Original Paper

NeuroImmunoModulation

Neuroimmunomodulation 2013;20:79–86
DOI: 10.1159/000345177

Received: July 30, 2012
Accepted after revision: October 12, 2012
Published online: December 12, 2012

Neuroimmune Interactions in Sjögren's Syndrome: Relationship of Exocrine Gland Dysfunction with Autoantibodies to Muscarinic Acetylcholine Receptor-3 and Mental Health Status Parameters

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Key Words
Sjögren's syndrome · Antimuscarinic acetylcholine receptor-3 antibody · Secretory dysfunction · Systemic lupus erythematosus · Rheumatoid arthritis · ELISA · Mental health status

Abstract
Objectives: Antimuscarinic acetylcholine receptor-3 (m3AChR) autoantibodies have been described in primary Sjögren's syndrome (pSS). The aim of this study was to compare various methods for their detection and to assess the contributions of anti-m3AChR and other immunological and psychosocial factors to the pathomechanism of secondary SS (sSS). ***Methods:*** Sixty-five rheumatoid arthritis (RA) patients, 103 systemic lupus erythematosus (SLE) patients, 76 pSS patients and 50 controls were compared. Three immunodominant epitopes of m3AChR were synthesized and used in ELISA. Two extracellular epitopes were also prepared in fusion with glutathione-S-transferase and one in conjugation with bovine serum albumin. Mental health status was assessed with the 36-item Short-Form Health Survey and Functional Assessment of Chronic Illness Therapy fatigue scale. Correlations were evaluated between glandular function and anti-m3AChR positivities and specificities, features of SLE and RA, and mental health parameters. ***Results:*** Fourteen RA and 27 SLE patients had sSS. The autoantibody levels to all epitopes of m3AChR were significantly higher in pSS and SLE patients than in the controls. The fusion protein forms discriminated RA from pSS and SLE; furthermore, the YNIP fusion protein also distinguished pSS from SLE. The prevalence and the mean levels of all autoantibodies did not differ statistically between sicca and non-sicca SLE or RA patients. Glandular dysfunction correlated with higher age in SLE and RA and an impaired health-related quality of life in SLE. ***Conclusions:*** The second and third extracellular loops of m3AChR are antigenic in pSS. Immunoassays with antigens as fusion peptides demonstrate the best performance. Sicca SLE patients have worse mental health status. Anti-m3AChR antibodies represent a peculiar example of neuroimmune interactions.

Introduction

Sjögren's syndrome (SS) is an autoimmune disease with multisystem involvement. It is characterized by chronic inflammation of the exocrine glands, particularly the lachrymal and salivary glands, and a wide vari-

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ety of further immune-mediated organ involvement [1]. In the affected secretory tissues, focal lymphocytic infiltration can be observed. The fundamental symptoms are decreased tear and saliva production, which lead to keratoconjunctivitis sicca and xerostomia, respectively. SS often presents as a secondary condition, when it overlaps with various systemic autoimmune diseases; in this case it is termed secondary SS (sSS), in contrast with primary SS (pSS) as a separate entity.

It has previously been observed that the extent of salivary gland damage caused by lymphocytic infiltration is not proportional to the salivary flow impairment [2]. This indicates the role of other underlying mechanisms, such as the functional inhibition of fluid secretion. It is well known that the autonomic nervous system modulates saliva production through the functionally dominant subtype 3 muscarinic acetylcholine receptor (m3AChR) on acinar cells. An immune-mediated mechanism has been hypothesized to alter the glandular function in the target organ by means of autoantibodies which block the postsynaptic muscarinic receptors [3–5].

Indeed, we and several other groups have demonstrated the presence of circulating autoantibodies directed against the m3AChR in patients with pSS [6–12], and their binding to muscarinic receptors on human salivary gland acinar cells has also been confirmed [13]. Although several animal models and human data support the importance of anti-m3AChR antibodies in pSS, these data mostly originate from functional assays [14–17], and a validated immunodiagnostic test is still not available. The exact epitope specificity of anti-m3AChR has also remained unidentified, which hampers their detection. Moreover, the prevalence and pathogenetic role of anti-m3AChR antibodies in sSS have not been systematically examined.

