Do we need new diagnostic criteria for Sjögren’s syndrome?

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Summary

Diagnostic and classification criteria for Sjögren’s syndrome (SS) continue to evolve as more is learned about SS and about autoimmune diseases in general. Among diagnostic or classification criteria for SS that are in current use, most include various and variable combinations of results from questions about symptoms and objective tests, many of which are not specific to SS. Given the rapid increase of genetic knowledge about other autoimmune diseases and the potential of finding and testing new biological agents to treat SS, selection of patients who have as uniform a disease process as possible becomes an important goal to better understand and treat this prevalent autoimmune disease. Such is the goal and promise of the latest entry into the SS classification criteria field.

Twelve sets of diagnostic or classification criteria for Sjögren’s syndrome (SS) have been proposed between 1965 and 2012. They were developed at different stages in the evolution of our understanding of this important autoimmune disease. Our knowledge of SS and human autoimmune diseases has expanded greatly during that time and diagnostic and classification criteria for SS have continued to evolve.

Before looking at the steps in this evolution, differences between “diagnostic” and “classification” criteria need to be understood. Classification criteria are conceptually the same as diagnostic criteria [1] and the difference between them is best thought of in terms of context. Diagnostic criteria are generally used in the context of clinical assessment of individual patients, which includes the clinician’s judgment of individual circumstances. Classification criteria represent a standard required of patients to be admitted to a study of that disease or a therapeutic trial. Classification criteria usually are reviewed and approved by a relevant professional organization. Ideally however, these two types of criteria should be as similar as possible.
**Sjögren’s syndrome diagnostic chronology**

**The Pioneers**
Henri Gougerot, a French dermatologist and prolific observer and reporter in the medical literature, described in 1925 that progressive dryness of the eyes was only one component of a generalized condition, which could include dryness in the mouth, larynx, nose and vulva [2]. Henrik Sjögren, a Swedish ophthalmologist, described in his 1933 doctoral thesis “a general disease which attacks chiefly the eyes as well as the lacrimal and salivary glands” [3]. Based on his study of 19 patients with a particular form of lacrimal dysfunction, for which he coined the term keratoconjunctivitis sicca (KCS), he also documented in some of those patients “deforming” arthritis and symptoms and signs of salivary dysfunction.

**NIAMD criteria**
In a study from the former United States National Institute of Arthritis and Metabolic Diseases (NIAMD), SS was defined in 1965 as “a triad of keratoconjunctivitis sicca (‘dry eyes’), xerostomia (‘dry mouth’), and rheumatoid arthritis (RA) or other connective tissue disease” based on the study of 62 patients at the National Institutes of Health (NIH) Clinical Center [4]. This landmark study provided the first SS diagnostic criteria: “Two of the three major components are... sufficient for the diagnosis.” This was a large, comprehensive and valuable study (44 pages long), but it used the ambiguous term “xerostomia” in its definition and diagnostic criteria to represent the salivary/oral component of SS. At that time, the term did not distinguish between symptoms or signs of dry mouth, or what means might be used to determine its presence or absence, in contrast to clearer identification of the other two components of the triad.

In this study, 37% of SS patients had only the ocular and salivary components without another defined connective tissue disease (CTD), but did have systemic manifestations including chronic pulmonary disease, myositis, non-thrombocytopenic purpura, Raynaud’s phenomenon, leukopenia, hypergammaglobulinaemia, and positive tests for rheumatoid factor, antinuclear antibody and specific precipitating nuclear antibodies [4].

**Martin Shearn**
Subsequent diagnostic criteria were presented in a monograph on SS of extraordinary depth by Martin Shearn [5]. He proposed criteria for “Definite SS” consisting of “either” objective evidence of KCS “or” characteristic pathologic features in the lacrimal or salivary glands.

He further proposed criteria for “Probable SS” consisting of two of the following three features:
- 1: recurrent or chronic “idiopathic” salivary gland swelling;
- 2: unexplained xerostomia;
- 3: connective tissue disease.

