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Classification criteria of Sjögren's syndrome

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ABSTRACT

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disease that affects typically the exocrine glands causing mucosal dryness. Dry eyes and mouth are considered by far the most common and early symptoms of the disease but systemic complications may also occur. In 1993, the preliminary European criteria were proposed and widely accepted, consisting of both subjective and objective criteria. Almost ten years later, these classification criteria were revised by introducing more stringent rules and precise diagnostic procedures leading to the currently used American-European Consensus Group (AECG) criteria. The AECG criteria have been largely employed to conduct epidemiologic and clinical studies of patients with SS and proved to be more specific compared to the preliminary European criteria. The recent American College of Rheumatology/Sjögren's International Collaborative Clinical Alliance (ACR/SICCA) criteria that are based exclusively on objective tests, the stringency of the AECG criteria and the potential therapeutic use of biologic agents in SS clearly set the need for new classification criteria. Whether the new diagnostic approach will further encompass subclinical and early forms of the disease remains to be addressed by the scientific community.

1. Introduction

Sjögren's syndrome (SS) is characterized by periepithelial lymphocytic infiltration of the salivary and lacrimal glands that causes destruction of glandular tissue and produces mucosal dryness [1]. The same immunological process can be also observed around the epithelial structures of other organs including the liver, the kidneys and the lungs and is considered an early feature of the disease. Sicca symptoms are usually present in the majority of patients with primary Sjögren's syndrome (pSS) at the time of diagnosis while a half of them experience parotid swelling at that time [2]. A subset of patients has mixed monoclonal cryoglobulins and low C4 complement levels. These findings connote a pre-existing B cell monoclonality in these subjects that remains clinically silent [3]. These patients may develop in the future, extraepithelial manifestations including glomerulonephritis, purpura and peripheral neuropathy and lymphoproliferative malignancies that affect mortality and morbidity of pSS [4,5]. Therefore, the clinical spectrum of SS is composed of two distinct components: the systemic complications mentioned previously and the subjective but disabling manifestations related to mucosal dryness.

Diagnostic criteria must be strict, well defined and include both clinical manifestations and laboratory abnormalities of the disease. Ideally, the included items should exhibit high level of sensitivity and specificity and define a unifying clinicopathological frame that encompasses also the most common and specific features of the disease. Although the clinical spectrum of a disease might be wide, it is not necessary to be reflected in the diagnostic set of criteria, as is the case for the disease activity and damage indexes. On the other hand, the involved diagnostic procedures should be cheap, easily applicable and not invasive if possible, considering that large cohorts are usually recruited in clinical studies. It is fundamental for diagnostic criteria to be widely accepted with the highest level of agreement among the investigators to guide both clinical and basic research. International consensus on such an issue enhances data collection and processing to further insight into the pathogenetic mechanisms as well as the clinical and therapeutic aspects of the disease. The American-European Consensus Group (AECG) criteria are the currently used classification criteria for Sjögren's syndrome (SS), derived after proper modifications and revisions from the preliminary European criteria [6,7]. However, issues concerning the restrictive and stringent nature of the AECG criteria, suggest that the scientific community should discuss extensively the concept of a new classification system for patients with SS.

2. Historical aspects

In 1933, Sjögren published a series of 19 female patients with dry eyes, the majority of whom had also rheumatoid arthritis [8,9]. During the next years, it became apparent that mucosal dryness was the major clinical characteristic of SS and that although it

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shared common features with Mikulicz disease, constituted a distinct entity [9]. The clinical picture of SS was further enriched while serological and histologic data revealed the autoimmune background of the disease [10–13].

In 1965, Bloch et al. studied the characteristics of 62 patients with Sjögren's syndrome defined by the usage of the triad: dry eyes, dry mouth and rheumatoid arthritis or other connective tissue disease [8]. For SS diagnosis any two of the three criteria had to be fulfilled, suggesting that SS might present either as a primary or as a secondary entity accompanying other systemic autoimmune diseases. Three years later, Chisholm and Mason introduced the performance of minor labial salivary gland biopsy to assess histopathologically the involvement of salivary glands in SS, estimating the focus score as defined by Waterhouse and Doniach [14,15]. In this study, it was shown that the presence of at least one focus of lymphocytes per 4 mm^2 (focal sialadenitis) was a consistent and specific finding of SS. Subsequently, Daniels et al. expanded the spectrum of oral component in SS by means of objective measurements including minor labial salivary gland biopsy among other tests. The authors concluded that the histopathologic lesion of focal sialadenitis could be used as an objective diagnostic criterion of SS and that labial salivary gland biopsy besides the establishment of the diagnosis, could offer to the exclusion of other entities such as lymphoma, sarcoidosis and amyloidosis [16].