The pathogenesis of sSS is heterogeneous and not completely clear. The histological alterations in the salivary glands of sSS overlapping various systemic autoimmune diseases are variable, as is the clinical picture [18–20]. Sicca symptoms are common not only in definite SS, but also in fibromyalgia, chronic fatigue syndrome and various other noninflammatory chronic diseases [21, 22]. In these conditions, chronic stress and an altered neuroendocrine homeostasis have been hypothesized as causes of the exocrine insufficiency, modulated by an autonomic nervous system dysfunction.

The present study had two major objectives. First, we wished to determine the antigenic epitope of m3AChR which interacts with autoantibodies from pSS, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) patients and also to assess the presence and clinical correlates of the receptor-specific autoantibodies in the studied disease groups. Accordingly, we attempted to develop an appropriate immunodiagnostic method for the detection of these antibodies. As sSS is an entity with a complex pathogenesis, our second objective was to address the relative contributions of immunological factors, and in particular anti-m3AChR antibodies, and mental health status to the elicitation of the sicca complex arising in pSS, SLE and RA.

Patients and Methods

Patients

Data on 65 patients with RA and 103 with SLE were compared with those on 76 pSS patients and 50 healthy controls. The disease groups were classified according to the appropriate international criteria, namely the 2010 RA criteria of the American College of Rheumatology/European League against Rheumatism [23], the modified 1982 SLE criteria of the American College of Rheumatology [24] and the 2002 American-European Consensus Criteria (AECC) for SS [25]. The mean age of the RA patients (11 male and 54 female) was 58 years (22–82); that of the SLE patients (9 male and 94 female) was 48 years (25–74), and that of the pSS patients (2 male and 74 female) was 56 years (30–76).

All the RA and SLE patients were systematically evaluated with regard to the presence of a sicca complex; following the AECC for SS, subjective sicca complaints were regarded as present if at least 1 of the 3 questions included in these criteria was answered positively, while an objective exocrine deficiency was evaluated by means of the Schirmer test and the measurement of unstimulated whole saliva production. Sicca complex was established if subjective sicca symptoms of both the eye and the mouth were associated with at least 1 positive objective test on at least 2 separate occasions. Determination of the presence of sSS as classified by the AECC was also attempted, but since labial salivary gland biopsy was not performed in several patients for ethical reasons, these assessments are available for only a proportion of the patients.

The protocol was approved by the Human Investigation Review Board of the University of Szeged, Faculty of Medicine, and the study was performed in accordance with the principles of the Declaration of Helsinki. A variety of disease-specific clinical and immunoserological parameters of the patients were collected, and selected clinical and laboratory variables, including the immunoserological profile of SLE and RA, are presented in table 1.

The impact of immunosuppressive and anticholinergic medication on the exocrine function was assessed. Therapies with proven anticholinergic effect were evaluated, including antihistaminic, antidepressant, antipsychotic, antispasmodic, antiemetic and antiepileptic drugs. RA and SLE patients were on the usual immunosuppressive therapies, mostly low-dose corticosteroid, methotrexate, leflunomide, chloroquine, rarely sulphasalazine, azathioprine, cyclosporin A, cyclophosphamide, mycophenolate mofetil, tumor necrosis factor-α inhibitor or anti-CD20 biologic agents. Treatment with none of the studied medications showed a correlation with the presence of sicca complex (data not shown).

Table 1. Characteristic clinical and laboratory variables of SLE (n = 103) and RA patients (n = 65)

SLE (n = 103)	%	RA (n = 65)	%
Polyarthritis	89.2	Rheumatoid nodules	12.5
Photosensitivity	70.6	Pulmonary fibrosis	4.7
Nephritis	30.4	RF	84.4
Serositis	28.4	Anti-MCV	77.9
Nervous system	21.6	Anti-SSA	9.5
Anti-dsDNA	74.2	Anti-SSB	7.1
Anti-SSA	50.5		
Anti-SSB	38.6		
Low C3, C4	67.6		

Anti-dsDNA = Antibody to double-stranded DNA; anti-SSA = anti-Sjögren's syndrome A; anti-SSB = anti-Sjögren's syndrome B; C3 = complement-3; C4 = complement-4; RF = rheumatoid factor; anti-MCV = antimutant citrullinated vimentin.

