The relationship between the presence of autoantibodies, indicators of local and systemic inflammation, the serum concentration of B-cell activating factor (BAFF) and the intensity of salivary gland infiltration in patients with primary Sjögren’s syndrome – a preliminary study

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Abstract

Objectives: The aim of this study was to find markers related to activation of B cells, which show a correlation with the systemic inflammation markers – erythrocyte sedimentation rate and C-reactive protein and with the intensity of in situ inflammation.

Material and methods: Forty-one primary Sjögren’s syndrome (pSS) patients (33 female, 8 male) of the mean age 52.9 ±15 years were included. A group of 20 healthy volunteers was applied as a control. Erythrocyte sedimentation rate (ESR), concentration of gamma-globulins, C-reactive protein (CRP) and rheumatoid factor (RF) were measured by routine laboratory tests. Titres of antinuclear antibodies (ANAs) were determined by the indirect immunofluorescence method, while anti-SS-A/SS-B antibodies were detected by both the dot-blot method and an enzyme immunoassay. The concentrations of BAFF in sera were measured by sandwich ELISA. Biopsies of minor salivary glands were taken and the focus score (FS) was calculated. Correlations between quantitative variables were assessed using the Spearman correlation coefficient (r).

Results: Serum concentrations of BAFF was significantly higher in the pSS patients than in the control group. The study revealed a statistically significant correlation between ANAs titre and the FS (r = 0.421). Anti-SS-A/Ro and anti-SS-B/La antibodies positively correlated with ESR. There was also a positive correlation between the gamma globulin level and the titres of all tested autoantibodies.

Conclusions: The positive correlation between ANAs and FS confirms the importance of these autoantibodies in the local inflammatory process. The positive correlation between anti-SS-A/SS-B antibodies and ESR suggests involvement of these antibodies in generalization of the inflammatory response. In the pSS group serum concentrations of BAFF were statistically significantly higher than healthy volunteers. All presented results confirm the role of activity of B cells in the course of pSS.

Key words: Sjögren’s syndrome, autoantibodies, B-cell activating factor.

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Introduction

Primary Sjögren’s syndrome (pSS) is a chronic autoimmune disease characterized by gradual irreversible damage and functional impairment of the exocrine glands, the lacrimal and salivary glands in particular. In the course of pSS, the involvement of internal organs, especially of the lungs, kidneys, peripheral and central nervous system and of blood vessels may also occur. It is estimated that pSS affects from 0.1% to even 3.0% of the general population and is undoubtedly more frequently diagnosed in women than in men (the female/male ratio is 9:1) [1, 2].

The primary Sjögren’s syndrome pathogenesis is still unclear, and therefore it is a subject of intensive research. It is believed that in susceptible patients with a genetic predisposition to pSS (i.e. with the presence of HLA-B8, HLA-Dw3, HLA-DR3 and HLA-DRw52 genes), and with the interferons (IFN) signature (the up-regulation of genes induced by type I interferons), the epithelial damage caused by environmental factors results in the release of autoantigens. This starts the cascade of autoimmune processes leading to pSS development [3, 4].

Among the environmental factors responsible for pSS development, special attention is paid to viral infections, including those with Epstein-Barr virus (EBV), human T-cell lymphotropic virus type-1 (HTLV-1), cytomegalovirus (CMV), human retrovirus 5 (HRV-5), human intracisternal A-type retrovirus (HIAP) and hepatitis C virus (HCV) [5]. The involvement of bacterial infections, e.g. Helicobacter pylori [6] or Chlamydia psittaci [7], and of UV radiation has also been proposed. In addition, hormonal disorders leading to oestrogen deficiency and dysfunction of the hypothalamic–pituitary–gonadal (HPG) axis are considered as pSS co-initiators [8, 9]. The activation and maturation of B lymphocytes seems to play a key role in pSS development. The diagnosis of pSS is confirmed when two of the three above-described conditions are fulfilled [15–18].

