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BRIEF REPORT

Adrenal Autoimmunity in Primary Sjögren's Syndrome

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Objective. **To evaluate the prevalence of antibodies to 21-hydroxylase (anti-21[OH]), a marker of autoimmune adrenal disease, in a cohort of patients with primary Sjögren's syndrome (SS) and to investigate whether the presence of anti-21(OH) correlates with clinical, serologic, and salivary gland features of the disease.**

Methods. **Sera from 63 consecutive patients with primary SS, 32 patients with autoimmune thyroid disease (AITD), and 20 healthy controls were obtained and anti-21(OH) levels were determined by radioimmunoassay. Clinical, serologic, and histopathologic features were recorded, and a short Synacthen test was used to assess adrenal function reserve. Seven available minor salivary gland (MSG) tissue specimens from patients in the primary SS cohort were also assessed for interferon-α (IFNα), BAFF, and interleukin-21 (IL-21) cytokine transcripts, which are all implicated in B cell activation.**

Results. **Anti-21(OH) positivity was detected in 17.5% and 28.1% of primary SS and AITD patients, respectively, and in none of the healthy controls. While no evidence of adrenal insufficiency was detected in any of the patients studied, a blunted rate of increase in cortisol levels was observed in patients with detectable serum autoantibodies against 21(OH), compared to their anti-21(OH)–negative counterparts. A strong correlation between the serum titer of anti-21(OH) antibodies and expression of IFNα, BAFF, and IL-21 messenger RNA in MSG tissues was also detected.**

Conclusion. **Adrenal autoimmunity occurs in almost 20% of patients with primary SS in association with markers of B cell activation. Although the presence of adrenal autoantibodies was not associated with adrenal insufficiency in the present study, there was a blunted adrenal response, suggesting the need for further followup and monitoring of adrenal function in patients with primary SS who are positive for the autoantibodies.**

Primary Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of salivary and lachrymal glands, clinically manifesting as oral and ocular dryness, respectively. B cell activation has long been considered a disease hallmark associated with hypergammaglobulinemia, cryoglobulinemia, and autoantibody production (1). Furthermore, it has been proposed that type I interferon (IFN)/BAFF axis activation (2–5) and, recently, interleukin-21 (IL-21) (6) are significant pathogenetic contributors. The autoantibodies most commonly found in sera from patients are against non–organ-specific antigens, such as Ro/SSA–La/SSB ribonucleoprotein complexes. In addition, it has been previously reported that other, organ-specific autoantibodies, such as antibodies against thyroid and mitochondrial antigens, frequently occur in SS overlapping with autoimmune thyroid disease (AITD) and primary biliary cirrhosis, respectively (1).

Abnormalities of the hypothalamic–pituitary–adrenal (HPA) axis in patients with primary SS, which manifest as blunted cortisol responses to corticotropin-releasing hormone stimulation, have been previously reported and were attributed to either blunted adrenocorticotropic hormone (ACTH) release from the pituitary gland or a primary adrenal defect (7). Antibodies to 21-hydroxylase (anti-21[OH]), a major adrenal autoantigen, are currently used to identify patients at increased risk of developing autoimmune adrenalitis. Autoimmune adrenalitis is the most common cause of

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adrenal insufficiency in developed countries and is characterized by lymphocytic infiltration and destruction of the adrenal glands. In cross-sectional studies, the prevalence of autoantibodies against 21(OH) in patients with Addison's disease has been estimated to range from 65% to 95%. This frequency tends to be higher in patients with shorter disease duration, declining over the years to a frequency of 60% after 35 years of followup. In individuals with evidence of diseases other than adrenal organ–specific autoimmune diseases, the presence of antibodies to 21(OH) has been shown to predict progression to overt autoimmune failure over 6 years in ~15% of patients (8). However, there is currently no information regarding the presence of antibodies against adrenal antigens and the effect that their presence may exert on adrenal function in patients with primary SS.

