Prevalence of Antibodies Against α-Fodrin in Sjögren's Syndrome: Comparison of 2 Sets of Classification Criteria

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ABSTRACT. ***Objective.*** To compare the prevalence of antibodies against α-fodrin in Sjögren's syndrome (SS) classified according to San Diego and European Community Study Group (ESG) criteria.

Methods. The prevalence and mean concentrations of IgA and IgG autoantibodies against α-fodrin were determined and compared in patients with SS classified either according to San Diego criteria or to criteria of the ESG by ELISA.

Results. IgA antibodies against α-fodrin were detected in 88% and IgG antibodies against α-fodrin in 64% and either of these antibodies in 93% of 85 patients classified according to San Diego criteria. Antibodies against Ro were present in 38% of these sera. IgA antibodies against α-fodrin were detected in 61%, IgG antibodies against α-fodrin in 51%, and any of these antibodies in 73% of 51 patients classified according to the ESG criteria. The mean concentrations of both IgA and IgG antibodies against α-fodrin that seem to correlate with disease activity were higher in patients classified according to the San Diego criteria.

Conclusion. Antibodies against α-fodrin are detectable in almost all sera obtained from patients with SS classified according to the San Diego criteria and are significantly more prevalent than antibodies against Ro. The lower prevalence of the autoantibodies in patients classified according to the ESG criteria reflects the lower specificity of these criteria for SS. (J Rheumatol 2003;30:2157–9)

Key Indexing Terms:
SJÖGREN'S SYNDROME α-FODRIN

Sjögren's syndrome (SS) is a frequent connective tissue disorder affecting up to 0.5% of Caucasians[1,2]. No laboratory marker that is both specific and sensitive has been available for the diagnosis of the disease[3,4]. Thus establishing a diagnosis of SS has been difficult. Various sets of classification criteria have been developed. The San Diego criteria[5] are highly stringent, but may lack sensitivity. In addition, a salivary gland biopsy, rarely performed in many centers, is required. The criteria of the European Community Study Group (ESG)[6], on the other hand, are sensitive, but regarded as less specific[7].

A number of autoantibodies have been examined as possible markers for SS. Antibodies against Ro and rheumatoid factors (RF) lack specificity and antibodies against La lack sensitivity[8,9]. However, recently IgA and IgG antibodies against α-fodrin have been described as both sensitive and specific markers for primary SS[10-12]. A commercial ELISA kit for detection of IgA and IgG antibodies against α-fodrin is available.

We compared the prevalence of antibodies against α-fodrin in well defined patients with SS classified according to the San Diego criteria and those classified according to the ESG.

MATERIALS AND METHODS

Patients. Fifty-one patients with SS were recruited from the outpatient clinics of the university hospitals in Tel Aviv, Israel, and Munich, Freiburg, and Hannover, Germany. All patients provided signed informed consent. In Israel, 85 patients with SS had been classified according to the San Diego criteria[13]. In Germany, patients were recruited from the university hospitals in Freiburg (n = 22), München-Bogenhausen (n = 11), and Hannover (n = 18). They all fulfilled the criteria of the ESG. Therefore, all patients from Germany were required to have antibodies against Ro (SSA) in addition to sicca syndrome. In contrast, only 38% of the patients classified according to the San Diego criteria had antibodies against Ro. The 2 groups of patients did not differ with regard to age, disease duration, percentage of

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females, or non-exocrine manifestations of SS (prevalence of polyneuropathy, myositis, vasculitis, and arthritis; data not shown).

Detection of antibodies against α-fodrin by ELISA. IgA and IgG antibodies against α-fodrin were determined using a commercial ELISA kit (Aesku.Lab Diagnostika, Wendelsheim, Germany) according to the manufacturer's instructions. In this ELISA, the N-terminal part of α-fodrin (base pairs 1–1784) is used as antigen. The ELISA procedure and evaluation of sera obtained from 85 SS patients classified according to the San Diego criteria were performed in Israel. All sera obtained from 51 patients with SS classified according to the criteria of the ESG were examined in Hannover, Germany.