Antigen Preparation

Three immunodominant epitopes of the human m3AChR were predicted by means of the computer software Peptide Companion version 1.231 (Coshisoft/PeptiSearch); peptide amino acids (aa) 184–227 (AGSE) from the second extracellular loop of the receptor, where the ligand binding region is localized, peptide aa 506–521 (YNIP) from the third extracellular loop and peptide aa 360–377 (TRIC) from the third intracellular loop were selected as antigens.

Multiple forms of these antigens were prepared for ELISA to test whether modification of m3AChR peptides could enhance the antigenicity and improve the detection of the autoantibodies specific to the respective peptides. First, short linear peptides were synthesized with solid-phase peptide synthesis as described previously [6]. We then constructed recombinant fusion proteins containing the peptides AGSE and YNIP fused with glutathione-S-transferase (GST), because it was our previous experience that this protein microenvironment can enhance the assumption of an appropriate physiological conformation [26]. Briefly, peptide-coding DNA sequences were assembled from synthetic oligonucleotides and cloned into expression vectors in fusion with GST; the fusion product was expressed in *Escherichia coli* and purified by affinity chromatography [for details, see 6]. Finally, the epitope with the highest predicted antigenicity (AGSE) was also prepared in multiple conjugation to bovine serum albumin (BSA) in an attempt to enhance the sensitivity of the assay. We compared the performances of the ELISA systems by using the different forms of the antigens.

ELISA Techniques

Microtiter plates were coated with the above-mentioned antigens (AGSE: 1 μg/ml; YNIP and TRIC synthetic peptides: 2 μg/ml; GST fusion products and BSA-conjugated antigen: 10 μg/ml). After incubation overnight at 4°C, patient sera were added at a dilution of 1:200 in PBS-Tween followed by peroxidase-labeled antihuman IgG (1:2,500 in PBS-Tween; Sigma-Aldrich Hungary, Budapest). Optical density (OD) was read at 492 and 620 nm after the addition of ortho-phenylenediamine to the samples. Measurements were made in duplicate, and appropriate numbers of negative controls were used for every microtiter plate. For the GST- or BSA-conjugated proteins, the specific corrected OD characterizing the m3AChR-specific epitope within an individual sample was calculated by subtracting the OD for the GST or BSA protein from that for the GST-m3AChR peptide fusion protein or BSA-AGSE conjugate. As the absolute OD values for the negative controls varied from plate to plate, the OD values of the patients' samples were normalized to the mean of the controls for every plate by dividing the OD of the test sample by the cutoff (mean + 2 SD of the negative control OD values). The resulting relative OD values were used for the calculations.

Mental Health Status Assessments

Physical and mental health were assessed with the following validated questionnaires: the 36-item Short-Form Health Survey (SF-36) and the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale [27, 28]. The SF-36 consists of 36 questions which represent multiple indicators of mental and physical health, including behavioral function and dysfunction, distress and well-being, objective reports and subjective ratings, and both favorable and unfavorable self-evaluations of general health status [27]. The FACIT fatigue scale is a short, 13-item tool that measures an individual's level of fatigue during the usual daily activities over the past week.

Statistical Methods

The differences in mean autoantibody concentrations between the studied groups were assessed with analysis of variance with Bonferroni's correction as a post hoc test. The occurrences of positivities to the various antigenic epitopes were compared between the different patient and control groups with the χ^2 test. The demographic, clinical and immunoserological parameters, the levels of anti-m3AChR antibodies specific to the various antigens and the SF-36 and FACIT results were compared between the RA and SLE patients with or without sicca complex through use of the Student t test or Fisher's exact test, as appropriate, depending on whether continuous or categorical variables were tested. Levels of $p < 0.05$ were taken as statistically significant. The statistical analyses were performed with SPSS 15.0 software.