In the present study, we aimed to evaluate the prevalence of antibodies to 21(OH) in a cohort of patients with primary SS and to investigate whether their presence could be related to evidence of primary adrenal insufficiency. Additionally, we sought to explore potential associations between anti-21(OH) titers and clinical, serologic, and histopathologic disease parameters, including B cell–activating cytokine gene expression in salivary gland tissue.

PATIENTS AND METHODS

Study groups. We studied 63 consecutive patients with primary SS, who fulfilled the American–European Consensus Group criteria (9) and were followed up at the University of Athens School of Medicine, Department of Pathophysiology and at the General Hospital of Athens "G. Gennimatas," Department of Rheumatology. Thirty-two patients with AITD (mainly Hashimoto thyroiditis) followed up at the Outpatient Endocrinology Clinic at the University of Athens School of Medicine Department of Pathophysiology, as well as 20 healthy controls, were also studied. The age and sex composition was similar in all 3 groups.

Serum samples were collected during routine followup visits and stored at −20°C until assayed. Clinical, serologic, and histopathologic features were recorded after thorough review of chart notes. The following features were noted: arthralgias, arthritis, oral and ocular dryness (documented by subjective and objective measures), salivary gland enlargement, Raynaud's phenomenon, lung involvement (documented by pulmonary function testing and radiography and/or computed tomography), pulmonary involvement (manifested as small airways disease or restrictive airways disease, documented by pulmonary function testing), interstitial nephritis (documented by urine-specific gravity of <1.010 or pH of >6 on at least 2 consecutive measurements after fluid restriction), glomerulonephritis (documented by biopsy), liver involvement (documented by biopsy showing changes compatible with primary biliary cirrhosis in the setting of increased levels of liver enzymes or antimitochondrial antibodies), palpable purpura, vasculitis, peripheral neuropathy (verified by nerve conduction studies), lymphoma development (diagnosed by histologic assessment), anti-Ro/SSA and/or anti-La/SSB autoantibodies, rheumatoid factor (RF), low C3 and C4 levels, cryoglobulinemia, hypergammaglobulinemia (total gamma globulin levels >2 gm/liter), and leukopenia (white blood cell count <4,000/mm^3). Due to common underlying histopathologic features, the combined presence of interstitial nephritis, peribronchial disease, and autoimmune cholangitis was recorded as periepithelial involvement (1).

The study was approved by the Ethics Committee of Laikon General Hospital and the General Hospital of Athens "G. Gennimatas." All patients provided informed consent prior to study entry.

Minor salivary gland (MSG) biopsy. Available MSG biopsy samples (n = 7) from patients with primary SS (all women; ages 48–65 years at time of biopsy) were examined at the Department of Pathophysiology of the School of Medicine at the University of Athens, as a routine part of the diagnostic evaluation for SS. A focus score was determined for each MSG biopsy sample, as previously described (9).

Anti-21(OH) antibody estimation. Anti-21(OH) antibodies were assessed using a commercial radioimmunoassay (21-OH Antibody Kit; RSR Ltd.). Briefly, calibrators, control specimens, and patient specimens were allowed to interact overnight with highly purified recombinant ^{125}I 21-OH. After overnight incubation, solid-phase protein A was added to precipitate antibody-bound labeled 21(OH). The cutoff for positivity was 1 units/ml, according to the manufacturer's instructions.

Short Synacthen test. The secretory cortisol reserve of the adrenal cortex was evaluated after adrenal stimulation using synthetic ACTH (tetracosactide [Synacthen]). Briefly, 250 μg of Synacthen was injected intravenously, and blood cortisol measurements were obtained at 0, 30, and 60 minutes in 11 patients with primary SS (5 of the 11 patients had positive serum anti-21[OH] antibodies, and 6 age- and sex-matched patients with negative anti-21[OH] antibodies served as controls). Patients with past or current exposure to corticosteroids were excluded from adrenal function testing. A normal response to the test was defined as a serum cortisol concentration of >500 nmoles/liter at 30 or 60 minutes poststimulation (10). The percentage increase in the cortisol level from baseline was also determined, defined as the ratio between the absolute increment in cortisol levels and the baseline cortisol levels (×100). The Synacthen test was performed at 9:00 AM in all patients.

