Original paper

Reumatologia 2015; 53, 6: 321–327
DOI: 10.5114/reum.2015.57638

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

Maria Maślińska[1], Ewa Kontny[2], Brygida Kwiatkowska[1]

[1]Early Arthritis Clinic, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland
[2]Department of Pathophysiology and Immunology, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland

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.

Address for correspondence:
Maria Maślińska, Early Arthritis Clinic, National Institute of Geriatrics, Rheumatology and Rehabilitation, Spartańska 1, 02-637 Warsaw, Poland, e-mail: maslinskam@gmail.com
Submitted: 31.12.2015; **Accepted:** 19.01.2016

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 pathogenesis. B cell activation is supported by reactivity of the innate immune cells, i.e. plasmacytoid dendritic cells (pDCs), to the toll-like receptor (TLR) ligands, especially nucleic acids recognized by TLR-3, TLR-7 and TLR-9. Activated pDCs produce interferons, which strongly stimulate secretion of B cell activating factor (BAFF). BAFF belongs to the tumour necrosis factor ligand superfamily and is a major stimulator of B cell maturation and differentiation. In addition, BAFF supports differentiation of T helper (Th) cells into the type 1 (Th1) subset producing type II interferon γ (IFN-γ). B cell activation is triggered by B cell receptor (BCR)-mediated antigen recognition and is initiated in the germinal centres (GC) of secondary lymphoid organs [10]. However, it may also be an antigen-independent process, supported directly by BAFF stimulation in peripheral lymphoid organs, mainly in the splenic marginal zone [11].

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 in their work [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 mm^2 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	60
time since diagnosis*	33	1.85	2.55	1	0	9	0	3
Men								
age	8	55.4	10.9	55	36	72	50	62
time since diagnosis*	8	1.38	1.06	1	0	3	1	2

**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*

Table II. Comparison of clinical and laboratory data in women and men with pSS

		Female		Men		*p*
		N	median	*N*	median	
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
Systemic inflammation	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

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

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.

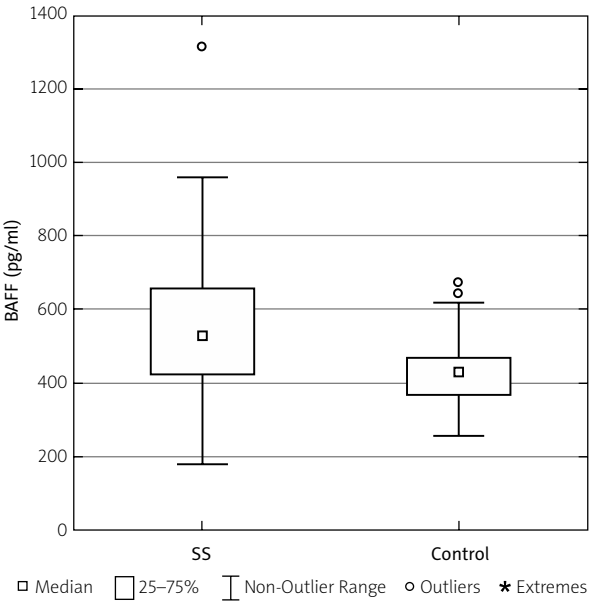

Fig. 1. BAFF serum concentration in pSS patients compared with control group.

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

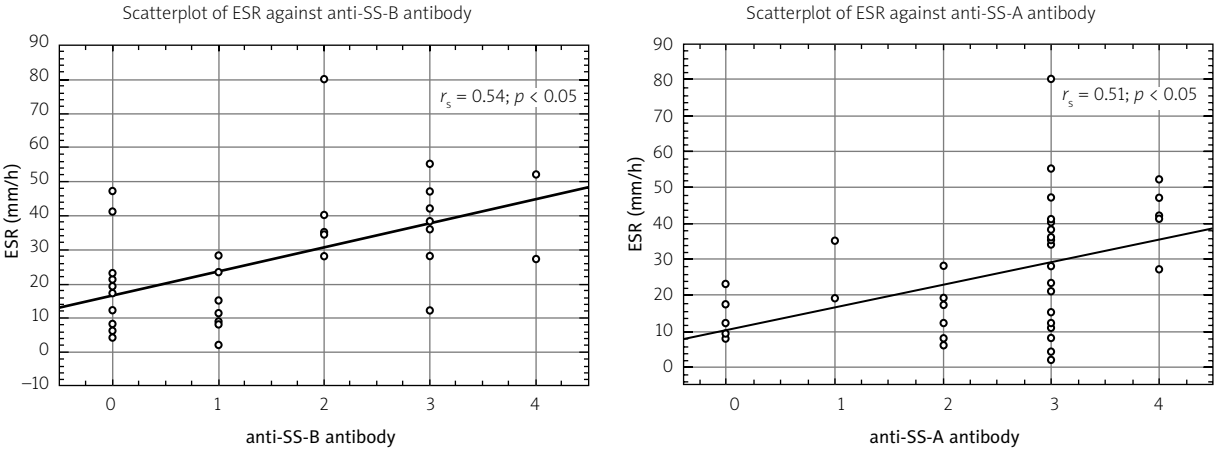

Fig. 2. Correlations between anti-SS-A/Ro, anti-SS-B/La and ESR in pSS study group.