These criteria differed significantly from the NIAMD criteria by supporting a definite diagnosis of SS based on manifestations in only one organ system and by proposing criteria for a probable diagnosis. These diagnostic criteria have not been widely cited but this initial monograph is memorable for the quality, breadth and depth of its coverage of SS.

**San Francisco criteria**
In 1972, a multi-disciplinary Sjögren’s Syndrome Clinic at the University of California, San Francisco began evaluating patients under the initial direction of Dr. Norman Talal, who had begun his studies of SS at the NIAMD in 1963. To deal with the ambiguity of the term “xerostomia” and the need for objective criteria to diagnose KCS, the new SS Clinic assigned specific tests for the salivary and ocular components of SS. In applying the NIAMD two-out-of-three definition of SS, xerostomia (the salivary component of SS) was diagnosed by a labial salivary gland (LSG) biopsy having a defined threshold of focal lymphocytic infiltrates (focus score > 1 focus/4 mm²) [6] to semi quantitatively assess the degree of lymphocytic infiltration [7]. KCS was defined by diffuse, punctate, or blotchy rose bengal staining of the air-exposed corneal conjunctival epithelium [8] and an unanesthetized Schirmer test < 10 mm/5 min [9]. These new criteria were applied to 100 prospectively diagnosed patients [10] and presented at the first International Symposium on Sjögren’s Syndrome (ISSS) in 1986.

**Primary vs. Secondary Sjögren’s syndrome**
Beginning in the mid 1970s, patients who presented with both the ocular and salivary components of SS, but without RA or another connective tissue disease, were often referred to as having “sicca syndrome,” and this term was used as a synonym for SS. In 1979, a bifurcation was proposed by classifying primary SS (pSS) and secondary SS (sSS), based on the presence

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**Glossary**

<table>
<thead>
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<th>Abbreviation</th>
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<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
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<td>CTD</td>
<td>Connective tissue disease</td>
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<td>ISSS</td>
<td>International Sjögren’s Syndrome Symposia</td>
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<td>KCS</td>
<td>Keratoconjunctivitis sicca</td>
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<td>LSG</td>
<td>Labial salivary gland</td>
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<td>NIAMD</td>
<td>National Institute of Arthritis and Musculoskeletal diseases (now NIAMS)</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>RA</td>
<td>Rheumatoid arthritis</td>
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<td>SICCA</td>
<td>Sjögren’s International Collaborative Clinical Alliance</td>
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1In 1986, this NIH institute was renamed the National Institute of Arthritis, Musculoskeletal and Skin diseases (NIAMS).
or absence of RA or another connective tissue disease [11]. The study further underlined in primary SS patients the presence of other systemic features such as purpura, lymphadenopathy, renal or pulmonary disease, or lymphoma, which support and add to previous observations.

**Copenhagen criteria**

Chronologically, the next diagnostic criteria for SS were developed in Denmark and Sweden during the late 1970s, published in 1981 [12], and based on an ocular and salivary definition of SS (see below). The diagnosis of KCS is made with the presence of two out of three:

- 1: unanesthetized Schirmer test \( \leq 10 \) mm/5 min;
- 2: tear break-up time \( \leq 10 \) s, and/or;
- 3: rose bengal staining \( \geq 4 \) on the van Bijsterveld scale [13].

The diagnosis of xerostomia is made with the presence of any two out of four tests:

- 1: unstimulated whole salivary flow \( < 1.5 \text{ mL/15 min} \);
- 2: LSG biopsy with focus score \( > 1 \text{ focus/4 mm}^2 \);
- 3: decreased uptake or secretion in salivary scintigraphy, and/or;
- 4: abnormal sialography (removed subsequently [14]).