The overproduction of BAFF in pSS is thought to lead to the hyperactivity of B cells, which in turn causes the release of autoantibodies, primarily against ribonucleoproteins (anti-SS-A/Ro and anti-SS-B/La). In the salivary glands of patients with pSS, an increased number of memory B cells specific to these self ribonucleoproteins was observed [12]. Apart from the effects of the production of autoantibodies, human salivary gland (HSG) B cells can also cause cell damage through direct influence, as demonstrated by Varin and colleagues [13]. They proved that HSG B cells can, by causing the translocation of protein kinase C delta (PKC δ) to the nucleus in epithelial cells, induce apoptosis of these cells.

In the infiltrates of exocrine glands, characteristic for Sjögren’s syndrome, the subpopulation of CD4+ T lymphocytes predominates initially, but later, in more advanced stages of the disease, there is an increase of B cell number and these cells may form GC-like structures. Due to the persistent stimulation of B-cells, pSS is associated with a more than 40-fold higher risk of developing lymphoma, as compared to the healthy population. Therefore, the search for early markers of diagnosis of lymphomas and the factors triggering their development should be of particular importance in pSS.

The clinical symptoms of pSS include a variety of general complaints such as chronic fatigue, weakness, arthralgia and myalgia, as well as more specific symptoms such as the feeling of eye and mouth dryness resulting from inflammation and immune-mediated destruction of the lacrimal and salivary glands. The abnormal secretion may affect all the mucous membranes, e.g. of the urogenital tract, leading to kidney disorders with the deterioration of glomerular filtration rate and tubule-interstitial changes. The inflammation and the autoimmune process may lead to changes in internal organs – especially in the lungs – with the development of interstitial tissue changes and fibrosis in their final stages, and to vascular inflammation and changes in the peripheral nerves and central nervous system [14].

Diagnosis is usually fairly late, as the course of the disease yields unspecific symptoms. The current diagnostic criteria focus on: (1) confirming the eye dryness, known as keratoconjunctivitis sicca (KCS), demonstrated by the ocular staining score method (OSS); (2) immunological changes, such as the presence of antibodies specific to SS-A, SS-B or nuclear antigens (ANAs), in titres equal to or greater than 1 : 320, with concomitant existence of rheumatoid factor (RF) of the IgM class; (3) typical infiltrates in the salivary glands evaluated numerically as the focus score (FS). The diagnosis of pSS is confirmed when two of the three above-described conditions are fulfilled [15–18].
The main objective of our study was to find markers related to the activation of B cells, such as B cell activating factor (BAFF), antinuclear antibodies (ANAs) or specific to pSS autoantibodies (SS-A/Ro, SS-B/La), which show a correlation with the systemic inflammation markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and with the intensity of in situ inflammation, i.e. lymphocyte infiltration in minor salivary glands – focus score (FS).

Material and methods

Our group included 41 patients (80% female and 20% male) with established diagnosis of pSS. The control group consisted of 20 healthy volunteers (15 women and 5 men) of the mean age 45 years (min. 20, max. 71). The study was approved by the Ethics Committee of National Institute of Geriatrics, Rheumatology and Rehabilitation, and signed informed consent forms were obtained from patients. Characteristics of the patient group are shown in Table I.

In the course of diagnostics basic laboratory tests were performed, including establishing inflammatory parameters such as ESR and serum concentration of CRP (range 0–10 mg/l). Moreover, the concentrations of gamma globulins (g/dl) and of rheumatoid factor (RF) of IgM class (normal range < 34 IU/ml) were measured in sera, using routine laboratory tests. The titres and the patterns that the antinuclear autoantibodies make were determined by the indirect immunofluorescence (IF) method using slides with HEp2 (ANA Hep-2) as an antigen, while anti-Ro/SSA, and anti-La/SSB antibodies were detected by both the dot-blot and an enzyme immunoassay (EliA IgG test Unicap 100 Phadia GmbH). The first method allowed semiquantitative evaluation of antibodies based on the strength of their reaction with a specific antigen, while in the second assay values > 10 U/ml were considered to be positive according to the reference range.

