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Serum B lymphocyte stimulator and beta2-microglobulin correlation with autoantibody secretion and systemic involvement in primary Sjögren’s syndrome

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3: Rhumatologie, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg
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Key words: Beta2-microglobulin, BLyS, BAFF, anti-SSA/SSB, primary Sjögren’s syndrome

Running Title: Serum B lymphocyte stimulator and beta2-microglobulin analysis in primary Sjögren’s syndrome.

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ABSTRACT

Objective. In primary Sjögren’s syndrome (pSS), extraglandular involvement might result from more intense stimulation of autoreactive B cells. Thus, markers for B-cell activation could be useful in clinical assessment of the disease. We aimed to investigate the association of serum B lymphocyte stimulator (BLyS) and beta2-microglobulin (β2m) levels with autoantibody production and extraglandular involvement in pSS.

Patients and methods. Levels of serum BLyS and β2m were analysed in 177 patients with primary SS according to American-European consensus group criteria. Levels of serum β2m were serially determined in 25 patients.

Results. Autoantibody secretion (presence of anti-SSA antibody alone or of both anti-SSA and anti-SSB) was associated with increased serum BLyS and β2m levels. Surprisingly, no correlation was observed between BLyS and β2m levels (P = 0.36). Serum levels of β2m and C-reactive protein and positive anti-SSB antibody results were associated with extraglandular involvement on univariate analysis (P < 10^-4, P = 0.003 and P = 0.004, respectively). Level of serum β2m was also significantly increased in patients with extraglandular involvement in patients without autoantibodies (1.75 ± 0.7 mg/L vs 1.39 ± 0.5 mg/L, P =0.039). Multivariate analysis showed extraglandular involvement associated only with increased serum β2m levels (P = 0.035, OR 2.78 [95% CI 1.07-7.22]). Among the 25 patients who had serial determinations of serum β2m, serum β2m levels were increased in all patients with disease flare and decreased in 3 patients, following therapy. Serum BLyS, gammaglobulin, IgG, and rheumatoid factor (RF) levels were not associated with features of systemic involvement.

Conclusion. Serum β2m and BLyS explore B-cell activation differently in pSS. Serum β2m assessment could be helpful in pSS, a disease for which few activity markers exist.
Primary Sjögren’s syndrome (pSS) is an autoimmune disorder characterized by lymphocytic infiltration of salivary and lachrymal glands leading to xerostomia and xerophtalmia. Polyclonal B-cell activation and systemic production of autoantibodies are the hallmarks of the disease (1). Patients with pSS are at increased risk for the development of B-cell non-Hodgkin’s lymphoma (2, 3). Some evidence suggests that such lymphomas could arise from autoreactive B cells (4). Other systemic complications, such as synovitis; myositis; vasculitis; or renal, lung, neurological involvement or purpura, might occur. Patients with positive results for anti-SSA antibody or anti-SSA and anti-SSB antibodies have more frequent extraglandular complications than patients with negative results (5). This higher frequency of extraglandular involvement might be the result of more intense stimulation of autoreactive B cells. Thus, quantitative B-cell activation markers, such as serum beta2-microglobulin (β2m) and B lymphocyte stimulator (BLyS; also known as BAFF, TALL-1, THANK, zTNF4 or TNFS13B) levels, could be used clinically to assess disease activity.

Beta2-microglobulin is the invariant chain of the major histocompatibility complex (MHC) class I molecules (6). The β2m serum level is increased in patients with renal insufficiency (7), lymphoplasmocytic monoclonal proliferations (multiple myeloma and lymphoma (8-10) and human immunodeficiency virus (HIV) infection (11,12), being correlated with disease outcome and prognosis. Interestingly, in previous studies, β2m was found to be elevated in serum, in salivary and in synovial fluid of patients with pSS (13-16).

BLyS, a recently described member of the tumor necrosis factor (TNF)-ligand family (17,18), is essential to the control of B-cell maturation and survival (19). Transgenic BLyS mice have a high number of B cells in peripheral blood, high levels of serum autoantibodies, and systemic lupus erythematosus (SLE)-like symptoms. In addition, lymphocytic infiltrates, similar to those observed in pSS patients, develop in these mice (20). In human autoimmune diseases, BLyS serum levels have been found to be increased in patients with SLE (21) and pSS (22), and correlated with serum autoantibody titres.

