Classification Criteria in Sjögren's Syndrome

4

Chiara Baldini

Introduction

Sjögren's syndrome (SS) is a complex systemic autoimmune disease which primarily affects salivary and lacrimal glands, leading to a persistent dryness of the mouth and eyes due to the lymphocytic infiltration and functional impairment of the exocrine glands [1]. The disease, however, encompasses a very large spectrum of clinical and biological manifestations ranging from a benign exocrinopathy to a complex systemic disorder with possible lymphoproliferative complications [2]. The complexity of SS is furthermore increased by the fact that SS may occur alone, as a primary condition (pSS), or in association with other autoimmune systemic diseases, including rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis [3]. The heterogeneity of the disease is probably one of the most important reasons explaining the various classification criteria sets for SS that have been proposed over the years since the 1970s. In 2016, an international agreement was found for the definition of SS, based on the so-called "European–American Consensus Group (EACG) criteria," which requires the presence of either focal lymphocytic infiltrates in minor salivary glands with a focus score of 1 or more, or anti-SSA autoantibodies [4]. These criteria have opened up new epidemiological and clinical studies, thus representing a crucial cornerstone in the field. Herewith, we provide an historical overview on SS criteria mentioning also possible future steps towards improving SS patients' classification.

C. Baldini (✉)
Rheumatology Unit, University of Pisa, Pisa, Italy

The "Old" Classification Criteria Sets for Primary Sjögren's Syndrome

Several different classification criteria sets have been proposed for SS over the years [5]. The traditional criteria sets most widely used in the past, include the San Francisco criteria (proposed in 1975 and subsequently revised in 1984) [6, 7], the Copenhagen [8], the Japanese [9], the Greek [10] and the San Diego criteria, all proposed in 1986 [11]. The Japanese criteria have been subsequently updated over the years and the latest version was proposed in 1999 [12] (see Table 4.1).

Nearly all of them included items focusing on the dysfunction and the inflammation of the lacrimal and salivary glands in the context of a systemic autoimmune response. Nonetheless, there exist a number of important differences between them.

Firstly, except the Copenhagen one, all the criteria sets were using the terminology "probable" and "definite" SS, whereas the Copenhagen and the Greek criteria differentiated primary from secondary Sjögren [8, 10]. Secondly, some of the classification criteria sets included items focusing on both patients' subjective symptoms and objective findings, whereas some others included exclusively the objective findings. Thirdly, as far as ocular tests were concerned, differences emerged regarding the tests used, the range and the cut-off levels of normal values, and the requirement of solely one abnormal test to allow the diagnosis of keratoconjunctivitis sicca (the Greek criteria) [10] or at least two abnormal tests (the San Francisco [6], Copenhagen [8], Japanese [9], and San Diego criteria [11]) (see Table 4.1).

Regarding major salivary gland involvement, nearly all of the five criteria sets included salivary flow rate assessment. Sialometry was, nonetheless, performed by collecting either unstimulated or stimulated salivary flow. Only the Japanese criteria used abnormal sialography as a criterion for salivary gland assessment [9]. In contrast, the Copenhagen criteria employed salivary gland scintigraphy to provide a functional evaluation of all salivary glands [8]. The minor salivary

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Table 4.1 "Old" classification criteria

