Classification Criteria of Sjögren's Syndrome

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Chiara Baldini and Stefano Bombardieri

19.1 Introduction

Primary Sjögren's syndrome (pSS) is a complex autoimmune disease characterized by a progressive dysfunction of the salivary glands associated to a variety of systemic manifestations, including lymphoproliferative disorders [1–3]. Thus, pSS can be considered as a heterogeneous autoimmune entity possessing both organ-specific and systemic features and encompassing a wide spectrum of clinical manifestations, serological abnormalities, and scattered complications [4–9]. The complexity of SS clinical presentation is moreover increased by the fact that SS may occur alone, as a primary condition, or in association with other connective tissue diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc), as secondary SS (sSS) variants [10–13]. This complexity makes it difficult to classify the disease and to identify a homogeneous group of patients with a common etiopathogenesis or prognosis. This is probably the most important reason for explaining why it remains an unresolved issue to reach a scientific consensus on universally accepted classification criteria for pSS [14, 15]. The American-European Consensus Group (AECG) criteria are the currently used classification criteria for Sjögren's syndrome (SS) and were derived after proper modifications and revisions from the preliminary European criteria [16, 17]; nonetheless, the recent American College of Rheumatology/Sjögren's International Collaborative Clinical Alliance (ACR/SICCA) criteria [18] that are based exclusively on objective tests clearly set the need for the scientific community to discuss extensively the concept of a new classification system for patients with SS [19–21].

Herewith a critical historical overview of the different criteria sets for SS will be provided from the beginning up to the more recent proposals.

C. Baldini • S. Bombardieri (✉)
Rheumatology Unit, University of Pisa, via Roma 67, Pisa, Italy
e-mail: s.bombardieri@int.med.unipi.it

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19.2 Sets of Classification Criteria Proposed for pSS over the Time: The Long Journey to the Preliminary European Criteria 1993

During the First International Seminar on pSS, held in Copenhagen in May 1986, the four – at that time – most widely used criteria for definition of pSS were presented. Namely, the four different sets of criteria were the Copenhagen (1976) [22], the Japanese (1977) [23], the Greek (1979) [24], and the San Diego criteria (1986) [25]. In 1975, the San Francisco criteria for SS had been previously proposed in the USA [26]. Table 19.1 summarizes their similarities and dissimilarities. All these criteria sets were mainly focused on assessing the glandular signs and symptoms of the disease utilizing different procedures with different (and in many cases still not assessed) levels of sensitivity, specificity, and reliability. The attitude of the criteria sets versus the histology and the serological patients' profiles differed significantly from one set to another. In particular, the Copenhagen and the Japanese criteria were focused mainly on the objective assessment of functional impairment of the salivary and lachrymal glands, while histology and serology were not considered obligatory for diagnosis. 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.

Overall, in spite of their differences, these proposed classification criteria might hypothetically select and correctly classify patients affected by pSS, when used by single groups of investigators, but they were not free from disadvantages. The San Francisco criteria, for example, emphasizing the specificity of focal sialadenitis on minor salivary gland biopsies and the role of the objective tests in the diagnosis of pSS, appeared to be quite stringent and not completely able to properly diagnosed patients with a milder sicca syndrome, especially at the onset of the disease. The Copenhagen criteria on the other hand required the presence of two abnormal test assessing the dryness of the eyes and two abnormal tests assessing the dryness of the mouth, but they did not require as a mandatory item the salivary gland biopsy. Another drawback of the Copenhagen criteria was moreover that they pointed out that it was up to the local pSS center to decide which objective tests to select, and therefore, the tests used may vary slightly from center to center. Finally, another potential drawback was represented by the fact that some of the criteria sets did not consider the presence of autoantibodies.

During the First International Seminar on pSS, the comparison of all these criteria sets made it possible to focus on the lack of homogeneity in the diagnostic tools for pSS and therefore on the potential discrepancies observed in clinical studies and/or in the epidemiological surveys [27].