To confirm the eye dryness and keratoconjunctivitis sicca (KKS), Schirmer’s test (score of less than 5 mm/5’) and the ocular staining score (OSS) (score ≥ 3 points) using lissamine green and fluorescein staining were performed, respectively. The concentrations of BAFF in serum samples were measured by sandwich enzyme-linked immunosorbent assay (ELISA), using a commercially available kit (Quantikine ELISA Human BAFF/BlyS/TNFSF13B immunoassay, R&D Systems, Minneapolis, MN, USA). Focal sialadenitis was confirmed in minor salivary gland biopsy, the severity of which was determined by the focus score (FS) – the number of mononuclear cell infiltrates containing at least 50 inflammatory cells in a 4 mm² glandular section. A score > 1 was considered positive. Statistical analysis was performed using the STATISTICA version 10.0 software. The distribution of continuous variables was assessed using the Shapiro-Wilk test. All variables apart from “age” were not normally distributed. Continuous variables are shown as the median and interquartile range, while categorical variables are shown as the number and percentage. Correlations between quantitative variables were assessed with the Spearman correlation coefficient. Results at p < 0.05 were considered statistically significant.

Results

In patients with pSS there were no significant differences between women and men in terms of OSS, FS and ESR values and CRP and BAFF concentrations. The sole difference between these groups was for the presence of anti-SS-B/La antibodies, which occurred only in 23 (56.1%) female patients. Comparison of all variables according to gender in patients with pSS is shown in Table II.

In the pSS group 4 patients (9.75%) presented pulmonary involvement with interstitial changes, 2 patients had cryoglobulins (4.87%) and 4 (9.75%) patients had anti-mitochondrial antibodies – M2 (anti-AMA-M2 antibodies) without clinical symptoms of primary biliary cir-

Table I. Characteristics of the study group with pSS

| Parameter                  | N  | Mean SD | Median | Min | Max | Q-1 | Q-3 |
|----------------------------|----|---------|--------|-----|-----|-----|-----|
| Female                     |    |         |        |     |     |     |     |
| age                        | 33 | 52.3    | 16.6   | 52  | 23  | 86  | 41  |
| time since diagnosis*      | 33 | 1.85    | 2.55   | 1   | 0   | 9   | 0   |
| Men                        |    |         |        |     |     |     |     |
| age                        | 8  | 55.4    | 10.9   | 55  | 36  | 72  | 50  |
| time since diagnosis*      | 8  | 1.38    | 1.06   | 1   | 0   | 3   | 1   |

*Time of diagnosis – is expressed in years period from diagnosis to the time of the research. This time it is not unequivocal from the real onset of the disease
rhosis (PBC). In 2 cases diagnosis of marginal zone lymphoma type MALT was confirmed. Serum BAFF levels in the pSS study group were significantly higher than in the control group of healthy volunteers (Fig. 1).

In the pSS patient group there was a weak positive correlation ($r = 0.311$, $p$-value < 0.05) between the time since diagnosis and the presence of anti-SS-A autoantibodies, suggesting that these antibodies are synthesized in the late stage of disease. No such association was found either for other tested autoantibodies or BAFF serum concentrations (data not shown).

ANA antibodies were found in 87.8% of patients with pSS in a significant titre over 1 : 320, and five patients (12.2%) had low titres of ANAs, among which anti-SS-A antibodies were present. SS-A/Ro specific antibodies were found in 35 pSS patients (85.36%) and correlated with higher ESR and higher gamma globulin levels, as well as presence of SS-B/La specific antibodies. The above-described positive correlations were statistically significant ($p$-value < 0.05). Anti-SS-A antibodies were found more frequently than anti-SS-B antibodies (85% and 56% respectively). Anti-SS-A and anti-SS-B antibodies statistically significantly correlated with ESR ($r = 0.513$; $r = 0.540$ respectively) (Fig. 2) but did not correlate with CRP level.

A statistically significant correlation between gamma globulins level and presence of SS-A ($r = 0.398$, $p$-value < 0.05), anti-SS-B ($r = 0.427$), RF ($r = 0.481$), ANAs ($r = 0.498$) and ESR ($r = 0.399$) was found, as expected. The correlation between gamma globulins and ESR is shown in Figure 3.