	Copenhagen (1976)	Japanese (1977)	Greek (1979)	San Diego (1986)	San Francisco (1975, 1984)
Subjective dry eye	–	+	+	–	–
Subjective dry mouth	–	+	+	+	–
Exclusively objective abnormalities	+	–	–	–	+
History of parotid gland swelling	–	+	+	–	–
Ocular tests:					
Schirmer-I test	+ (≤10 mm/5′)	+ (≤10 mm/5′)	+ (≤10 mm/5′)	+ (<9 mm/5′)	+ (≤10 mm/5′)
Break-up time	+ (≤10 s)	–	–	–	+
Rose Bengal (van Bijsterveld score)	+ (≥4)	+(≥2)	+ (≥4)	+(≥4)	+(≥4)
Fluorescein test	–	+	–	+	–
One abnormal test as evidence of KCS	–	–	+	–	–
At least two abnormal tests as evidence of KCS	+	+	–	+	+
Oral parameters:					
Unstimulated whole saliva	+	–	–	+	–
Stimulated parotid flow rate	–	–	+	+	–
Scintigraphy	+	–	–	–	–
Sialography	–	+	–	–	–
Minor salivary glands biopsy	>1	>1	≥2	≥2	>1
Minor salivary glands biopsy mandatory criterion	No	No	Yes	Yes	Yes
Antinuclear antibodies	–	–	–	+	–
Anti-SS-A/Ro	–	–	–	+	–
Anti-SS-B/La	–	–	–	+	–
IgM-RF	–	–	–	+	–
Terminology probable/definite SS	–	+	+	+	+
Terminology pSS/sSS	+	–	+	–	+

glands biopsy was included in all the criteria sets. However, both the Greek and the San Diego criteria considered the minor salivary gland biopsy to be mandatory with a focus score ≥2 as a crucial prerequisite for the diagnosis of SS [10, 11]. On the contrary, the San Diego criteria specified that an abnormal minor salivary gland biopsy was necessary only for "definite" SS, whereas the category of "probable" SS could be fulfilled in the absence of a biopsy [11]. According to the Copenhagen criteria [8], a patient could have been diagnosed as having SS without an abnormal salivary gland biopsy, while, finally, according to the Japanese criteria, a lachrymal gland biopsy could replace the minor salivary glands biopsy [9]. As far as the modalities for performing the biopsy were concerned, all the criteria adopted the guidelines which had been previously proposed by Daniels et al. in 1975 [6], in which focal sialadenitis had been differentiated from chronic nonspecific sialadenitis, defining a focus as a cluster of at least 50 mononuclear cells. To diagnose primary SS, an average focus score per 4 mm^2 was required, based on the histological evaluation of at least four glands. Moreover, according to Daniels, the biopsy sample had to be obtained through clinically normal mucosa, and lobules characterized by nonspecific infiltrates had to be excluded from the evaluation [6].

Finally, for the first time, the San Diego criteria had utilized for the diagnosis of SS the presence of autoantibodies (antinuclear antibodies, anti-SS-A/Ro, anti-SS-B/La, and IgM-RF) [11].

Overall, in spite of their differences, these proposed classification criteria hypothetically could have been able to select and correctly classify patients affected by SS, when used by a single group of investigators. However, the major limitation of these criteria was that they never had been validated in multicenter studies or by means of standard statistical approaches, making comparison of epidemiological studies difficult. Furthermore, in many cases, the sensitivity, specificity, and reliability of the procedures followed for the definition of the disease remained yet to be assessed.

The Preliminary European Criteria of the Epidemiology Committee of the Commission of the European Community

In 1988, the Epidemiology Committee of the Commission of the European Community decided to support a multicenter study to reach a consensus on classification criteria for SS. The study began in 1989 and ended in 1993 with the

definition of the Preliminary European Classification Criteria for SS [13]. It is noteworthy that for the first time criteria were derived directly from a real patient cohort. The European criteria were based on a six-item set and any four of these six items were considered to be required for the diagnosis. These items included (i) ocular symptoms, (ii) oral symptoms; (iii) ocular signs (defined by positive Schirmer-I test and/or Rose Bengal score); (iv) findings indicating salivary gland involvement assed by parotid sialography, scintigraphy, or unstimulated salivary flow; (v) focal sialadenitis observed in lip biopsy; and (vi) presence of autoantibodies. For primary SS, the presence of four out of six items showed high sensitivity (93.5%) and specificity (94%). Some exclusion criteria were also added to this classification set for SS, in particular the presence of preexisting lymphoma, acquired immunodeficiency syndrome, sarcoidosis, and graft-versus-host disease. The diagnosis of secondary SS was applied for those subjects in whom SS occurs in the presence of an associated connective tissue disease, or with the exclusion of the autoantibody item, four out of the remaining five items were met.