RNA isolation. Total RNA was isolated from MSG samples according to standard procedures, with the RNeasy Mini kit (Qiagen).

Preparation of complementary DNA (cDNA). Total messenger RNA (mRNA) was reverse transcribed using a Superscript III reverse transcriptase system (Invitrogen). Oligo(dT) primer was used to amplify mRNA, specifically, and an RNase inhibitor was included to prevent degradation.

Real-time quantitative polymerase chain reaction (qPCR). Real-time qPCR was used to quantify specific cDNA using a Bio-Rad SYBR Green intercalating fluorophore system with a Bio-Rad iCycler thermocycler and fluorescence detector. Primers for IFNα2, BAFF, IL-21, and tumor necrosis factor α (TNFα) genes were used in the PCR on the MSG biopsy–derived cDNA samples, and expression of mRNA for these genes was determined. The amount of hypoxanthine guanine phosphoribosyltransferase cDNA was quantified in the samples to control for background gene expression. Then, the threshold values were recorded for each sample in the logarithmic portion of the amplification curve. Melting curve analysis was used to ensure the specificity of the amplification product, and all inconsistent results were discarded. The specific sets of primers used were as follows: BAFF (accession no. NM_006573) forward AGTTCAAGTAGTGATATGGATG, reverse GGGAGGATGGAAACACAC; GAPDH (accession no. NM_002046) forward CAACGGATTTGGTCGTATT, reverse GATGGCAACAATATCCACTT; IFNa2 (accession no. NM_000605) forward CTTGAAGGACAGACATGAC, reverse TGTGCTGAAGAGATTGAAG; IL-21 (accession no. AF254069) forward GCTGAAGTGAAAACGAGACCAAG, reverse CCCAAGAAGATGACCATCAGACAG; TNF (accession no. NM_000594) forward AGGTCTACTTTGGGATCATTG, reverse GGGGTAATAAAGGGATTGGG.

Statistical analysis. Fisher's 2-sided exact test and the Mann-Whitney test were used to compare qualitative and quantitative characteristics, respectively, between patient groups (GraphPad Prism 5 software package). For univariate analyses, P values less than 0.05 were considered significant. Correlations were performed using Spearman's nonparametric test. Total cortisol response after ACTH stimulation was calculated using the integrated area under the curve (AUC) by the trapezoidal method. The AUC was compared between groups using an independent t-test.

RESULTS

Demographics. Age distribution and ratio of women to men did not differ significantly among the groups studied. Patients with primary SS had a mean ± SD age of 58.1 ± 11.6 years; the ratio of women to men was 14.75:1 in this group. Patients with AITD had a mean ± SD age of 52.2 ± 13.3 years; the ratio of women to men was 5.4:1. Healthy controls had a mean ± SD age of 51.9 ± 14.7 years; the ratio of women to men was 19:1.

Prevalence of antibodies to 21(OH) in patients and controls. Significantly higher anti-21(OH) antibody titers were detected in patients with primary SS and patients with AITD compared to controls (median 0.2 units/ml [range 0.01–5.02] in the primary SS group and 0.18 units/ml [range 0.06–1.7] in the AITD group, versus 0.08 units/ml [range 0.01–0.35] in the controls) ($P <$ 0.0001, for comparisons of each patient group versus controls). There were no differences between the 2 patient groups (Figure 1A). The prevalence of anti-21(OH) positivity was 17.5% and 28.1% in patients with primary SS and patients with AITD, respectively, whereas none of the healthy controls demonstrated such reactivity.

Clinical and serologic associations with anti-21(OH) status in patients with primary SS. Patients with primary SS were subdivided further into 2 groups based on the presence or absence of anti-21(OH) antibodies (Table 1). Patients in the anti-21(OH)–positive group had a decreased prevalence of subjective ocular dryness (54.5% versus 88.4%; $P = 0.017$) and increased rates of leukopenia (36.4% versus 9.6%; $P = 0.04$). Although not statistically significant, there was a trend toward lower C4 levels in the anti-21(OH)–positive primary SS group.