Results

Anti-m3AChR Detection

The mean levels of anti-m3AChR antibodies depending on the method of antigen preparation and epitope specificity in the three disease groups and the healthy controls can be seen in figure 1. Significantly higher mean autoantibody levels to the peptide sequences corresponding to the second (AGSE) and third (YNIP) extracellular loops were detected in both the pSS and the SLE patients than in the controls, while the RA patients exhibited only a borderline significant difference (p = 0.067) versus controls. This technique using short peptide sequences failed to make further distinctions be-

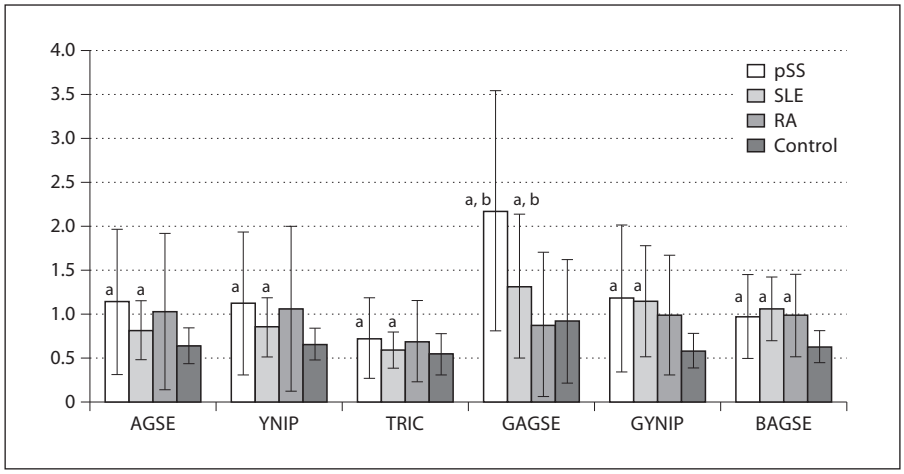

Fig. 1. Mean relative OD values of anti-m3AchR antibodies measured with ELISA. The mean values of all studied anti-m3AChR antibodies were significantly higher in both pSS and SLE patients than in the controls. GST-AGSE also discriminated pSS and SLE from RA. [a] $p < 0.05$ versus control; [b] $p < 0.05$ versus RA. GAGSE = GST-AGSE fusion peptide; GYNIP = GST-YNIP fusion peptide; BAGSE = BSA-AGSE multiple-conjugated peptide.

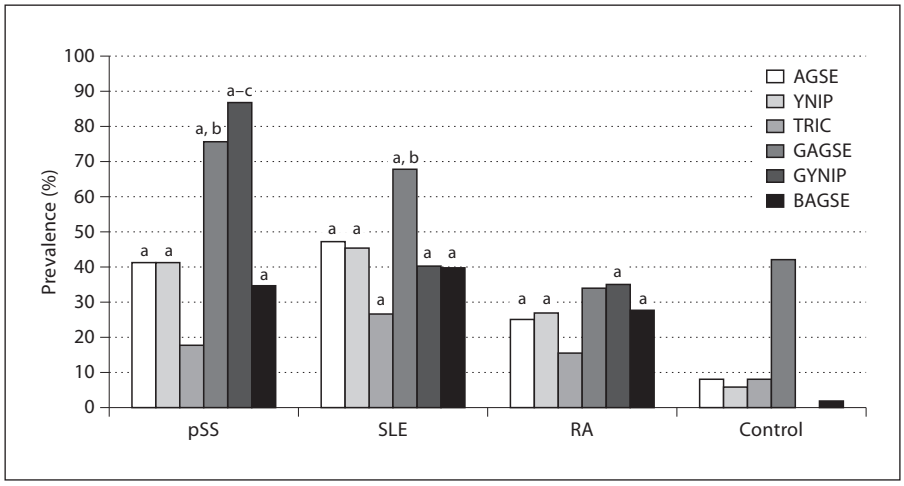

Fig. 2. The prevalences of anti-m3AChR antibody positivities in the three disease groups and the controls. The prevalence of GST-YNIP showed a significant difference between pSS and the other groups. GST-AGSE discriminated pSS and SLE from RA and the controls. [a] $p < 0.05$ versus control; [b] $p < 0.05$ versus RA; [c] $p < 0.05$ versus SLE. GAGSE = GST-AGSE fusion peptide; GYNIP = GST-YNIP fusion peptide; BAGSE = BSA-AGSE multiple-conjugated peptide.