Subsequently, the criteria set was then validated in a survey carried out in a different population of patients and controls showing a high sensitivity (97.5%) and specificity (94.2%) [14].

After their validation, the European classification criteria achieved wide acceptance by the scientific community in view of their accuracy. Nonetheless, the European criteria for the classification of SS generated extensive discussion. The key point of the debate was that these criteria could be fulfilled in the absence of either autoantibodies or positive findings on labial salivary gland biopsy and then could also be met by patients with sicca symptoms but without primary SS. Furthermore, a criteria set in which two out of six items comprised subjective complaints formed a major obstacle to correctly classify those patients with SS but no symptoms.

The 2002 American–European Consensus Group Criteria

By 2002, a joint effort was undertaken by the European Study Group on Classification Criteria for SS and a group of American experts to broaden the acceptance of the SS classification criteria. The American–European Consensus Group, maintaining the previous European scheme of six items, introduced the obligatory rule that for a definite diagnosis of SS either the minor salivary gland biopsy or autoimmune serology had to be positive (see Table 4.2) [15]. It was also specified that Schirmer-I test should be performed with standardized paper strips in unanesthetized closed eyes, following the European and the Japanese tradition. Moreover, as the Rose Bengal test was not available in many countries, other ocular dye scores (i.e., fluorescein stain and lissamine green) were proposed. These modified criteria also defined a positive minor salivary gland biopsy as the presence of at least one focus of lymphocytes, specifying that it/they had to be adjacent to normal appearing mucous acini per 4 mm^2 glandular tissue. Moreover, it was decided to add hepatitis C virus (HCV) infection as an exclusion criterion, considering that the sicca symptoms observed in patients with SS in association with HCV needed to be differentiated from primary SS.

Table 4.2 American–European Consensus Group criteria 2002

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's I test, performed without anesthesia (<5 mm in 5 minutes) 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 minutes) 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

The American–European Consensus Group criteria were published in 2002 and adopted as the gold standard in Europe and the USA [15]. The acceptance of the AECG criteria probably represented one of the most significant achievements of clinical research in pSS. The availability of a definite classification criteria set able to select patients with homogeneous and comparable clinical, serological, and histological features delineated a starting point for

clinical and therapeutic studies [5]. Before the AECG criteria, the number of studies assessing the incidence and the prevalence of pSS in the general population was to be counted on one hand. Moreover, those few studies had produced highly heterogeneous results, mainly because of differences in diagnostic criteria. Binard A. et al. [16] carried out a systematic review of published epidemiological studies of pSS considering all publications published between January 1966 and June 2006. Overall, the prevalence of pSS estimated according to the Preliminary European criteria varied from a minimum of 0.35 (95%CI, 0.17–0.65) to a maximum of 3.59 (95% CI, 2.43–5.08), according to the Copenhagen criteria from 0.77 (95% CI, 0.44–1.25) to 2.7 (95% CI, 1–4.5) and according to the AECG criteria from 0.05 (95% CI, 0.048–0.052) to 0.6 (95% CI, 0.24–1.39). For example, the prevalence of pSS, estimated according to the Preliminary European criteria, was 1.67–2.5 higher than the prevalence of pSS according to AECG criteria [16]. Due to the high specificity, the AECG criteria attracted heavy criticism from various sides.

On one hand, the greater specificity of the AECG criteria enabled investigators to identify more homogeneous cohorts of patients with predictable advantages in clinical trials. The AECG criteria have thus been employed as inclusion criteria in several randomized clinical trials (RCTs) carried out in pSS. For example, the AECG criteria have been adopted in RCTs assessing the safety and the efficacy of etanercept [17], dehydroepiandrosterone [18], and rituximab [19]. Other spin-offs were valid activity indexes for pSS, including the recently developed EULAR Sjögren's syndrome disease activity index (ESSDAI) [20] and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) [21]. Consistent with data on the performance of the AECG criteria in clinical practice and in research, there was a general agreement that stringency might represent both strength and weakness of the AECG criteria at the same time when compared with the preliminary European criteria. On one hand, stringency guarantees the homogeneity of the patients enrolled in clinical trials or epidemiological studies and, in some instances, shape the sensitivity and the specificity with regard to pSS as an autoimmune disease.