Associations of adrenal secretory reserve with anti-21(OH) status in patients with primary SS. To determine whether the presence of antibodies to 21(OH) could connote impaired adrenal function, 5 patients with primary SS who were positive for anti-21(OH) and 6 age- and sex-matched patients who were negative for anti-21(OH) underwent a short Synacthen test. There was no evidence of adrenal insufficiency in any of the patients studied irrespective of the presence of anti-21(OH) antibodies, and total cortisol response determined by AUC calculation did not differ significantly between the 2 groups tested ($P = 0.1$). How-

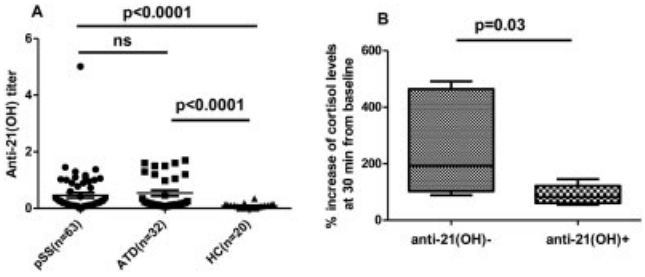

Figure 1. A, Increased titers of antibodies to 21-hydroxylase (anti-21[OH]) in patients with primary SS (pSS) and patients with autoimmune thyroid disease (ATD) versus healthy controls (HC). Symbols represent individual subjects; horizontal lines show the median. NS = not significant. **B,** Blunted percentage increase of cortisol levels at 30 minutes compared to baseline in patients with primary SS with detectable serum autoantibodies against 21(OH) (anti-21[OH] positive, n = 5), compared to the anti-21(OH)–negative primary SS subset (anti-21[OH] negative, n = 6). Data are shown as box plots. Each box represents the 25th to 75th percentiles. Lines inside the boxes represent the median. Lines outside the boxes represent the 10th and the 90th percentiles.

Table 1. Demographic, clinical, and serologic features in the anti-21(OH)–positive and the anti-21(OH)–negative primary Sjögren's syndrome groups*

	Anti-21(OH) negative (n = 52)	Anti-21(OH) positive (n = 11)	*P*
Age, mean (range) years	58.2 (33–85)	64.6 (45–82)	0.4
Sex, no. female/male	48/4	11/0	1
Disease duration from diagnosis, mean ± SD years	8.6 ± 7.0	8.2 ± 3.3	0.8
Dry eyes (subjective)	46 (88.5)	6 (54.5)	0.017
Positive Schirmer's test	33 (67.3)	9 (81.8)	0.48
Dry mouth (subjective)	42 (80.8)	9 (81.8)	1
Salivary gland enlargement	9 (17.3)	4 (36.4)	0.21
Whole salivary flow, mean ± SD ml/15 minutes	2.3 ± 3.1	1.1 ± 0.9	0.89
Arthralgia/arthritis	36 (69.2)	7 (63.6)	0.73
Raynaud's phenomenon	15 (28.8)	3 (27.3)	1
Purpura	5 (9.6)	1 (9.1)	1
Glomerulonephritis	0 (0)	0 (0)	1
Peripheral neuropathy	1 (1.9)	0 (0)	1
Periepithelial involvement (lung, kidney, liver)	14 (26.9)	1 (9.1)	0.27
Non-Hodgkin's lymphoma	4 (7.7)	2 (18.1)	0.28
Leukopenia (≤4,000/mm^3)	5 (9.6)	4 (36.4)	0.04
ANA positivity (titer ≥1:160)	49 (94.2)	11 (100)	1
RF positivity (≥20 IU/ml)	25 (53.2)	7 (70)	0.48
Hypergammaglobulinemia	31 (63.3)	7 (63.6)	1
Anti-Ro/SSA and/or anti-La/SSB positivity	38 (73.1)	8 (72.7)	1
Low C4 levels (≤16 mg/dl)	13 (26)	6 (54.5)	0.08

