interferon-alpha treatment for xerostomia of Sjögren's syndrome. *Br J Rheumatol* 1993; 32: 52-4.
17. HANEJI N, NAKAMURA T, TAKIO K *et al*.: Identification of alpha-fodrin as a candidate autoantigen in primary Sjögren's syndrome. *Science* 1997; 276: 604-7.