On the other hand, requiring that any given patient with SS must have either anti-SSA and/or SSB autoantibodies (item vi) or a positive lower lip biopsy (item iv) or both implied that an invasive technique was mandatory simply to fulfill classification criteria. This also could lead to the exclusion from the diagnosis of pSS of those patients with a focus score between 0 and 1 and negative anti-Ro/SSA, who may nonetheless have a similar outcome over the follow-up as the AECG patients [5]. There was, therefore, a general concern that the 2002 classification criteria did not cover the broad clinical and immunological heterogeneity of pSS.

The ACR/EULAR 2016 Classification Criteria

In 2012, the Sjögren's International Collaborative Clinical Alliance (SICCA) issued new classification criteria, which were swiftly endorsed by the American College of Rheumatology (ACR). These criteria were developed using a consensus methodology among 20 experts and data derived from 1362 patients. This classification criteria set for defining a case as SS required the presence of at least two of the following three items: (1) positive serum anti-SSA and/or anti-SSB or (positive rheumatoid factor and antinuclear antibody titer >1:320); (2) ocular staining score >3; or (3) presence of focal lymphocytic sialadenitis with a focus score >1 focus/4 mm^2 in labial salivary gland biopsy samples [22]. A comparative study of the AECG and ACR criteria performed in 2014 found a high concordance rate of 0.81, but also clearly showed that some items, especially for ocular involvement, needed further revision [23–25]. Indeed, difficulties in clinical studies raised by the coexistence of the two criteria sets resulted in international confusion. In 2016, all this resulted in the development of a new consensual classification criteria set for pSS combining features of the earlier ACR and AECG criteria. The new criteria set was validated jointly by ACR and EULAR committees in order to provide a common "language" to the scientific community enabling to select homogeneous patients to be included in epidemiological, clinical, and therapeutic studies (Table 4.3) [4].

The methodology used in the development of the 2016 ACR/EULAR criteria for pSS provided a weighted scoring system applicable in daily routine clinical practice. This ACR/EULAR criteria set differs from the earlier AECG criteria in many aspects. First of all, the new ACR/EULAR criteria excluded oral and ocular symptoms from the classification criteria in favor of more objective items. However, the heritage of the questionnaire for glandular symptoms—a key point of the "old" AECG criteria will live on as a tool to screen patients with suspicious pSS. Noteworthy, the 2016 ACR/EULAR criteria are indeed intended to be applied to any patient with at least one symptom of ocular or oral dryness (based on AECG questions). The other new entry criterion was the suspicion of SS due to systemic fea-

Table 4.3 *ACR/EULAR Classification Criteria* 2016 for primary Sjögren syndrome

Item	Weight
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥1	3
Anti-SSA (Ro) +	3
Ocular staining score ≥5 (or van Bijsterveld score ≥4) on at least one eye	1
Schirmer ≤5 mm/5 min on at least one eye	1
Unstimulated whole saliva flow rate ≤0.1 ml/min	1