Clinicians need clinically relevant biological markers of pSS, which could also be used in clinical trials of new drugs. Thus, we investigated whether the serum levels of biological markers of B-cell activation were correlated with autoantibody secretion and extraglandular involvement.
PATIENTS AND METHODS

Patients

Blood samples were collected from 177 Caucasian patients (170 females and 7 males, mean age 56.6 ± 13.5 years), with pSS as defined by the American-European consensus group criteria (including a focus score ≥ 1 on labial salivary gland, or the presence of anti-SSA or anti-SSB antibodies) (23), who successively attended the Department of Rheumatology of Hôpital de Bicêtre, Le Kremlin Bicêtre, and of Hôpital de Hautepierre, Strasbourg, France. Clinical and immunological features of the population study are summarized in Table 1. Extraglandular involvement was defined as the presence or confirmed records of purpura, lung, and neurological involvement, synovitis, myositis, vasculitis, lymphadenopathy, enlarged spleen, or lymphoma during the evolution of the disease. Raynaud’s phenomenon was not included among the extraglandular manifestations. Because we studied β2m level, which can be modified in patients with impaired renal function, we decided not to include patients with proved interstitial kidney disease. Extraglandular involvement was present in 73 (41.2%) patients: 57 patients had extraglandular involvement at the time of the blood tests, and 16 had confirmed records of systemic involvement. Seventeen patients had two or more clinical features of systemic involvement.

Laboratory analysis

In all patients, antinuclear antibodies were detected by indirect immunofluorescence with the HEp-2000 substrate, which consists of HEp-2 cells transfected with Ro60-kd complementary DNA (Immunoconcepts, Sacramento, CA). Rheumatoid factor and A, G and M immunoglobulin serum values were determined by nephelometry. Serum levels of C3 and C4 were determined by nephelometry (Prospec nephelometer, Dade Behring, Manburg, Germany) in 146 patients. Normal values were 0.68-1.32 g/L for C3 and 0.14-0.33 g/L for C4. Anti-SSA and anti-SSB antibody levels were determined by use of commercial ELISA in all patients. The commercial Varelisa Ro antibody test (a recombinant SSA ELISA; Pharmacia-Upjohn, Freiburg, Germany) uses both baculovirus-expressed recombinant Ro52 and Ro60 coated in an unspecified ratio. The commercial Varelisa La antibody test (Pharmacia-Upjohn, Freiburg, Germany) uses recombinant La (48 kD). All the positive anti-SSA/SSB results obtained by ELISA were confirmed by counter-immunoelectrophoresis with purified antigens obtained from rabbit and rat thymus powder (Pel Freez, Arkansas, USA) or from human spleen extract (Laboratoire d’Immuno-Pathologie, Hôpital Saint-Louis, Paris, France) and reference sera. One hundred and eleven out of the 177 patients (62.7%) had anti-SSA antibody, 58 of them (32.8%) having also anti-SSB antibody (Table 1). No patient had anti-SSB antibodies without anti-SSA antibodies.

The β2m serum level was determined with use of nephelometry (Array 360 system, Beckman Coulter). The diagnostic ranges had been established by the manufacturer in order to include 100% of a reference population of 136 healthy controls. A β2m serum value of 2.11 or more was considered increased, according to
the manufacturer’s recommendations. Patients with impaired renal function (serum creatinine value ≥ 120 µmol/L), previous lymphoma or multiple myeloma were excluded from the β2m analysis, since these conditions are known to be associated with increased serum levels of β2m. The β2m serum level was analysed in 154 patients. Serial determinations of serum β2m were performed in 25 patients.