In 1988, 2 years after the First International Seminar on pSS held in Copenhagen in 1986, a workshop was held in Pisa sponsored by the Epidemiology Committee of the Commission of the European Communities (EEC-COMAC) involving 29 experts, representing 11 European countries and Israel. The aim of this collaboration was to define and validate simple standardized diagnostic tools for pSS and to design a multicenter study to define classification criteria for SS [17, 28]. The

Table 19.1 Similarities and dissimilarities of the historical criteria sets for SS: Copenhagen, Japanese, Greek, San Diego, and San Francisco criteria

	Copenhagen (1976)	Japanese (1977)	Greek (1979)	San Diego (1986)	San Francisco (1975, 1984)
Definition of probable/definite SS	–	+	+	+	+
Definition of pSS/sSS	+	–	+	–	+
Subjective xeroftalmia	–	+	+	–	–
Subjective xerostomia	–	+	+	+	–
Objective tests exclusively (no subjective symptoms)	+	–	–	–	+
Parotid gland swelling (history)	–	+	+	–	–
Ocular tests:					
Schirmer-I test	+ (≤10 mm/5′)	+ (≤10 mm/5′)	+ (≤10 mm/5′)	+ (<9 mm/5′)	+ (≤10 mm/5′)
Breakup time	+ (≤10 s)	–	–	–	+
Rose bengal (van Bijsterveld score)	+ (≥4)	+(≥2)	+ (≥4)	+(≥4)	+(≥4)
Fluorescein test	–	+	–	+	–
At least two abnormal tests as evidence of KCS	+	+	–	+	+
Oral tests:					
Unstimulated whole saliva	+	–	–	+	
Stimulated parotid flow rate	–	–	+	+	–
Scintigraphy	+	–	–	–	–
Sialography	–	+	–	–	–
Minor salivary obligatory criterion	No	No	Yes	Yes	Yes
Focus score (minor salivary glands biopsy)	>1	>1	≥2	≥2	>1
Serological findings					

(continued)

Table 19.1 (continued)

	Copenhagen (1976)	Japanese (1977)	Greek (1979)	San Diego (1986)	San Francisco (1975, 1984)
Antinuclear antibodies	–	–	–	+	–
Anti-SS-A/Ro	–	–	–	+	–
Anti-SS-B/La	–	–	–	+	–
IgM-rheumatoid factor	–	–	–	+	–

novelty was represented by the fact that previously proposed classification criteria had generally been formulated by experts on the basis of clinical experience or derived from data coming from a single center. The preliminary European classification criteria, on the contrary, represented the first attempt to create the criteria for pSS through a multicenter study aimed at deriving and validating standardized methodologies directly from real patients. A simple questionnaire (20 questions: 13 regarding the ocular involvement and 7 regarding the oral involvement) for dry eyes and dry mouth was validated. Data from 480 patients (240p SS and 240 controls) were gathered. Univariate and multivariate analysis and stepwise multiple regression were used to select those questions and combinations of questions that showed the best performance in correctly classifying patients and controls. Thus, a simplified questionnaire consisting of three questions for dry eyes and three for dry mouth emerged from this section of the study. For part II, each center recruited 40 patients – 10 with pSS, 10 with sSS, 10 with other connective tissue disorders (CTDs) without SS, and 10 controls. The CTD diagnoses were made on the basis of the standard criteria for the various diseases, while the diagnosis of pSS was based at the best of the clinical skills of the expert observer clinician as gold standard. In these patients a limited set of proposed diagnostic tests were validated (including Schirmer-I test, rose bengal test, tear breakup time, tear fluid lactoferrin level, stimulated and unstimulated saliva flow, biopsy of the minor salivary glands, parotid sialography, and salivary gland scintigraphy). The exact procedure to be followed for each test was described in the protocol. The data in part II were subjected to the same analysis of part I, with the addition of a classification tree in order to determine the optimal classification strategy. From the analysis the consensus group established a set of four objective criteria for the diagnosis of SS. These four criteria and the two subjective criteria are presented in Table 19.2. The preliminary European criteria were based on any four out of six items including ocular and oral symptoms (such as oral and ocular dryness), ocular and oral signs (such as positive Schirmer-I test, rose bengal score, parotid sialography, scintigraphy, and unstimulated salivary flow), immunological parameters, and focal sialadenitis. For primary pSS, the presence of four out of six items had good sensitivity (93.5 %) and specificity (94 %). Some exclusion criteria were also added to this classification set for pSS and, namely, preexisting lymphoma, acquired immunodeficiency syndrome, sarcoidosis, and graft-versus-host disease [17].

Table 19.2 European preliminary criteria for Sjögren's syndrome

I. Ocular symptoms: a positive response to at least one of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms: a positive response to at least one of the following questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs – that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
1. Schirmer-I test (≤5 mm in 5 min)
2. Rose bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)
IV. Histopathology: focus score ≥1 on minor salivary gland biopsy (focus defined as an aggregation of at least 50 mononuclear cells; focus score defined as the number of foci per 4 mm^2 of glandular tissue)
V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
1. Unstimulated whole salivary flow (<1.5 ml in 15 min)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts
3. Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
VI. Autoantibodies: presence in the serum of the following autoantibodies:
1. Antibodies to Ro(SSA) or La(SSB) antigens or both
2. Antinuclear antibodies
3. Rheumatoid factor
Exclusion criteria
Preexisting lymphoma
Acquired immunodeficiency syndrome (AIDS)
Sarcoidosis
Graft-versus-host disease

Furthermore, for the diagnosis of sSS, all the serological tests were excluded, and the consensus group established that it was sufficient, the presence of at least three out five items.