In 1986, during the first international seminar on Sjögren's syndrome, the four most used diagnostic sets of classification criteria for SS were presented (Copenhagen, Japanese, Greek and California) [17]. The Copenhagen and the Japanese criteria were focused mainly on the objective ascertainment of functional impairment of the salivary and lacrimal glands while histology and serology were not considered obligatory for diagnosis [18,19]. The Greek proposal emphasized the role of focal sialadenitis and the subjective complaints of the disease while the California criteria introduced the presence of autoantibodies and histopathology as distinct items [20,21]. In general terms, these sets of criteria were characterized by high specificity and low sensitivity mainly because of their inability to assess mucosal dryness (both ocular and oral) as a distinct and major subjective component of the disease and to propose reliable methods to confirm its presence. The proposed objective tests had slight differences regarding the normal limits but a concern was raised to employ both focal sialadenitis and the autoimmune nature of the disease expressed by the presence of autoantibodies in the diagnostic set of criteria. The different sets of criteria reflected the diagnostic heterogeneity of SS in the scientific community as well as the diversity in the perception of the disease among the research groups. However, this seminar offered the platform for further discussion and highlighted the need to compose and unify all these different approaches with respect to increase both sensitivity and specificity of such diagnostic tools.

3. The preliminary European criteria

In 1988, after a preliminary workshop where specific questionnaires assessing dry mouth and eyes as well as objective methods and procedures estimating the oral and ocular component of the disease were carefully and detailed designed and agreed [22], a multicenter study was conducted to define classification criteria for SS. Twenty nine experts form 26 centers and 12 countries participated and the study was conducted in two phases [7]. In phase I, the preliminary questionnaires were applied in 480 patients (both SS and aged and sex matched controls) and after multivariate regression analysis, a simplified three item questionnaire for eye and mouth dryness separately was developed. In phase II, specific proposed tests including labial salivary biopsy and serology were performed in 246 pSS patients, 201 secondary SS patients, 113 patients with other autoimmune disease and 133 healthy controls. The participants proposed a new set of 6 diagnostic criteria: 2 subjective and 4 objective. To establish a diagnosis of definite pSS any 4 out of the 6 following criteria should be fulfilled: 1) Dry eyes defined by at least a positive answer out of three related questions 2) Dry mouth defined by at least a positive answer out of three related questions 3) Ocular signs confirmed by abnormal Schirmer's test, Rose Bengal score or other ocular dye score 4) focus score $\geq$1 on minor labial salivary gland biopsy 5) Salivary gland involvement confirmed by parotid sialography, scintigraphy or reduced unstimulated salivary flow 6) autoantibodies including ANA, RFs, anti-Ro/SSA and/or anti-La/SSB. The estimated sensitivity for requiring 3 out of 6 criteria for pSS was 99.1% but specificity was rather low reaching 57.8%. On the contrary, with the inclusion of any 4 items, sensitivity and specificity were found 93.5% and 94% respectively. Four years later, these classification criteria were applied in a multicenter study of 157 SS patients and 121 non SS healthy controls whereas sensitivity was found 97.5% and specificity 94.2% [23].

The preliminary European criteria were the first validated classification criteria with high sensitivity and specificity that were adopted and accepted universally. The major modifications were based in the introduction and assessment of the subjective elements of dryness that were clearly defined and represented by distinct and equal weighting items. Furthermore, certain and few objective tests were chosen as confirmatory procedures for both oral and ocular involvement. Histology and autoantibodies were also employed as distinct items to enhance the specific character of the disease. The six item classification system proved to distinguish successfully patients from healthy controls and at the same time to reveal those patients with sicca symptoms who were suffering from SS.

4. The American-European Consensus Group criteria

The preliminary European criteria raised objections concerning the biased misclassification of patients who could fulfill the items for ocular and oral symptoms and signs but not the histological or the autoimmunity criterion [24,25]. Consistently, subjects with subclinical complaints could be easily excluded especially at disease onset, since these patients needed to satisfy all the rest of the objective criteria to be classified as having pSS. The American-European Consensus Group (AECG) proposed new revised classification criteria to broaden the acceptance of the preliminary European criteria [6]. A ROC curve analysis was performed to assess the accuracy of different combinations of criteria after collecting data from 76 pSS patients, 41 patients with different autoimmune diseases and 63 cases with sicca symptoms but no SS. It was found that the best combination of accuracy, sensitivity and specificity was achieved when 4 out of the 6 criteria were satisfied but at least focal sialadenitis or ant-Ro/anti-La antibodies was included (92.7%, 89.5% and 95.2% respectively). Similarly, when 3 out of 4 objective criteria were met both sensitivity and specificity remained high (84.5% and 95.2% respectively). Thus new revised rules were proposed: pSS could be diagnosed when any 4 out of 6 criteria were met as long as either the item of serology or that of histology was satisfied. Additionally, when 3 out of the 4 objective criteria were fulfilled a diagnosis of definite pSS could be made. Besides these modifications, the presence of ANA and RF was removed from the involved autoantibodies and more exclusion entities were added. However, the key point of the AECG classification criteria was the introduction of focal sialadenitis or the presence of the anti-Ro/SSA and/or anti-La/SSB autoantibodies as an obligatory criterion to emphasize the specific nature of the disease, leading towards a more restrictive and stringent direction compared to the preliminary European criteria.