A sandwich ELISA for measuring the soluble form of BLyS was performed, with modifications of previously described procedures in 137 patients. All serum samples were successively stored at −70°C and sent to the Division of Clinical Immunology and Rheumatology, University of Alabama (Birmingham, AL, USA), for serum BLyS assessment. Briefly, 96-well plates were coated with 2 µg/ml purified murine anti-BLyS monoclonal antibody (clone 3D4, mlgG1) in phosphate buffered saline (PBS) at 4°C overnight and blocked with 1% bovine serum albumin (BSA)/PBS. All specimens were diluted 1:10 in 3% BSA/PBS and incubated on the ELISA plate at 37°C for 4 hours. After being washed, the plate was incubated first with 0.2 µg/ml biotin-conjugated polyclonal anti-BLyS antibody and then with 1:30,000 diluted horseradish peroxidase-conjugated streptavidin (Southern Biotechnology, Birmingham, AL, USA). To avoid the confounding effect of RF activity, an mlgG1 isotype was used as a background control for the capture antibody with each specimen. The reaction was developed with trimethylbenzidine substrate (Sigma, St Louis, MO, USA) and read in an E-Max plate reader (Molecular Devices, Sunnyvale, CA, USA). The absorbance values in the mlgG1 control wells were subtracted from the corresponding anti-BLyS capture wells and were typically <10% of total absorbance. The values obtained with parallel serum and plasma samples did not differ. A standard curve of serial dilutions of recombinant BLyS was incorporated into each assay. BLyS normal values had been previously determined in 47 healthy volunteers using the same ELISA in the same laboratory (median serum BLyS level of 2.49 ng/mL [25th-75th centile range 1.96-2.96]) (22). The serum value of β2m and BLyS were simultaneously available for 114 patients.

**Statistical Analysis**

Chi-square testing (with Yates' correction, when appropriate) was used to assess the differences in frequencies for qualitative values. ANOVA was used to analyse the association between serum β2m, BLyS, and gammaglobulin Ig G, A, and M levels and extraglandular involvement. The results were validated by checking normality of the residues for each test. The Holm’s sequential Bonferroni procedure for multiple tests was used to correct P values according to the number of tests done in each series of comparisons (24). Multivariate analysis was performed with use of logistic regression, which included significant risk factors of extraglandular involvement according to results of the univariate analysis. Statistical analysis involved use of the SPSS 11.5 program.
RESULTS

Association between auto-antibody production and serum β2m and BLyS levels.

In 56 (36.4%) patients, the serum β2m level was increased. The mean serum β2m value was significantly higher in patients with anti-SSA and anti-SSB antibodies (2.43 ± 0.9 mg/L) than in patients with anti-SSA antibody alone (1.82 ± 0.9 mg/L) and in patients without autoantibodies (1.5 ± 0.6 mg/L, \( P < 10^{-4} \); Figure 1, Table 2). In addition, the level of serum β2m was significantly correlated with that of serum RF (\( r = 0.33, P = 0.001 \)), gammaglobulin (\( r = 0.41, P = 0.001 \)), IgG (\( r = 0.42, P = 0.001 \)), C4 (\( r = -0.3, P = 0.001 \)) and with erythrocyte sedimentation rate (ESR) (\( r = 0.39, P = 0.001 \)).

The mean BLyS serum level was higher in patients with anti-SSA antibody alone or with anti-SSA and anti-SSB antibodies (6.6 ± 8.8 and 5.9 ± 6 ng/mL, respectively) than in patients without autoantibodies (4.2 ± 6.8 ng/mL, \( P = 0.05 \); Figure 1, Table 2), although this did not reached significance after statistical correction for multiple tests. In addition, the serum level of BLyS was highly correlated with that of RF (\( r = 0.58, P = 0.001 \)), IgM (\( r = 0.39, P = 0.001 \)) and gammaglobulin (\( r = 0.37, P = 0.002 \)) but not IgG.

Although serum levels of both β2m and BLyS were associated with the presence of anti-SSA or anti-SSB antibodies, no correlation was observed between levels of β2m and BLyS (\( r = 0.08, P = 0.36 \)).

Association between β2m and BLyS levels and extraglandular involvement.