Detection of Ro, La, and RF. Autoantibodies against Ro and La antigens were determined using commercially available ELISA or Western blot systems according to the respective manufacturer's instructions (Pharmacia & Upjohn GmbH, Freiburg, Germany). RF were determined in a nephelometric assay (Behring, Marburg, Germany).

Statistical evaluation. Sera obtained from 85 patients with SS classified according to the San Diego criteria were segregated into those with and without IgA or IgG antibodies against α-fodrin. The presence of antibodies against SSA (Ro) was compared between groups. Associations of antibodies against α-fodrin and Ro were calculated using Fisher's exact test. Probabilities of association of less than 0.05 were regarded as statistically significant.

For comparison of antibodies against α-fodrin in patients with SS according to the San Diego and ESG criteria, only the mean and standard deviation of positive antibody values were calculated. Means of IgA and IgG antibodies against α-fodrin were compared between the 2 groups of patients using Student's t test.

RESULTS

Prevalence of IgA and IgG antibodies against α-fodrin: the San Diego criteria. IgA antibodies against α-fodrin were detected in 75 (88%) (Figure 1) and IgG antibodies against α-fodrin in 54 (64%) sera obtained from 85 patients with SS (Figure 2). IgA and/or IgG antibodies against α-fodrin were detected in 79 (93%) of these sera (data not shown). Antibodies against Ro were detected in 39% and 30% of sera with and without IgA antibodies against α-fodrin, respectively, and in 41% and 32% of sera with and without IgG antibodies against α-fodrin, respectively. Antibodies against La were detected in 21% and 10% of sera with and without IgA antibodies against α-fodrin, respectively, and in 21% and 16% of sera with and without IgG antibodies against α-fodrin, respectively. Thus, neither IgA nor IgG antibodies against α-fodrin were associated with the presence of antibodies against Ro or La and RF (data not shown).

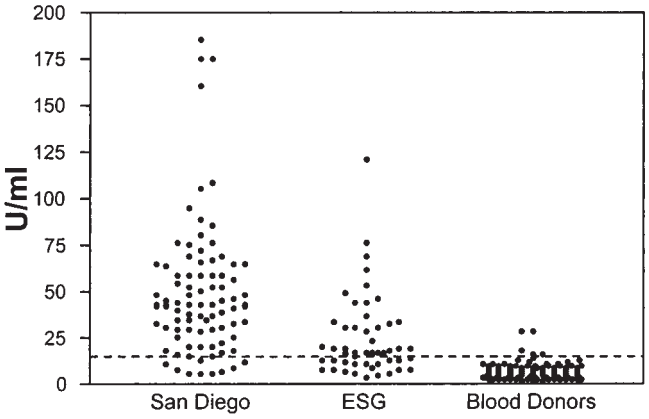

Figure 1. Distribution of IgA antibodies against α-fodrin in patients with primary SS according to San Diego criteria (n = 85), according to ESG criteria (n = 51), and in 157 blood donors. The cutoff is shown as a broken line.

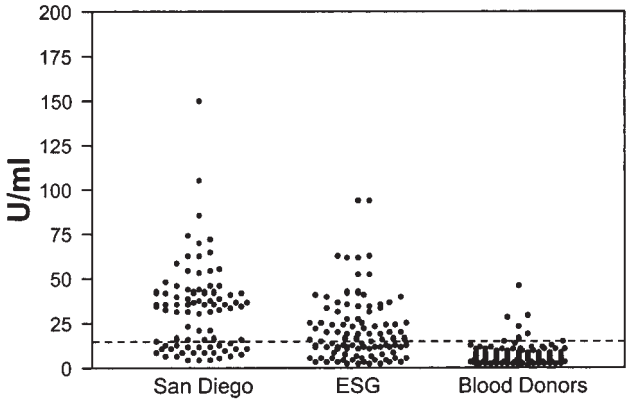

Figure 2. Distribution of IgG antibodies against α-fodrin in patients with primary SS according to San Diego criteria (n = 85), according to ESG criteria (n = 51), and in 157 blood donors. The cutoff is shown as a broken line.

Prevalence of IgA and IgG antibodies against α-fodrin: the ESG criteria. IgA antibodies against α-fodrin were detected in 5/11 (45%) sera from Munich, 14/22 (64%) sera from Freiburg, 13/18 (72%) sera from Hannover, and in 32/51 (63%) sera altogether (Figure 1).