tween the pSS, SLE and RA patients. When the AGSE peptide was presented in fusion with GST, this form displayed significantly lower mean antibody levels in RA as compared with the other two patient groups. ELISA using the BSA conjugate failed to identify antibodies with sufficient group-discriminative power, although the mean autoantibody levels to this antigen were higher in all three diseases than in the controls. It also became evident that the TRIC peptide, which is located in the intracellular portion of the m3AChR, reacted with only a small proportion of the sera and therefore cannot be regarded as antigenic in these diseases.

An assessment of the prevalence of the studied antibodies confirmed and further clarified the results (fig. 2). Autoantibodies to the short peptide sequences of AGSE and YNIP occurred at significantly higher frequencies in all disease groups than in the controls. Furthermore, the use of GST fusion forms also revealed differences between the patient groups; the prevalences of GST-AGSE and GST-YNIP were elevated in both pSS and SLE as compared with RA. Furthermore, antibodies to GST-YNIP were also able to discriminate between pSS and SLE patients, as these antibodies occurred at significantly higher frequency in pSS than in SLE, though in SLE they were still significantly more prevalent than in RA or in the controls. In summary, short peptide sequences detected anti-m3AchR with relatively high specificity but low sensitivity, whereas fusion with GST preserved the specificity and enhanced the sensitivity of detection of anti-GST-YNIP. Multiple peptide conjugation to BSA did not improve the sensitivity of the ELISA (table 2).

Clinical Correlations

In the second part of the study, we sought clinical, immunological and psychosomatic correlates of the sicca complex arising in SLE or RA patients. Sicca symptoms

Table 2. Sensitivity and specificity of the tests for the detection of anti-m3AChR antibodies to discriminate between pSS and healthy controls

	Sensitivity	Specificity
AGSE	41.2%	92.0%
YNIP	41.2%	94.0%
TRIC	17.6%	92.0%
GAGSE	75.6%	58.1%
GYNIP	86.5%	100.0%
BAGSE	34.7%	98.2%

ELISA with the short synthetic peptide sequences had high specificity but low sensitivity in the detection of anti-m3AChR. Fusion with GST preserved the specificity and enhanced the sensitivity of the detection of antibodies to the YNIP sequence. Multiple peptide conjugation to BSA did not improve detection. GAGSE = GST-AGSE fusion peptide; GYNIP = GST-YNIP fusion peptide; BAGSE = BSA-AGSE multiple-conjugated peptide.

Table 3. Differences in the clinical features and selected SF-36 items of the sicca and non-sicca SLE patients

	Non-sicca (n = 76)	Sicca (n = 27)	p
Clinical features, %			
Organic brain syndrome	1.3	11.1	0.056
Stroke	0	7.4	0.068
Anti-SSA	45.9	62.9	0.098
Nephritis	34.6	18.5	0.091
Lymphopenia	57.3	37	0.056
SF-36, mean values			
Role-physical	39.33	35.05	0.081
Vitality	46.71	41.70	**0.005**
Social functioning	42.68	38.04	**0.041**
Mental health	42.12	36.82	**0.048**
Mental composite score	44.01	38.52	**0.035**

Higher SF-36 mean values represent better health status.

Significant differences are shown in bold. Anti-SSA = anti-Sjögren's syndrome A.

were common in both SLE and RA patients; the sicca complex was verified in 14 RA patients (21.5%) and 27 SLE patients (26.2%). We compared the sicca and non-sicca patients with regard to the aspects of age, disease duration, disease-specific organ involvement, immunoserology and mental health status parameters, as well as antimuscarinic receptor antibody positivity and epitope specificity. Decreased saliva production correlated with increasing age in both SLE and RA. Furthermore, in the SLE patients with sicca complex, organic brain syndrome, stroke and anti-SSA antibody positivity occurred more frequently, whereas nephritis and lymphopenia were seen more rarely than in the non-sicca SLE patients, all with borderline significance (table 3). It is noteworthy that the SLE patients with sicca syndrome demonstrated significantly impaired mental health parameters on the SF-36, specifically on the 'role-physical', vitality, social function and mental health domains and the composite mental score, as compared with the non-sicca SLE patients (table 3). Conversely, the FACIT fatigue scale did not reveal differences between the subgroups of sicca and non-sicca SLE patients. In contrast, in the RA patients, no clinical or immunological correlates other than increasing age were identified that could discriminate between those with or without sicca complex; moreover, none of the parameters that characterize quality of life (SF-36) or fatigue (FACIT) were found to correlate with the presence of sicca syndrome. Finally, although anti-m3AChR antibodies specific to the second or third extracellular loops occurred in both SLE and RA patients, the prevalence and the mean levels of these autoantibodies were not statistically different between the patient subgroups of SLE or RA with or without sicca complex.