Among 13 potential predictive factors tested, only 3 were associated with extraglandular involvement on univariate analysis (Table 3): a high serum β2m level value (2.2 ± 0.9 mg/L in patients with extraglandular involvement vs 1.7 ± 0.8 mg/L in those without, \( P < 10^{-4} \) ) (Figure 2), presence of anti-SSB antibody (43.8% of patients with extraglandular involvement vs 25% of those without, \( P = 0.004 \)), and high CRP level (10.5 ± 10.9 mg/L in patients with systemic disease vs 6.1 ± 2.8 mg/L in those without). Increased serum BLyS, gammaglobulin, IgG value, anti-SSA antibody...
alone, decreased C3 or C4 levels and ESR were not associated with extraglandular involvement (Table 3).

Multivariate analysis included significant risk factors identified with univariate analysis: serum β2m, positive results for anti-SSB antibody and CRP level. Since the data concerning CRP were not available for the whole population, a second, more potent model of logistic regression included serum β2m level and presence of anti-SSB antibody. Multivariate analysis showed extraglandular involvement associated only with increased serum β2m levels in the model including serum β2m, positive anti-SSB results and CRP level (P = 0.035, OR 2.78 [95% CI 1.07-7.22]), and also in the model including serum β2m and positive anti-SSB results (P = 0.018, OR 2.41 [95% CI 1.16-4.98]). Interestingly, level of serum β2m was increased with extraglandular involvement in patients without autoantibodies (1.75 ± 0.7 vs 1.39 ± 0.5 mg/L, P =0.039) and in patients with anti-SSA antibody alone (2.11 ± 0.8 vs 1.66 ± 0.6 mg/L, P = 0.07), but not in patients with anti-SSA and anti-SSB antibodies (2.53 ± 0.9 vs 2.32 ± 0.9 mg/L, P = 0.5; Figure 3). Accordingly, in patients with increased serum β2m level, extraglandular involvement was independent of the presence of anti-SSB antibody (58.1% of patients with anti-SSB versus 57.1% of patients without antibody, P > 0.9).

The serum β2m level was high with all clinical manifestations, except neurological involvement. However, because of the small number of individual extraglandular manifestations, high serum β2m level was not significantly associated with their presence, except for presence of purpura (2.39 ± 0.8 vs 1.86 ± 0.86 mg/L, P = 0.04). Serum BLyS level was not significantly associated with any individual clinical manifestations. Neither increased serum β2m nor BLyS levels were significantly associated in patients with Raynaud’s phenomenon (RP) (β2m: 2 mg/L and 1.8 mg/L in patients without RP, respectively, P = 0.15; BLyS: 6.2 ng/mL and 5.2 ng/mL in patients with and without RP, respectively, P = 0.46).

Patients with extraglandular involvement were not significantly older and did not have longer disease duration than patients without extraglandular involvement (56.2 ± 14.6 vs 57.2 ± 12.5 years, P = 0.6, and 12.1 ± 7 vs 12.4 ± 7.1 years, P = 0.75, respectively). Serum β2m level was not significantly higher in patients with active extraglandular disease at the time of the blood tests than in patients with confirmed records of extraglandular involvement during evolution of the disease (2.3 ± 1.1 vs 1.9 ± 0.9 mg/L, P = 0.12). Serum creatinine level was not significantly different in patients with increased serum β2m levels (77.1 ± 11.9 vs 75.7 ± 13.8 µmol/L, P = 0.53).