IgG antibodies against α-fodrin were detected in 5/11 (45%) sera from Munich, 13/22 (60%) sera from Freiburg, 7/18 (39%) sera from Hannover, and in 25/51 (49%) sera altogether (Figure 2).

At least one of the α-fodrin antibodies was detected in 6/11 (55%) sera from Munich, 17/22 (77%) sera from Freiburg, 13/18 (72%) sera from Hannover, and in 36/51 (71%) sera altogether (data not shown).

With respect to specificity, IgA antibodies against α-fodrin were detected in 5/157 (3%), IgG antibodies against α-fodrin in 6/157 (4%), and either of these antibodies in 10/157 (6%) blood donors from Germany. In blood donors from Israel, IgA and IgG antibodies against α-fodrin were present in 1/50 (2%) sera, respectively.

The average values of antibodies against α-fodrin were compared between patients classified according to San Diego and ESG criteria. Only patients with autoantibodies were considered for the calculation. The mean concentration of IgA antibodies against α-fodrin was significantly higher in patients classified according to the San Diego than according to the ESG criteria (55.4 ± 35.3 vs 39.8 ± 38.8 U/ml; p = 0.046). In addition, the mean concentration of IgG antibodies against α-fodrin was also significantly higher in patients classified according to the San Diego than the ESG criteria (43.3 ± 22.2 vs 32.8 ± 17.8 U/ml; p = 0.037).

DISCUSSION

SS is an autoimmune disease of unknown etiology. Its leading symptoms, dry eyes and dry mouth, are observed in 5–10% of the European population[1], mainly as a consequence of physiological gland atrophy during aging. Due to the previous lack of specific laboratory markers, it has been debated how the subset of patients with sicca syndrome caused by the autoimmune disorder SS should be classified. The San Diego criteria are arguably the most stringent in classification of SS. We therefore used such patients for the initial evaluation of prevalence of antibodies against α-fodrin in SS, and detected IgA antibodies in 88% and IgG antibodies against α-fodrin in 64% of the sera, with a specificity of 97% and 96%, respectively. Ninety-three percent of the patients had IgA and/or IgG antibodies against α-fodrin.

Since antibodies against α-fodrin were a sensitive marker for definite SS according to the San Diego criteria and their prevalence did not differ between blood donors from Germany and Israel, we used them to compare the ESG and San Diego criteria. The prevalence of IgA and/or IgG antibodies against α-fodrin in primary SS was between 55% and 77% in 3 centers using the ESG criteria (average 71%) compared to 93% in a center using the San Diego criteria. Thus, the specificity of the ESG criteria seems to be lower than that of the San Diego criteria. Moreover, the average concentrations of both IgA and IgG antibodies against α-fodrin were significantly lower in SS patients classified according to the ESG criteria, although only sera with antibody concentrations above the cutoff were considered. The concentrations of antibodies against α-fodrin correlate with the degree of lymphocytic infiltration in salivary glands (M. Tishler, personal communication). In addition, the concentration of IgA antibodies against α-fodrin rapidly decreases in patients treated with glucocorticosteroids for extraglandular complications of SS (unpublished data). Therefore, antibodies against α-fodrin seem to correlate with inflammatory activity in SS. The ESG criteria seem to be able to detect patients with lower disease activity and therefore are more sensitive than the San Diego criteria.

The European criteria were modified recently after a US–European consensus conference and now require the presence of antibodies against Ro for classification of SS, unless a pathological salivary gland biopsy was obtained. However, we have not detected an association of antibodies against Ro with antibodies against α-fodrin in the patients with SS classified according to the San Diego criteria. Both IgA and IgG antibodies against α-fodrin were significantly more prevalent in these patients than antibodies against Ro (prevalence only 38%). Antibodies against Ro have been shown to be associated with the haplotype HLA-B8/DR3[14]. Therefore, a substantial number of patients with SS and a different genetic background will be lost if Ro antibodies are used to define the autoimmune etiology of SS.

Due to the high prevalence of antibodies against α-fodrin in patients with SS classified according to the San Diego criteria, they seem suitable to define patients for clinical studies and should be evaluated in further conferences on classification of SS.

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