* In the anti–21-hydrolase (anti-21[OH])–negative group, data on some parameters were not available for all patients, as follows: Schirmer's test (n = 49), antinuclear antibody (ANA) (n = 52), rheumatoid factor (RF) (n = 47), hypergammaglobulinemia (n = 49), and C4 levels (n = 50). In the anti-21(OH)–positive group, data on RF were not available for all patients (n = 10). Except where indicated otherwise, values are the number (%) of patients.

ever, a reduced percentage increase in cortisol levels at 30 minutes compared to baseline was observed in those who were positive for anti-21(OH), compared to their anti-21(OH)–negative counterparts (Figure 1B) (mean ± SD 89 ± 47% versus 255 ± 177%, respectively; P = 0.03). The mean ± SD cortisol levels at 0, 30, and 60 minutes in the anti-21(OH)–positive group were 613 ± 288 nmoles/liter, 1,185 ± 571 nmoles/liter, and 1,337 ± 632 nmoles/liter, respectively. The corresponding values in the anti-21(OH)–negative group were 279 ± 130 nmoles/liter, 939 ± 431 nmoles/liter, and 938 ± 227 nmoles/liter.

Association with B cell–activating cytokines in salivary gland tissue of patients with primary SS. In Figure 2, associations between anti-21(OH) titers and cytokine mRNA levels in matched MSG tissue samples are illustrated. A strong correlation between the serum titer of anti-21(OH) antibodies and expression of mRNA for the B cell–activating cytokines IFNα (r = 0.93, P = 0.0067), BAFF (r = 0.88, P = 0.0333), and IL-21 (r = 0.94, P = 0.0167) in salivary gland biopsy samples was noted (Figures 2A–C). In contrast, no statistically significant correlations between

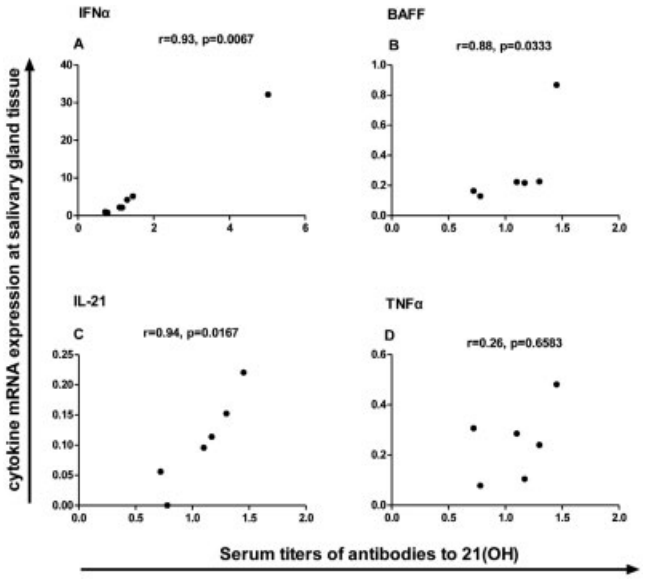

Figure 2. A–C, Strong correlation between titers of antibody to 21-hydroxylase (anti-21[OH]) and B cell–activating cytokine (interferon-α [IFNα] [**A**], BAFF [**B**], and interleukin-21 [IL-21] [**C**]) mRNA levels in salivary gland tissue. **D,** No statistically significant association between anti-21(OH) titers and salivary gland tumor necrosis factor α (TNFα) mRNA expression.

expression of TNFα mRNA in salivary gland biopsy samples and anti-21(OH) titers was noted (Figure 2D).

DISCUSSION

The present study is the first to demonstrate a higher prevalence of adrenal autoimmunity on the basis of elevated anti-21(OH) titers in patients with primary SS. Patients with primary SS and positive anti-21(OH) titers exhibited a decreased prevalence of subjective ocular dryness and increased rates of leukopenia compared to those who were negative for anti-21(OH). Furthermore, serum anti-21(OH) titers strongly correlated with the expression of IFNα, BAFF, and IL-21 mRNA in MSG tissue. This finding suggests that these B cell–activating cytokines could be responsible for or contribute to the generation of an autoimmune response against organ-specific autoantigens (in this instance, the adrenal gland). While the presence of B cell hyperactivity in the setting of SS has been previously associated with leukopenia (11), the presence of sicca symptoms, either ocular or oral, does not often correlate with the degree of inflammation, implying that additional neurohormonal contributors might account for the observed dryness (7).