**Longitudinal study of 25 patients**

Twenty-five patients without lymphoma or renal function impairment had serial determinations of serum β2m levels (mean number of samples per patient: 2.6 ± 1.3 [range: 2-7]; mean follow-up period: 23.5 ± 11.4 months). Sixteen patients showed no clinical change and no marked increase in serum β2m level. Six of the 9 patients who experienced a significant increase in serum β2m level (a 50% increase and/or an
increase above the normal value of 2.1 mg/L) had changed clinical symptoms. Four patients had systemic involvement (synovitis, 2; bronchic and bronchiolar involvement, 1; purpura, 1), and 2 patients had disease flare (polyarthralgias, 1; parotiditis and keratitis, 1). Swollen joint count (SJC) and β2m level of one patient with polysynovitis (SJC= 9, β2m= 4.32 mg/L, without treatment) had a parallel course after the beginning of methotrexate (MTX) and hydroxychloroquine (HQ): SJC= 0, β2m = 2.52 mg/L; SJC = 2, β2m = 2.79 mg/L; SJC= 6, β2m = 2.97 mg/L, successively. A concomitant decrease of SJC and β2m was also observed in another patient with polysynovitis (SJC= 4, β2m= 3.97 mg/L, without treatment) after the beginning of HQ: SJC= 2, β2m= 4.18 mg/L; SJC= 0, β2m= 3.6mg/L; SJC= 0, β2m= 2.44 mg/L, successively. The serum β2m of a patient with distal bronchic and bronchiolar involvement treated with azathioprine rose from 1.81 to 2.59 mg/L during a lung flare, and normalized (1.74 mg/L) as the clinical situation improved. One patient had a concomitant decrease of the frequency of purpura flares and of serum β2m level (3.18 mg/L, without treatment; 2.97 and 2.7 mg/L under HQ, successively). One patient, who developed polyarthralgias, had a marked increase of serum β2m from 1.96 to 3.22 mg/L. One patient with uncomplicated sicca eye symptoms and parotiditis, who developed severe keratitis, had a concomitant increase of serum β2m level from 2.1 mg/L to 2.4 mg/L.

DISCUSSION

In this study including 177 patients with pSS, serum BLyS and β2m both correlated with autoantibody secretion, but were not associated with each other. Extraglandular involvement was associated only with increased serum β2m levels on multivariate analysis. Limitations of our study include its transversal design and choice of a composite clinical parameter, extraglandular involvement (presence or confirmed records of systemic features during the evolution of disease). Interestingly, we confirmed the association between increased gammaglobulin, IgG, RF levels, decreased C4 level, and anti-SSA/SSB autoantibodies.

To our knowledge, this is the first time that was demonstrated the parallelism between the increase of serum β2m and spreading of the immune response from anti-SSA antibody alone to anti-SSA and anti-SSB. Only one previous study showed that patients with either anti-SSA or anti-SSB antibodies had a higher mean serum β2m level than patients without these autoantibodies (25).

The specific function of serum β2m remains unknown in pSS, as in other lymphoproliferative diseases. Beta2m stabilizes the tertiary structure of the MHC-class I alpha chain (6) and is required for the loading of peptides and presentation of processed antigens to CD8+ T cells (26). As well, the potential role of β2m as an initiator of inflammatory response, apoptosis-inducing factor, or inhibitor of dendritic cells has been reported (27-29). Serum β2m could help process some autoantigens such as SSA or SSB, by antigen-presenting cells, as demonstrated in study of exogenous antigens such as hepatitis B surface antigen particles (30). But, more
probably, serum β2m level could be only a non specific marker of immune activation, since it is correlated with other classical markers of B cell activation.

We confirmed the association between serum BlyS level and autoantibody production and the correlation between serum BlyS and gammaglobulin, IgM and RF levels (22).

Unexpectedly, although serum β2m and BlyS levels were both associated with autoantibody production, they were not associated with each other. The respective biological origin of serum BlyS and β2m might account for such a discrepancy. Indeed, BlyS is expressed by monocytes, dendritic cells and, in pSS, T cells infiltrating labial salivary cells (31). Its increase in pSS can be considered a pathogenic trigger of B-cell activation. Conversely, β2m can be expressed by all nucleated cells, including B cells. Thus, increased serum β2m could reflect a later and more global stage of immune activation than increased serum BlyS.

Serum BlyS level was not associated with features of systemic involvement, possibly because BlyS has no known direct proinflammatory properties. In addition, the role of serum BlyS as a disease activity marker is controversial in SLE; one study found an association between serum BlyS levels and SLEDAI (32), whereas another study did not (33). Further longitudinal study is required to investigate the role of serum BlyS level as marker of clinical activity in pSS. Likewise, serum IgG, C3 and C4 levels were not associated with extraglandular involvement. Thus, the clinical relevance of decreased serum IgG and gammaglobulin levels, observed during treatment with hydroxychloroquine in patients with pSS (34-36), might be poor.