In 1996, the criteria set was validated on a total of 278 cases (157 SS patients and 121 non-SS controls) collected from 16 centers in 10 countries, and the criteria confirmed to have a sensitivity of 97.5 % and a specificity of 94.2 % [29].

After their validation the European classification criteria received a large acceptance by the scientific community because of their good combination of sensitivity and specificity. In fact, when previously proposed, the criteria had been used to classify patients with pSS, and controls enrolled in the European study all showed a very high specificity (range 97.9–100 %) but a low sensitivity (range 22.9–72.2 %)

which make them less useful for epidemiological surveys. Other potential advantageous characteristics of the European criteria were that they distinguished between pSS and sSS but avoid the concept of definite/possible SS. Furthermore, they – as do the Copenhagen criteria – rely on unstimulated or basal tests and did not require as mandatory for the diagnosis invasive tests such as the minor salivary gland biopsy.

Nonetheless, during the subsequent International Symposia on SS, the European criteria for the classification of SS generated an extensive discussion. The key point of debate was that these criteria could be fulfilled in the absence of either autoantibodies or positive findings on labial salivary gland biopsy and, then, can also be met by patients with sicca symptoms, but not strictly primary SS. Furthermore, a criteria set in which two out of the six items were devoted to subjective complaints cannot allow to correctly classify patients with SS but without symptoms [30].

19.3 From the European Classification Criteria to the American-European Classification Criteria

The preliminary European criteria raised objections concerning the misclassification of patients who could fulfill the items for ocular and oral symptoms and signs but not the histological or the autoimmunity criterion. As a consequence of the abovementioned criticisms which were raised against them, the SS Foundation proposed that a joint effort be undertaken by the Europe Study Group on classification criteria for SS and a group of American experts. A detailed analysis of the European database of the patients and controls collected during the validation phase of the European Criteria was undertaken. A receiver-operating characteristic (ROC) curve of the revised criteria was constructed based on the analysis of 180 cases provided by 16 centers from 10 European countries. In more details, patient and control populations included 76 patients affected by pSS, 41 patients with a diagnosis of CTD without SS, and 63 control (no SS) subjects. Based on this, the ROC curve analyzes the condition "positivity of any four out of the six items" and the condition "positivity of four out of six items with the exclusion of the cases in which both serology and histopathology were negative"; the second condition had a lower sensitivity (89.5 % vs 97.4 %) but a higher specificity (95.2 % vs 89.4 %). The presence of any three of the four objective criteria items showed a slightly lower accuracy (90.5 %) but a specificity of 95.2 % and a sensitivity of 84.2 %. This combination was, therefore, judged reliable as well. The American-European Consensus Group, then, even maintaining the previous European scheme of six items, introduced the obligatory rule that for a definite diagnosis of pSS, either the minor salivary gland biopsy or serology had to be positive (see Table 19.3) [16]. Other modifications were proposed and included in the European criteria set to make the item definitions more precise. In particular, it was specified that Schirmer-I test should be performed with standardized paper strips in unanesthetized and closed eyes following the European and the Japanese tradition. Moreover, as rose bengal is not available in many countries, other ocular dye scores (i.e., fluorescein stain and lissamine green) were

Table 19.3 American-European Consensus Group Criteria. Revised international classification criteria for Sjögren's syndrome

I. Ocular symptoms: a positive response to at least one of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms: a positive response to at least one of the following questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs – that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
1. Schirmer-I test, performed without anesthesia (<5 mm in 5 min)
2. Rose bengal score or other ocular dye score (>4 according to van Bijsterveld's scoring system)
IV. Histopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score >1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue
V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
1. Unstimulated whole salivary flow (<1.5 ml in 15 min)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts
3. Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
VI. Autoantibodies: presence in the serum of the following autoantibodies:
1. Antibodies to Ro(SSA) or La(SSB) antigens or both
Revised rules for classification
For primary SS
In patients without any potentially associated disease, primary SS may be defined as follows:
(a) The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (histopathology) or VI (serology) is positive
(b) The presence of any 3 of the 4 objective criteria items (i.e., items III, IV, V, VI)
(c) The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey
For secondary SS
In patients with a potentially associated disease (for instance, another well-defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS
Exclusion criteria
Past head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficiency syndrome (AIDS)
Preexisting lymphoma