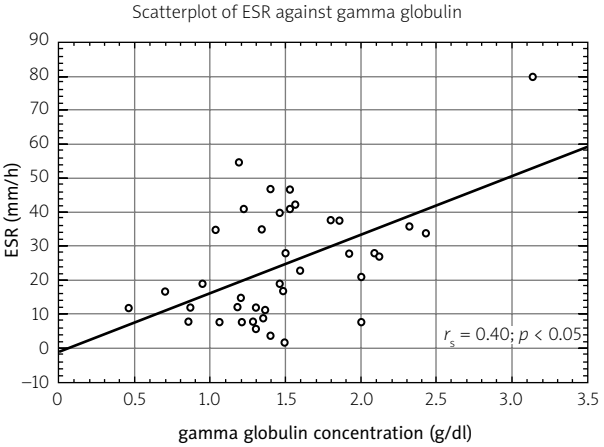

Fig. 3. Correlation between gamma globulins and ESR in pSS patients.

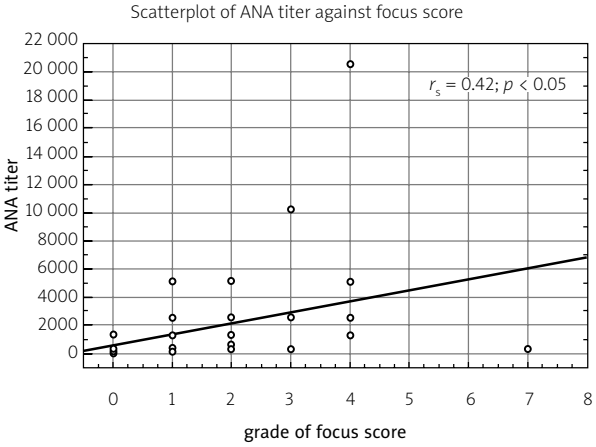

Fig. 4. Positive correlation between serum ANA titre and FS.

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 Malmo 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, polyneuropathy or diagnosis of marginal zone lymphoma (2 patients), all the symptoms confirming involvement of internal organs were present at the time

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 depends mainly 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.

The authors declare no conflict of interest.

Financing of the work – research grant NCN 2012/05/N/NZ5/02838.

References

1. Alamanos Y, Tsifetaki N, Voulgari PV, et al. Epidemiology of primary Sjögren's syndrome in north-west Greece, 1982–2003. Rheumatol Oxf Engl 2006; 45: 187-191.
2. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. Clin Epidemiol 2014; 6: 247-255.