Discussion

This study has revealed two distinct neuroimmune interactions that may contribute to the complex pathophysiology of pSS and sSS, namely autoantibody production that directly targets autonomic neurotransmitter receptors, specifically m3AChR, and an altered mental health status that may theoretically be regarded as a central inhibitory mechanism of the parasympathetic innervation of the salivary glands.

Anti-m3AChR autoantibodies have been hypothesized to bind to the m3AChR and block the parasympathetic neurotransmission [5, 14], thereby serving as an example of how a pathological immunological process can lead to organ dysfunction by inhibiting the normal function of the autonomic nervous system. Although several experimental settings, involving rodent tissues and cultured human salivary glands, have supported this concept, formal proof of the functional role of anti-m3AChR antibodies in humans is still lacking because the reliable detection of these autoantibodies has remained elusive. Convincing correlations between anti-

muscarinic receptor antibodies in SS and other systemic autoimmune diseases could therefore not be addressed.

We previously developed an ELISA assay involving the second extracellular loop of the human m3AChR as antigen and succeeded in demonstrating anti-m3AChR antibodies in the majority of pSS patients [6, 7]. Other investigators have also subsequently proved the presence of these autoantibodies, with frequencies in a rather wide range, and even proposed further epitopes on the m3AChR as the targets of the immune response in pSS, specifically on the third extracellular loop [10–12, 14, 28]; however, others have failed to confirm our results [17, 29, 30]. Furthermore, the role of anti-m3AChR antibodies in sSS, which occurs in a large proportion of patients with two common systemic autoimmune diseases, SLE and RA, has not been examined to date.

The results of the present study appear to confirm our previous findings that the second extracellular loop is antigenic in pSS and that the GST fusion construct is an appropriate mode of antigen presentation [26]. In addition, our findings support the recent results that the third extracellular loop also contains antigenic sequences in a considerable proportion of pSS patients (and also in some SLE and RA patients). Actually, anti-GST-YNIP has emerged as the diagnostically most useful antibody, as it discriminates pSS patients from controls with the best balance of specificity and sensitivity, and in pSS, these autoantibodies occurred more frequently not only than in the controls or the RA patients but also than in SLE. Of course, this apparently better diagnostic performance may be independent of the putative functional significance of the autoantibodies with various epitope specificities, and it should be noted that most of the previous results, including our own findings that directly visualized the binding of anti-m3AChR to the receptor in human salivary glands, favored the inhibitory role of anti-mAChR targeting the second extracellular loop, where the ligand-binding region is located. Therefore, we conclude that further validation of these results on larger patient populations and potentially more precise epitope mapping are needed to elucidate the exact epitope specificity and functional importance of these autoantibodies. Moreover, our data provide no indication as to whether anti-m3AChR antibodies may be related to the pathogenesis of sSS overlapping SLE or RA, although the examined patient population may well have been too small for definite conclusions to be drawn.

