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.
Primary Sjögren’s syndrome in childhood / J. Bartůňková et al.

**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 (xerophthalmia) (1, 2). The disease affects about 0.2% of adults and occurs approximately nine times more often in women than 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.
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Table I. Diagnostic criteria for pSS. Diagnosis of SS: 4 out of 6 criteria positive; suspected SS: 3 out of 6 criteria positive.

<table>
<thead>
<tr>
<th>Criteria of C. Vitali et al. for primary Sjögren’s syndrome in adults (ref. 6)</th>
<th>Suggested modifications for pediatric pSS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Subjective symptoms</td>
<td></td>
</tr>
<tr>
<td>1. Ocular symptoms (positivity = 1 positive sign out of a-c)</td>
<td>The feeling of: (a) dryness; (b) sand in the eyes; (c) use of artificial tears for &gt; 3 mos.</td>
</tr>
<tr>
<td>2. Oral symptoms (positivity = 1 positive sign out of a-c)</td>
<td>(a) feeling of dryness for &gt; 3 mos.; (b) enlargement of parotid glands; (c) need to drink liquids frequently to aid in swallowing dry foods.</td>
</tr>
<tr>
<td>II. Objective symptoms</td>
<td></td>
</tr>
<tr>
<td>3. Ocular dryness</td>
<td>Schirmer test, Bengal red coloration</td>
</tr>
<tr>
<td>4. Infiltration of organs by lymphocytes</td>
<td>Biopsy</td>
</tr>
<tr>
<td>5. Objective documentation of parotid gland involvement</td>
<td>Sialography, scintiscan</td>
</tr>
<tr>
<td>6. Laboratory abnormalities</td>
<td>Presence of one of the following autoantibodies: ANA, SS-A, SS-B or rheumatoid factor.</td>
</tr>
</tbody>
</table>

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/1), 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.

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

(+) 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.

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

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

<table>
<thead>
<tr>
<th>Pt.</th>
<th>ESR</th>
<th>IgG</th>
<th>C3, C4</th>
<th>ANA</th>
<th>ENA</th>
<th>ANCA, ds-DNA, anti-cardiolipin</th>
<th>RF</th>
<th>EBV-VCA, IgM</th>
<th>AMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n. or ↑</td>
<td>↑↑↑</td>
<td>normal</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>++</td>
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<tr>
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<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>normal</td>
<td>+++</td>
<td>+</td>
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</table>

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 antihista-
mamines without improvement of her clini-
cal status. She was referred to our de-
partment at the age of 13 by the hemato-
tologist 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 clini-
cal 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 (av-
erage dose of 2.5 - 5 mg daily) she was
free of infections, the number of leuko-
cytes normalized and the ANA titer
dropped to 1:100. No side effects of cortico-
steroid 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 gastroenterol-
yology 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 pro-
teinuria. Laboratory findings were typi-
cal for SS. A non-functioning kidney had
been removed early in childhood, so the
patient had only one kidney. Such pa-
tients often suffer from mild proteinuria
due to long-term glomerular hyperten-
sion, but clearly the possibility of inter-
stitial nephritis or mild glomeruloneph-
ritis related to Sjögren’s syndrome can-
not be excluded. Therapy with predni-
sone 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 cortico-
steroid treatment were observed.

Patient 5. The patient, now 24 years old,
presented at the age of 16 with symp-
toms of systemic vasculitis-Kawasaki-
like syndrome. Hypergammaglobulinemia
and high titers of ANA and RF were
found. She was lost to follow-up for sev-
eral years, but then returned at the age
of 23 with sicca syndrome accompanied by
recurrent vulvovaginitis, conjunctivi-
tis and dental caries. Laboratory inves-
tigations continued to show ANA posi-
tivity 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 infec-
tions, arthralgias and fatigue. Laboratory
investigation showed leukopenia and
high titers of ANA (1:1000) and anti-SS-
A antibodies. A small salivary gland bi-
opsy 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 corti-
costeroids. She has not yet shown any
clinical signs of sicca syndrome.

Patient 7. Symptoms in this patient start-
ed at the age of 16 in the form of recur-
rent abdominal pain and aphthous stom-
matitis, 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. Labora-
tory markers were compatible with the
diagnosis of pSS (hyperimmunoglobulu-
linemia, ANA speckled type 1:500, anti-
SS-A and SS-B positive, RF IgA and
IgM positive). A short course of pred-
nisone 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 labo-
atory 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 meta-
boic crisis. Severe hypokalemia led to in-
testinal paralysis and ileus. Central and
peripheral nervous system involvement
was manifested by polyradiculoneuritis
and meningoencephalitis, which quickly
resulted in quadraparesis. The diagno-
sis of SS syndrome was suspected be-
cause 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 methyl-
prednisolone and was continued there-
after with a combination of corticoster-
oids and cyclosporin A. Despite this ag-
gressive treatment, the course of the dis-
ease was twice complicated by severe
attacks of retrobulbar neuritis. Although
the metabolic changes were successfully
corrected, recovery was slow. Demyeli-
nating changes in the CNS were detected
by nuclear magnetic resonance. The par-
esis improved slowly, as did the initially
observed marked hepatosplenomegaly.
Severe osteoporosis developed as a con-
sequence of the corticosteroid treatment.
Renal tubular acidosis persists, requir-
ing daily correction. The current clinical
status of this patient is stable, although
laboratory investigation shows persist-
ent 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 pro-
posal for diagnostic criteria applicable
to pediatric onset pSS (Table V).

Discussion
In our experience the diagnosis of child-
hood Sjögren’s syndrome may be diffi-
cult. The clinical symptoms in children
do not fulfill the classical diagnostic cri-
tera 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
and/or pancreatic) were present in all of our
patients. These represent laboratory
symptoms seen in our group.

Taking into the account the clinical and
laboratory symptoms of non-specific
symptoms and the only
typical clinical presentation of the parotid
and/or pancreatic enlargement or recurrent
parotitis. On the other hand, laboratory
signs of continuing disease are present early
in the disease course. Laboratory immuno-
ological 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
to Sjögren’s syndrome; however, the ab-

ence of anti-ds-DNA, anti-cardiolipin
or antineutrophil cytoplasmic autoanti-
obodies and normal complement serum
level make the diagnosis of other system-
ic 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 labora-
tory signs of the parotid gland or pan-
creas 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, keratoconjunctivitis 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

References