3. Kallenberg CGM, Vissink A, Frans GM, et al. What have we learned from clinical trials in primary Sjögren's syndrome about pathogenesis? Arthritis Res Ther 2011; 13: 205.
4. Maślińska M, Przygodzka M, Kwiatkowska B, Sikorska-Siudek K. Sjögren's syndrome: still not fully understood disease. Rheumatol Int 2015; 35: 233-241.
5. Igoe A, Scofield RH. Autoimmunity and infection in Sjögren's syndrome. Curr Opin Rheumatol 2013; 25: 480-487.
6. Radić M. Role of Helicobacter pylori infection in autoimmune systemic rheumatic diseases. World J Gastroenterol 2014; 20: 12839-12846.
7. Fabris M, Dolcetti R, Pasini E, et al. High prevalence of Chlamydophila psittaci subclinical infection in Italian patients with Sjögren's syndrome and parotid gland marginal zone B-cell lymphoma of MALT-type. Clin Exp Rheumatol 2014; 32: 61-65.
8. Johnson EO, Skopouli FN, Moutsopoulos HM. Neuroendocrine manifestations in Sjögren's syndrome. Rheum Dis Clin North Am 2000; 26: 927-949.
9. Tzioufas AG, Tsonis J, Moutsopoulos HM. Neuroendocrine dysfunction in Sjogren's syndrome. Neuroimmunomodulation 2008; 15: 37-45.
10. Tincani A, Andreoli L, Cavazzana I, et al. Novel aspects of Sjögren's syndrome in 2012. BMC Medicine 2013; 11: 93.
11. Groom J, Kalled SL, Cutler AH, et al. Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjögren's syndrome. J Clin Invest 2002; 109: 59-68.
12. Aqrawi LA, Skarstein K, Bredholt G, et al. Autoantigen-specific memory B cells in primary Sjögren's syndrome. Scand J Immunol 2012; 75: 61-68.
13. Varin MM, Guerrier T, Devauchelle-Pensec V, et al. In Sjögren's syndrome, B lymphocytes induce epithelial cells of salivary glands into apoptosis through protein kinase C delta activation. Autoimmun Res 2012; 11: 252-258.
14. Smoleńska Ż, Bilińska M, Kujawska-Danecka H, Zdrojewski Z. Obwodowy układ nerwowy w pierwotnym zespole Sjögrena. Reumatologia 2013; 51: 202-209.
15. Shiboski SC, Shiboski CH, Criswell L, et al. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken) 2012; 64: 475-487.
16. Rasmussen A, Ice JA, Li H, et al. Comparison of the American-European Consensus Group Sjogren's syndrome classification criteria to newly proposed American College of Rheumatology criteria in a large, carefully characterised sicca cohort. Ann Rheum Dis 2014; 73: 31-38.
17. Rose-Nussbaumer J, Lietman TM, Shiboski CH, et al. Sjögren's International Collaborative Clinical Alliance Research Groups. Inter-grader Agreement of the Ocular Staining Score in the Sjögren's International Clinical Collaborative Alliance (SICCA) Registry. Am J Ophthalmol 2015; 160: 1150-1153.e3.
18. Whitcher JP, Shiboski CH, Shiboski SC, et al. Sjögren's International Collaborative Clinical Alliance Research Groups. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. Am J Ophthalmol 2010; 149: 405-415.
19. Sotoa ME, Hernández-Becerrila N, Perez-Chineya AC, et al. Predictive value of antinuclear antibodies in autoimmune diseases classified by clinical criteria: Analytical study in a specialized health institute, one year follow-up. Res Immunol 2015; 5: 13-22.
20. Theander E, Jonsson R, Sjöström B, et al. Prediction of Sjögren's Syndrome Years Before Diagnosis and Identification of Patients With Early Onset and Severe Disease Course by Autoantibody Profiling. Arthritis Rheum 2015; 67: 2427-2436.
21. Yoshimi R, Ueda A, Ozato K, Ishigatsubo Y. Clinical and pathological roles of Ro/SSA autoantibody system. Clin Dev Immunol 2012; 2012: 606195.
22. Hamza N, Bos NA, Cees GM. Kallenberg CG. B-cell populations and sub-populations in Sjögren's syndrome. Presse Méd 2012; 41: 475-483.
23. Huang Y, Cheng Q, Jiang Ch, et al. The Immune Factors Involved in the Pathogenesis, Diagnosis and Treatment of Sjogren's Syndrome. Clin Dev Immunol 2013; 2013: 160491.
24. Mariette X, Roux S, Zhang J, et al. The level of BLyS (BAFF) correlates with the titre of autoantibodies in human Sjögren's syndrome. Ann Rheum Dis 2003; 62: 168-171.
25. Mumcu G, Biçakçigil M, Yilmaz N, et al. Salivary and serum B-cell activating factor (BAFF) levels after hydroxychloroquine treatment in primary Sjögren's syndrome. Oral Health Prev Dent 2013; 11: 229-234.
26. Ittah M, Miceli-Richard C, Gottenberg EJ, et al. B cell-activating factor of the tumor necrosis factor family (BAFF) is expressed under stimulation by interferon in salivary gland epithelial cells in primary Sjögren's syndrome. Arthritis Res Ther 2006; 8: R51.
27. Daridon C, Devauchelle V, Hutin P, et al. Aberrant expression of BAFF by B lymphocytes infiltrating the salivary glands of patients with primary Sjögren's syndrome. Arthritis Rheum 2007; 56: 1134-1144.
28. Harrison M. Erythrocyte sedimentation rate and C-reactive protein. Aust Presc 2015; 38: 93-94.
29. Enocsson H, Sjöwall C, Skogh T, et al. Interferon-alpha mediates suppression of C-reactive protein: explanation for muted C-reactive protein response in lupus flares? Arthritis Rheum 2009; 60: 3755-3760.
30. Yaoa Y, Liua Z, Jallala B, et al. Type I interferons in Sjögren's syndrome. Autoimmun Rev 2013; 12: 558-566.