Sicca symptoms often develop in chronic illnesses other than pSS. The pathogenesis of sSS overlapping different systemic autoimmune diseases, including SLE, RA or scleroderma, is rather variable. An associated sSS alters the immunological phenotype of SLE, including the organ manifestations or the immunoserologic profile [19, 31]. Some studies have suggested that the probability of the development of sicca symptoms in RA is directly correlated with the cumulative disease activity and the degree of functional impairment, i.e. the burden of the chronic disease [32], while others did not find such associations [33]. A sicca syndrome clinically indistinguishable from SS also develops in a considerable proportion of patients with organ-specific autoimmune diseases, such as primary biliary cirrhosis, multiple sclerosis or gluten-sensitive enteropathy [34], and in other chronic non-immune-mediated illnesses, such as fibromyalgia or chronic fatigue syndrome [35]. Another example of such a nonautoimmune sicca syndrome is the 'sicca, asthenia, polyalgia syndrome'. It was revealed by Champey et al. [22] that the degree of deterioration of the quality of life – measured with the SF-36 as used in this study – directly correlated with the presence and severity of sicca symptoms in this syndrome. We therefore set out to examine whether mental health alterations, assessed with the SF-36 and the FACIT fatigue scale, may be associated with the development of a sicca syndrome in SLE or RA patients.

Through the investigation of considerable numbers of SLE and RA patients, we have obtained new information about the correlates of the development of sicca syndrome in these diseases, mostly in SLE. Some clinical and immunoserological features differed between SLE patients with sicca syndrome and those without it, with borderline significance. This is very similar to the findings of Manoussakis et al. [19] in a larger cohort of patients and to the results of a recent meta-analysis [36] and justifies the assessment of sicca syndrome in our SLE cohort. Moreover, the SLE plus sicca syndrome patients in this study were clearly different from those SLE patients in whom sicca symptoms were not present, in terms of a significantly higher occurrence of signs of psychological dysfunction, specifically lower vitality, a worse perception of their mental health, difficulties in physical functions reflecting the extent to which health interferes with usual daily activities such as work, studies or household duties, and worse scores on the composite index, which indicates a lower overall level of mental well-being as compared with the SLE patients without sicca symptoms. We have found only one publication in which health-related quality of life parameters were compared between SLE patients with or without sicca symptoms, and the findings of that study are similar to our own results in

that a lower perceived health-related status is correlated with salivary dysfunction [37]. Our results argue in favor of an association between the health-related quality of life parameters and the evolution of sicca symptoms. These mental alterations may be either consequences or causes of the sicca symptoms, or they may have a common background. Our study design is obviously not sufficient to allow an exploration of causal relationships, but some data do suggest that chronic stress has a direct impact on saliva production and may lead to chronic xerostomia [38, 39]. Salivary levels of cortisol and chromogranin A have been found to be increased in subjects with low salivary flow rates [40]. Profound alterations in neurotransmitter homeostasis in SS were long ago observed by Santavirta et al. [41]; both the vasoactive intestinal peptide and the neuropeptide Y contents (markers of parasympathetic and sympathetic nervous system activity, respectively) in the saliva were found to differ from those in healthy subjects. As indicated by the results of a number of other investigations [42, 43], it is reasonable to hypothesize that chronic stress, depression and several further features of the long-standing distress associated with a systemic autoimmune illness such as SLE [44] may negatively influence the salivary gland function and are factors that should be addressed during the care of these patients.

One limitation of our study is that many of the SLE and RA patients with sicca syndrome did not strictly meet the criteria of sSS. This is mostly explained by the fact that very few patients underwent labial salivary gland biopsy once the diagnosis of SLE and RA had been verified, mostly because of patient refusal, anticoagulant therapy or the lack of specific therapeutic consequences. However, it should be emphasized that all the sicca syndrome patients consequently gave positive answers to the sicca questionnaire on at least two separate occasions and had markedly and repeatedly low salivary and lachrymal flow rates. The variability of these test results was low (data not shown), and these patients could prudently be regarded as patients with sSS in clinical practice.

In summary, the results of the present study indicate that a probably polyclonal autoimmune reaction to multiple epitopes on the m3AChR is observed most prominently in pSS, but also in SLE and RA, and the fusion of these antigenic peptides to GST may – after further validation – be a promising laboratory test for further research and possibly for the diagnosis of pSS. Furthermore, an impaired level of psychosocial well-being and a dysfunctional stress response may be contributors to the pathogenesis of sSS in SLE.

Acknowledgments

L.K. is supported by a Bolyai János Scholarship from the Hungarian Academy of Sciences. The authors are grateful to Szivia Pördi for her excellent laboratory assistance.

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