Although not associated with overt adrenal insufficiency, the presence of antibodies to 21(OH) in our group of patients with primary SS was associated with adrenal hyporesponsiveness following ACTH stimulation, implying that the previously observed hypofunctional HPA axis in patients with primary SS could be explained by a primary adrenal defect (7). However, as adrenal damage may be an evolving process, further followup and subsequent testing of these patients are required to delineate the prognostic value of anti-21(OH) positivity. It is tempting to suggest that this alteration in adrenal glucocorticoid secretory pattern in patients with 21(OH) antibodies could identify a group of patients in whom more severe forms of primary SS could evolve due to a relative adrenal hyporesponsiveness. However, this needs to be further clarified by long-term studies and continuous evaluation of adrenal glucocorticoid reserve.

While studies of the prevalence of antibodies to 21(OH) in systemic autoimmune diseases are rather limited, there is growing evidence of an increased prevalence of concomitant autoimmune diseases in patients with autoimmune adrenalitis. A recent study revealed that concomitant autoimmunity was increased in more than half of patients with autoimmune adrenal disease, as evidenced by the presence of various autoantibodies against thyroid antigens, glutamic acid decarboxylase, insulin, and parietal cell H^+/K^+-ATPase, respectively (12). In autoimmune thyroiditis, clustering of β cell and adrenal autoimmunity has also previously been reported (13), while in primary SS, autoreactivities against thyroid and mitochondrial antigens, and to a lesser extent, aquaporin 4 and celiac-specific antigens, are known to occur (14). These findings support the notion that autoimmune clustering is possibly related to the presence of shared genetic, immunologic, and/or environmental contributors.

The association of antibodies to 21(OH) with IFNα, BAFF, and IL-21 expression in MSGs in the setting of primary SS might provide some clues regarding the etiology of distinct autoimmune responses against organ-specific and non–organ-specific autoantigens in the setting of systemic autoimmunity, possibly through induction of B cell hyperactivity. In a case of hairy cell leukemia, IFNα treatment has been shown to result in generation of polyglandular autoimmune disease type 2 expressed as AITD, Addison's disease, and premature ovarian failure, all of which were reversed upon discontinuation of IFN treatment (15).

The contributory role of type I IFN in antibody production both in vitro and in vivo has been previously shown through class-switch recombination, polarization of antibody responses toward IgG2a/IgG2c production, and induction of BAFF, a B cell survival factor implicated in SS pathogenesis through induction of transitional type 2 and marginal zone–like B cells in the salivary glands and of autoantibody production (5). IL-21, a pleiotropic cytokine produced by CD4 and natural killer T cells, has also been shown to promote B cell differentiation into plasma cells, while it has been recently identified as a cytokine that potentially contributes to SS pathogenesis. The latter result is also supported by the IL-21 heightened serum levels in SS patients in association with serum IgG1 levels and increased expression of IL-21 in the lymphocytic infiltrations of MSGs in SS (6).

In conclusion, autoimmune adrenal disease occurs in ~20% of patients with primary SS in association with adrenal hyporesponsiveness and markers of B cell activation, extending the list of currently known SS-associated organ-specific disorders. However, whether the presence of antibodies against 21(OH) defines a subset of primary SS characterized by more severe disease due to endogenous failure of suppression of a

hyperactive immune system needs to be addressed in followup studies.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Mavragani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Mavragani, Schini, Gravani, Kaltsas, Moutsopoulos.

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Analysis and interpretation of data. Mavragani, Schini, Gravani, Kaltsas, Moutsopoulos.

ROLE OF THE STUDY SPONSOR

Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer.

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