tures derived from the ESSDAI, allowing the classification of pSS for patients even without salivary and ocular symptoms, but with extra-glandular manifestations or B-cell activation markers. A weighted scoring system was then suggested, with 3 points each for presence of focal lymphocytic sialadenitis with a focus score >1 focus/4 mm^2 in labial salivary gland biopsy and positive anti-SSA antibodies and 1 point each for unstimulated whole salivary flow (UWSF) ≤0.1 mL/min, Schirmer's test result ≤5 mm/5 min and Ocular Staining Score (OSS) ≥5 or van Bijsterveld (VB) score ≥4. A weighted score ≥4 classifies the patient as having pSS. The new criteria also modified some technical items. The ocular staining score threshold was increased to 5, leading to a higher specificity compared to the previous score of 3. The immunological profile includes only SS-A(Ro) antibodies, while positivity for antinuclear antibodies and rheumatoid factor or for isolated anti-SS-B(La) were excluded being considered too unspecific. Considering the anti-SSA (Ro) profile, the criteria do not distinguish between the presence of both anti-Ro60 and anti-Ro52, anti-Ro60 alone, and isolated anti-Ro52. Regarding the exclusion of the anti-SSB/La positivity among the items, Baer et al. [26] showed that the anti-SSB(La)-positive/SSA-negative serologic profile was not associated with pSS phenotypic features. Danda et al. [27], moreover, observed that these patients were younger, much less likely to have a lymphocytic infiltrate found on pathological evaluation of minor salivary glands, and presented less frequently extra-glandular manifestations. Finally, the existing literature concordantly reports that anti-SSB(La)-positive/SSA-negative patients are quite uncommon. Finally, the novel criteria have underpinned the relevance of a severe salivary and lachrymal dysfunction for pSS classification. In fact, if patients do not have at the same time both a focal sialadenitis at the minor salivary gland biopsy and a positivity for anti-SSA(Ro) to be classified as affected by pSS, they must necessary present a severe ocular or oral involvement. This has to be taken into account particularly when using the novel criteria set to recruit patients in clinical trials, as patients are generally required to have a preserved glandular function to be included in RCTs [28].

Unmet Needs and Future Perspectives

The ACR/EULAR 2016 criteria undoubtedly represent a crucial step forward in classifying pSS patients. However, there are some issues to consider that could be improved in the coming years. First of all, in order to improve inter-reliability across pathologists, the interpretation of the minor salivary gland histopathology needs to be standardized. Fisher et al. [29] have recently published a consensus on how to perform labial salivary gland histopathology for the classification of SS and clinical trials, in which tissue requirements, identification of the characteristic focal lymphocytic sialadenitis, and evaluation of the focus score and the germinal centers were specified. Furthermore, Lucchesi et al. [30] proposed using a digital image analysis and a specific fraction area in the histological assessment of pSS salivary glands. A second point to consider is the incorporation of salivary gland ultrasound into the criteria [31]. Adding ultrasound as a criterion has been reported to increase the sensitivity of the American–European Consensus Group (AECG) criteria set from 77.9% to 87%, and similar results were obtained with the 2016 ACR/EULAR classification criteria [32, 33]. Recently, the international EULAR US-pSS Task Force reported the UTOPIA [34] (Ultrasound TO diagnose and classify PrImAry Sjögren's syndrome) study in which similar weight to ultrasound compared to minor items had been allocated, thus improving significantly the criteria sensitivity. Ideally, ultrasound may help to recognize pSS patients in an early phase of the disease, when the salivary flow might be still preserved. Cornec et al. [35] performed ultrasound in a prospective cohort of patients with suspected pSS and demonstrated that this imaging technique was able to distinguish patients with pSS from controls with a sensitivity of 62.8% and a specificity of 95.0%. Similarly, Baldini et al. [36] tested the accuracy of ultrasound for the early detection of pSS in patients with symptom duration of 5 years obtaining a sensitivity of 66%, and a specificity of 98%. The concept of early pSS is still in its infancy [37]. Considering that anti-SSA (Ro) autoantibodies are present for up to 18–20 years before the diagnosis of primary pSS is established, we may speculate that the combination of serology and ultrasound may help to classify the disease before overt glandular damage is manifest, even in the pediatric age [38, 39]. Finally, another issue on which the jury is still out, remains the performance of classification criteria for SS occurring in patients with other concomitant autoimmune diseases [3]. The concept of secondary SS has been largely debated and indeed, as a consequence of nomenclature, "secondary" SS has been often excluded from clinical trials [40]. Nowadays, a critical appraisal of this definition is ongoing and it is widely recognized that a change in terminology and more stringent classification may be reached in the next future.

In conclusion, all the available data have consistently demonstrated the global validity, usefulness, and feasibility of the ACR/EULAR 2016 criteria. Future research will allow the scientific community to optimize the criteria in order to define more precisely specific disease subsets as a prerequisite for precision therapy in SS.

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