We confirmed the association between extraglandular involvement and presence of anti-SSA+anti-SSB (37). The genetic determinism of the spreading of the autoimmune response (38), along with the relative stability of anti-SSB titers over time (39), preclude the use of anti-SSB antibodies as disease activity markers in daily practice.

The most interesting finding of this study was the association between serum β2m and extraglandular involvement on univariate and multivariate analysis. Regarding disease activity, beta2-microglobulin value might add significant information to routine measurements, such as ESR or quantitative immunoglobulin values (not associated with extraglandular involvement on univariate analysis) or CRP value (not associated with extraglandular involvement on multivariate analysis). Previously, serum β2m level was demonstrated to be increased in pSS patients with some individual clinical manifestations, such as distal renal tubular acidosis (40), disturbed lung function (41), or alveolitis (42). As well, results of a longitudinal cohort study showed that patients with pSS and subsequent lymphoma had higher baseline levels of serum β2m (43). Interestingly, multivariate analysis demonstrated that serum β2m added significant information regarding extraglandular involvement to that provided by positive anti-SSB antibody results. The increased level of serum β2m with extraglandular involvement in the subgroup of patients without autoantibodies as well as the high extraglandular involvement in patients with increased serum β2m levels, with or without anti-SSB antibody, are two additional strong arguments in
favor of the association between serum β2m level and clinical features, independently of presence of autoantibodies.

Our longitudinal follow-up of 25 patients added important information regarding the potential clinical interest of assessing serum β2m level. Interestingly, serum β2m levels appear to be sensitive to change. Thus, serum β2m level was increased in all patients with disease flare and decreased in three patients following a therapeutic response. This result confirmed that from a previous report detailing the evolution of serum β2m level in 9 patients, including 2 in whom lymphoma developed (13). Further longitudinal analysis, with a larger population, is needed to determine whether serum β2m levels could represent a relevant disease activity marker in pSS, as proposed by Oxholm (44).

In conclusion, serum β2m and BLyS explore B-cell activation differently in pSS. Serum β2m assessment could be helpful in pSS, a disease for which few activity markers exist (45-46). The potential use of this simple, widely available, and inexpensive blood test deserves prospective analysis. Should its role be confirmed, serum β2m level might also become a relevant surrogate marker for use in randomised controlled trials evaluating new drugs in pSS.
REFERENCES


Table 1. Clinical and immunological features of 177 patients with pSS.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enlarged parotid glands</td>
<td>52 (29.4)</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>61 (34.5)</td>
</tr>
<tr>
<td>Extraglandular involvement</td>
<td>73 (41.2)</td>
</tr>
<tr>
<td>Purpura</td>
<td>13 (7.3)</td>
</tr>
<tr>
<td>Synovitis</td>
<td>29 (16.4)</td>
</tr>
<tr>
<td>Myositis</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>Lung involvement(^1)</td>
<td>20 (11.3)</td>
</tr>
<tr>
<td>CNS involvement/ peripheral neuropathy</td>
<td>2 (1.1) / 16 (9)</td>
</tr>
<tr>
<td>Lymphoma(^2)</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>Medium-size vessels vasculitis/ lymphadenopathy / enlarged spleen</td>
<td>1 (0.5) / 4 (2.2) / 1 (0.5)</td>
</tr>
<tr>
<td>(\beta)2 serum level (mean ± S.D., mg/L (n = 154))</td>
<td>1.9 ± 0.9</td>
</tr>
<tr>
<td>BLyS serum level (mean ± S.D, ng/mL (n = 137))</td>
<td>5.5 ± 7.3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>68 (38.4)</td>
</tr>
<tr>
<td>Positive RF results</td>
<td>92 (51.9)</td>
</tr>
<tr>
<td>RF (mean ± S.D., IU/mL)</td>
<td>159.1 ± 344.8</td>
</tr>
<tr>
<td>Gammaglobulin serum level (mean ± S.D., g/L)</td>
<td>13.3 ± 6.7</td>
</tr>
<tr>
<td>IgG serum level (mean ± S.D., g/L)</td>
<td>15 ± 6.9</td>
</tr>
<tr>
<td>IgA serum level (mean ± S.D., g/L)</td>
<td>3 ± 1.5</td>
</tr>
<tr>
<td>IgM serum level (mean ± S.D., g/L)</td>
<td>1.6 ± 1.3</td>
</tr>
<tr>
<td>C3 serum level (mean ± S.D., g/L) (n = 146)</td>
<td>1 ± 0.3</td>
</tr>
<tr>
<td>C4 serum level (mean ± S.D., g/L) (n = 146)</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>ESR at 1(^{st}) hour (mean ± S.D., mm)</td>
<td>27.8 ± 23.4</td>
</tr>
<tr>
<td>CRP (mean ± SD, mg/L (n = 114)</td>
<td>8.4 ± 10</td>
</tr>
<tr>
<td>No anti-SSA or anti-SSB antibodies</td>
<td>66 (37.3)</td>
</tr>
<tr>
<td>Anti-SSA antibody only</td>
<td>53 (29.9)</td>
</tr>
<tr>
<td>Anti-SSA and anti-SSB antibodies</td>
<td>58 (32.8)</td>
</tr>
<tr>
<td>Focus score ≥1 on labial salivary gland (n = 168)</td>
<td>153 (91.1)</td>
</tr>
</tbody>
</table>