Importantly, the FS was positively correlated with the titre of ANAs ($r = 0.421$, $p$-value < 0.05) only (Fig. 4), implying involvement of these antibodies in the local inflammatory response. Unexpectedly, however, the FS correlated negatively with CRP ($r = -0.357$, $p$-value < 0.05) (not shown). The latest findings suggest the lack of simple dependence between the levels of local and systemic inflammation.

**Discussion**

Primary Sjögren’s syndrome is an autoimmune disease of diverse symptoms and of variable clinical picture. It is known that the dryness symptoms are not always severe enough for the patient to seek medical advice, and a quite mild course of the disease may cause many years of delay in the pSS diagnosis. Often, the increasing

| Table II. Comparison of clinical and laboratory data in women and men with pSS |
| --- |
| **Female** | **Men** | **p** |
| **N** | **median** | **N** | **median** | **p** |
| Eye dryness | OSS | 32 | 4.8 | 8 | 3.8 | 0.454235 |
| Schirmer’s test | 33 | 4.0 | 8 | 4.3 | 0.961424 |
| Infiltration of salivary glands | FS | 32 | 2.0 | 8 | 1.0 | 0.606870 |
| Autoantibodies | SS-A/Ro* | 33 | 3.0 | 8 | 3.0 | 0.322279 |
| SS-B/La* | 33 | 1.0 | 8 | 0.0 | 0.045042 |
| ANA titre | 33 | 1280.0 | 8 | 1280.0 | 0.662957 |
| RF (IU/ml) | 32 | 68.0 | 8 | 20.0 | 0.174258 |
| ESR (mm/h) | 33 | 23.0 | 8 | 26.0 | 0.859210 |
| CRP (mg/l) | 33 | 7.0 | 8 | 18.5 | 0.072558 |
| Gamma globulins (g/dl) | 32 | 1.5 | 8 | 1.3 | 0.069917 |
| BAFF (pg/ml) | 31 | 522.9 | 7 | 527.6 | 0.740261 |

*Semiquantitative test result from negative to strongly positive reaction (from 0 to 4)*

![Fig. 1. BAFF serum concentration in pSS patients compared with control group.](image-url)
Autoantibodies, inflammation, B-cell activating factor in primary Sjögren’s syndrome

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Dryness is the only symptom arising from the affected and dysfunctional organs, particularly from the exocrine glands, prompting further clinical investigation. The first obvious step in laboratory diagnosis of autoimmune diseases, including pSS, is an attempt to detect antinuclear antibodies (ANAs), usually by IF. Moreover, particular attention has to be paid to the titre in which ANAs are detected, as they may be present, in a low titre, in healthy individuals or in relatives of patients with autoimmune diseases. In the study group most patients had a high ANA titre. A positive correlation between the titre of ANAs and FS may confirm their importance in the local inflammatory process and B cell activation. It is known that ANA presence can precede the development of autoantibodies recognizing extractable nuclear autoantigens (ENA), that is SS-A/Ro and SS-B/La specific antibodies, which are characteristic for pSS [19, 20]. It was argued that ANA in a titre higher than 1 : 320, concomitant with the presence of RF, should be included in the new diagnostic criteria for pSS [6, 15].

Theander et al. tested serum samples obtained from 117 individuals before diagnosis of pSS [21]. Sera came from the Malmö pSS registry and 3 Swedish healthcare biobanks. They found that most often the occurrence of ANAs was followed by RF, anti-Ro60/SSA, anti-Ro52/SSA, and anti-La/SSB antibodies and concluded that these antibodies could precede the development of clinical symptoms of pSS for 18–20 years. However, in our study group, both ANA and anti-SS-A antibodies were present in the majority of patients despite the relatively short time that has passed since diagnosis (Table I). This may be evidence of the longer course of the disease than assumed. This is confirmed by the fact that in study group patients with pulmonary fibrosis or active interstitial changes, polynuropathy or diagnosis of marginal zone lymphoma (2 patients), all the symptoms confirming involvement of internal organs were present at the time

**Fig. 2.** Correlations between anti-SS-A/Ro, anti-SS-B/La and ESR in pSS study group.

**Fig. 3.** Correlation between gamma globulins and ESR in pSS patients.

**Fig. 4.** Positive correlation between serum ANA titre and FS.
of pSS diagnosis. It is known that also SS-A specific antibodies are associated with pSS and sicca symptoms. Theander et al. have shown that anti-SS-B/La antibodies were strongly associated with anti-SS-A/Ro60 antibodies, but are less frequent and usually did not occur separately [21]. This is confirmed by our results, where anti-SS-B antibodies were found in 56.1% of patients, and concomitantly with anti-SS-A/Ro antibodies. Moreover, we also observed that anti-SS-A antibodies were present in all cases of organ involvement.