(continued)

Table 19.3 (continued)

Sarcoidosis
Graft-versus-host disease
Use of anticholinergic drugs (since a time shorter than fourfold the half-life of the drug)

suggested to replace it. They also defined a positive minor salivary glands biopsy as one focus of lymphocytes or more specifying that it/they had to be adjacent to normal-appearing mucous acini per 4 mm^2 glandular tissue. Finally, a consensus on the list of exclusion criteria was also reached. In comparison to the exclusion criteria adopted by the European preliminary criteria, the category "anticholinergic" drugs was introduced instead of "antidepressant, antihypertensive, parasympatholytic drugs, and neuroleptic agents," the term sialadenosis was deleted, and the definition past head and neck radiation treatment added. Finally, it was decided to add the hepatitis C virus (HCV) infection as an exclusion criterion considering the sicca symptoms observed in some patients with HCV as one of the extrahepatic manifestations of the virus which has to be differentiated from SS.

For sSS it was established that in patients with a potentially associated disease, it has to be considered as indicative of the disorder and the presence of the item I or II plus any two from among items III, IV, and V [31].

Overall, the American-European Revised Classification Criteria, even preserving many aspects of the European preliminary criteria, appear to be more stringent [32, 33]. In particular in 2006, the comparability of the Copenhagen, San Diego, European, and AECG criteria sets was assessed prospectively, examining 222 consecutive patients referred to the Department of Rheumatology of Ljubljana. The authors found that 90 out of 222 patients (41 %) fulfilled at least one classification criteria set. The highest number of patients fulfilled the European criteria (36 %), followed by the Copenhagen criteria (28 %), the AECG criteria (26 %), and the San Diego criteria (9 %) sets. The AECG criteria resulted therefore to be highly specific and quite restrictive [32].

19.4 Classification Criteria for pSS: Present and Future

The AECG criteria represent the most commonly employed tool to classify patients with primary and secondary SS in clinical trials, in epidemiological studies, and in clinical practice, given their high sensibility and specificity [34–36]. However, according to results derived from clinical settings, the higher specificity of the AECG criteria in comparison with preliminary criteria might lead to the exclusion of a considerable proportion of patients with classical features and long-term outcome complications of SS [37, 38]. Recently, the American College of Rheumatology (ACR)/Sjögren's International Collaborative Clinical Alliance (SICCA) endorsed new classification criteria for pSS [18, 39, 40]. These criteria were derived from 1107 participants. According to the ACR/SICCA criteria, for SS diagnosis, two out of the following three are required: (a) positive anti-Ro/SSA and anti-La/SSB or

positive rheumatoid factor and ANA ≥1:320, (b) ocular staining score ≥3 (sum total score 0–12; 0–6 score for staining of the cornea with fluorescein, 0–3 score for staining of both the nasal and temporal conjunctivae with lissamine green), and (c) focal lymphocytic sialadenitis with focus score ≥1 in labial gland biopsy. The ACR/SICCA criteria do not target the general population but individuals suspected to be affected by SS and were aimed at selecting homogenous patients to be enrolled in clinical trials.

Interestingly, Rasmussen et al.[41] recently compared the performance of the new ACR and the AECG classification criteria for SS and found concordant results when applied to a homogeneous cohort of patients with sicca symptoms, providing no clear evidence for increased value of the new ACR criteria over the old AECG criteria from the clinical and biological perspective 11. In this scenario, the entire scientific community is making an international effort to create novel criteria able to overcome the limitations of both the existing criteria set. In fact, a major limitation of the ACR classification criteria is represented by the fact that they require an evaluation by a practitioner specialized in eyes and lip biopsy and may oversee patient's subjective symptoms; on the other hand, AECG criteria rely on the employment of obsolete objective tests like sialography and scintigraphy. From this perspective, the addition of salivary gland ultrasonography (SGUS) has been proposed in order to replace more painful or invasive tests [42–46]. Despite the encouraging results obtained, however, the employment of SGUS as an adjunctive item in classification criteria needs further validation and standardization. In parallel a number of studies have been designed searching for novel and specific biomarkers for pSS, but their results are still in progress [47–49].

In 2013, an ACR-European classification criteria working group has been found in order to elaborate novel classification criteria derived from the existing ones. In fact, the burden of creating a completely novel set of classification criteria has not appeared justified, considering the lack of novel specific biomarkers for the disease. Hopefully, the novel criteria will be able to select homogenous patients opening new avenues for clinical trials and epidemiological studies.

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