Results are expressed as number, (%), unless specified.
CNS = central nervous system; RF = rheumatoid factor; ESR = erythrocyte sedimentation rate.
\(^1\) Bronchic involvement (n= 7), bronchiolar involvement (n= 6), interstitial disease (n= 6), alveolar disease (n =1)
\(^2\) Patients with lymphoma were excluded from serum \(\beta\)2m analysis.
Table 2. Values for relevant serum markers in patients with pSS according to the presence of anti-SSA or anti-SSB antibodies.

<table>
<thead>
<tr>
<th>Marker</th>
<th>No antibody</th>
<th>Anti-SSA only</th>
<th>Anti-SSA and anti-SSB</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLyS (mean ± S.D., ng/mL)</td>
<td>4.2 ± 6.8</td>
<td>6.6 ± 8.8</td>
<td>5.9 ± 6</td>
<td>0.05</td>
</tr>
<tr>
<td>Beta2m (mean ± S.D., mg/L)</td>
<td>1.5 ± 0.6</td>
<td>1.82 ± 0.9</td>
<td>2.43 ± 0.9</td>
<td>&lt; 10^-4</td>
</tr>
<tr>
<td>Gammaglobulin (mean ± S.D., g/L)</td>
<td>10.3 ± 0.9</td>
<td>13.9 ± 4.5</td>
<td>16.7 ± 7.4</td>
<td>&lt; 10^-4</td>
</tr>
<tr>
<td>IgG (mean ± S.D., g/L)</td>
<td>10.8 ± 4.5</td>
<td>15.1 ± 5.4</td>
<td>19.7 ± 7.1</td>
<td>&lt; 10^-4</td>
</tr>
<tr>
<td>IgA (mean ± S.D., g/L)</td>
<td>2.5 ± 1.2</td>
<td>3.2 ± 1.8</td>
<td>3.4 ± 1.3</td>
<td>0.008</td>
</tr>
<tr>
<td>IgM (mean ± S.D., g/L)</td>
<td>1.5 ± 1.3</td>
<td>1.3 ± 0.7</td>
<td>1.7 ± 1.1</td>
<td>0.24</td>
</tr>
<tr>
<td>RF (mean ± S.D., IU/mL)</td>
<td>52.6 ± 216.5</td>
<td>156.8 ± 257.6</td>
<td>234.8 ± 423.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Decreased C3 level (%)</td>
<td>11.5</td>
<td>6.3</td>
<td>11.5</td>
<td>0.74</td>
</tr>
<tr>
<td>Decreased C4 level (%)</td>
<td>5.8</td>
<td>25.6</td>
<td>35.2</td>
<td>0.001</td>
</tr>
<tr>
<td>ESR (mean ± S.D., mm)</td>
<td>18.8 ± 18.8</td>
<td>29 ± 26</td>
<td>39 ± 29</td>
<td>&lt; 10^-4</td>
</tr>
<tr>
<td>CRP (mean ± S.D., mg/L)</td>
<td>7.6 ± 8.4</td>
<td>6.2 ± 2.9</td>
<td>8.8 ± 7.6</td>
<td>0.41</td>
</tr>
</tbody>
</table>

RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.
A minimum sequential critical value of $P = 0.017$ was considered statistically significant according to the number of tests done.
Table 3. Univariate analysis of extraglandular involvement in patients with pSS.