The aim of this study was to search for a relationship between B cell activation-associated factors, i.e. BAFF serum levels, presence of autoantibodies, and the intensity of systemic or local inflammation, evaluated by ESR and CRP or FS, respectively. Our results revealed higher BAFF concentration in sera of pSS patients compared to the control group – a finding that is consistent with others’ observations [22]. However, in contrast to the reports describing a positive correlation between serum BAFF concentration and the titre of several autoantibodies, including RF, as well as the inflammation-dependent fluctuation of systemic BAFF concentration [23, 24], we did not demonstrate such correlations. This discrepancy may be explained by the fact that in pSS autoreactive B cells are activated in target tissues (such as exocrine glands). Therefore a stronger relationship of autoantibody titres and/or inflammation intensity with local rather than systemic BAFF concentration should be expected. Indeed, other researchers have found higher concentrations of BAFF and autoantibodies in tears or saliva than in sera of pSS patients [25–27]. In our study the highest serum concentrations of BAFF were observed in patients with active interstitial changes in the lungs, polyneuropathy, with a diagnosed lymphoma and a patient with a large index of B cell proliferation in the salivary glands (not shown), suggesting the contribution of BAFF to a more severe clinical picture of pSS.

In the present study we found that ESR positively correlated with serum gamma globulin concentration and the titres of anti-SS-A/Ro and anti-SS-B/La antibodies. It should be underlined that ESR reflects the occurrence of physico-chemical phenomena, dependent on red blood cell rouleau formation and agglomeration of erythrocytes after attachment of various proteins, which include e.g. globulins, fibrinogen and haptoglobin. It is known that different acute phase proteins affect the outcome of the ESR, which proves its universal ESR significance as a marker of inflammation [28]. However, CRP is a sensitive, but nonspecific, acute-phase response marker. It is a protein which belongs to the pentraxin family of calcium-dependent ligand-binding plasma proteins. It is produced by the hepatocytes and its secretion mainly depends on the liver function. The increase of the concentration of CRP occurs rapidly within the first six hours after triggering activation of an inflammatory response (e.g. by bacterial infection, tissue damage) and rapidly decreases after the start of anti-inflammatory treatment. However, in autoimmune diseases, such as pSS, ESR may be a better indicator of the local and generalized chronic inflammation caused by tissue injury and release of autoantigens as well as by acute phase proteins other than CRP. In addition, in pSS patients there is an increased level of type 1 interferons that inhibit production of CRP in hepatocytes [29, 30].

The above phenomenon can explain the demonstrated weak negative correlation between inflammatory changes in minor salivary glands (FS) and CRP, observed in our study. Interestingly, FS positively correlated with ANAs but did not correlate with anti-SS-A/SS-B antibodies. This result may indicate that ANAs tend to be associated with local and anti-SS-A/SS-B antibodies with generalized inflammation.

Conclusions

The positive correlation between ANAs and FS found in our study seems to confirm the importance of these autoantibodies in the local inflammatory process in pSS patients.

On the other hand, the positive correlation between anti-SS-A/SS-B antibodies and ESR suggests implications of these antibodies in generalization of the inflammatory response.

In the tested group of pSS patients, serum concentrations of BAFF were statistically significantly higher than healthy volunteers, but correlated neither with the presence of autoantibodies nor intensity of inflammation. However, higher BAFF serum levels were observed in pSS patients with the involvement of internal organs, suggesting contribution of these cytokine to severity of the disease.

All our observations confirm the the role of B cells activity in the pathogenesis and course of pSS.
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