<table>
<thead>
<tr>
<th>Extraglandular involvement</th>
<th>Present (n = 73)</th>
<th>Absent (n = 104)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± S.D., years)</td>
<td>56.2 ± 14.6</td>
<td>57.2 ± 12.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean disease duration (mean ± S.D., years)</td>
<td>12.1 ± 7</td>
<td>12.4 ± 7.1</td>
<td>0.75</td>
</tr>
<tr>
<td>Anti-SSA only (%)</td>
<td>28.8</td>
<td>30.8</td>
<td>0.29</td>
</tr>
<tr>
<td>Anti-SSA and anti-SSB (%)</td>
<td>43.8</td>
<td>25</td>
<td>0.004</td>
</tr>
<tr>
<td>BLyS (mean ± S.D., ng/mL)</td>
<td>6.1 ± 9.4</td>
<td>5 ± 5</td>
<td>0.39</td>
</tr>
<tr>
<td>Beta2m (mean ± S.D., mg/L)</td>
<td>2.2 ± 0.9</td>
<td>1.7 ± 0.8</td>
<td>&lt; 10^-4</td>
</tr>
<tr>
<td>Gammaglobulin (mean ± S.D., g/L)</td>
<td>13.5 ± 7.3</td>
<td>13.2 ± 5.9</td>
<td>0.8</td>
</tr>
<tr>
<td>IgG (mean ± S.D., g/L)</td>
<td>15.8 ± 6.7</td>
<td>14.5 ± 6.8</td>
<td>0.28</td>
</tr>
<tr>
<td>IgA (mean ± S.D., g/L)</td>
<td>3 ± 1.4</td>
<td>3 ± 1.5</td>
<td>0.26</td>
</tr>
<tr>
<td>IgM (mean ± S.D., g/L)</td>
<td>1.6 ± 1.2</td>
<td>1.5 ± 1</td>
<td>0.44</td>
</tr>
<tr>
<td>RF (mean ± S.D., IU/mL)</td>
<td>159.2 ± 293.1</td>
<td>135.8 ± 330.4</td>
<td>0.66</td>
</tr>
<tr>
<td>Decreased C3 level (%)</td>
<td>13.8</td>
<td>12.3</td>
<td>0.99</td>
</tr>
<tr>
<td>Decreased C4 level (%)</td>
<td>29.3</td>
<td>17.1</td>
<td>0.12</td>
</tr>
<tr>
<td>ESR (mean ± S.D., mm)</td>
<td>30.6 ± 26.2</td>
<td>27.2 ± 25.9</td>
<td>0.42</td>
</tr>
<tr>
<td>CRP (mean ± S.D., mg/L)</td>
<td>10.5 ± 10.9</td>
<td>6.1 ± 2.8</td>
<td>0.003</td>
</tr>
</tbody>
</table>

A minimum sequential critical value of P = 0.0045 was considered statistically significant according to the number of tests done.
Figure 1. Mean serum β2m and BLyS level according to the presence of anti-SSA/SSB antibodies.
Figure 2. Beta2-microglobulin levels in patients with extraglandular involvement and in patients with only glandular involvement.

Bars represent mean values.
Figure 3. Mean serum beta2m value in 154 patients with pSS according to the presence of extraglandular involvement and anti-SSA/SSB antibodies.

Serum β2m (mg/L)
Serum B lymphocyte stimulator and beta2-microglobulin correlation with autoantibody secretion and systemic involvement in primary Sjögren's syndrome

Jacques-Eric Gottenberg, Marc Busson, Julien Cohen-Solal, Frédéric Lavie, Karim Abbed, Robert P Kimberly, Jean Sibilia and Xavier Mariette

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