Both KCS and xerostomia are needed for this diagnosis of SS, but objective evidence of a systemic component is not required. These criteria use objective tests and require multiple alternative tests for each component, providing flexibility to clinicians making the diagnosis. However, various alternative tests have been found not to be diagnostically equivalent. For example, salivary scintigraphy correlates strongly with salivary flow rate, but not with lymphocytic infiltration in labial salivary gland specimens [15].

**Japanese criteria**

Diagnostic criteria for SS were first published in Japanese in 1977 and translated [16] for the First International Seminar on Sjögren’s Syndrome. They defined “definite SS” with at least two of three ocular and salivary tests and “probable SS” by one of three different tests. In 1999, revised Japanese criteria for SS were developed in which the diagnosis of pSS is made when the patient has at least two of four of these tests:

- 1: LSG or lacrimal biopsy with a focus score \( \geq 1 \text{ focus per 4 mm}^2 \);
- 2: sialography with diffuse punctate sialectasis, or decreased stimulated whole salivary secretion and decreased function by sequential salivary scintigraphy;
- 3: Schirmer test \( \leq 5 \text{ mm/5 min} \) and rose bengal staining \( \geq 3 \) in van Bijsterveld scale, or Schirmer test \( \leq 5 \text{ mm/5 min} \) and fluorescein staining;
- 4: positive serum anti-Ro/SS-A, or anti-La/SS-B antibody

These revised criteria were first published in Japanese and later in English [17]. They offer clinicians wide choices of diagnostic tests that can be used, but some procedural details remain to be clarified along with adequate means for comparing the various combinations. The criteria for “probable SS” were discontinued.

**Greek criteria**

Investigators from the University of Ioannina in Greece presented preliminary diagnostic criteria for SS at the First International Seminar on SS in 1986 [18] which were then applied in subsequent studies. This criteria set diagnoses pSS when there is:

- 1: LSG biopsy specimen “Class 2” or higher [19] and;
- 2: parotid gland enlargement, or;
- 3: subjective xerostomia, or;
- 4: ocular rose bengal staining, in the absence of any other autoimmune disease.

In applying these criteria, one or two components of the NIAID SS triad are necessary to diagnose pSS. These criteria provide simplicity and cast a broad net for patients with early symptoms or signs associated with SS. However, it diagnoses pSS with the presence of as little as one SS component and uses a qualitative LSG assessment, which does not distinguish between the focal lymphocytic infiltration characteristic of the salivary component of SS and other common forms of chronic reactive inflammation [19].

**San Diego criteria**

In 1986, investigators at the Scripps Institute published proposed criteria for classification of SS with an important difference [20]. These were also presented at the First International Seminar on SS. This criteria set diagnoses “definite SS” when patients meet all four of the following, including the important addition of an assessment of the systemic component of SS through serum autoantibodies:

- 1: KCS with a Schirmer \( < 9 \text{ mm/5 min} \) and rose bengal or fluorescein staining;
- 2: symptomatic xerostomia and decreased resting and stimulated salivary flow;
- 3: lymphocytic infiltration in a LSG biopsy specimen with focus score \( \geq 2/4 \text{ mm}^2 \); and;
- 4: at least one of the following serum autoantibodies (rheumatoid factor \( \geq 1:160 \), antinuclear antibody \( \geq 1:160 \), positive SS-A or SS-B antibody).

A diagnosis of “possible SS” is made with any three of these four items. The criteria for “definite” pSS supports a definition of pSS in which all three components (ocular, oral, and systemic) must be present. These criteria reaffirm the systemic nature of pSS by requiring the presence of serum autoantibodies and by objective criteria for each of the three components of pSS. However, it does not define objective criteria for
ocular staining or salivary flow rate thresholds. The rigor of these criteria may not include patients with early or mild SS and the use of “definite” and “possible” criteria levels is controversial, and generally no longer favored.

**European criteria**

In 1988, a group of European investigators, held a workshop on diagnostic criteria for SS [21], which formed the basis for 26 centers in 12 countries to contribute data from an aggregate of 693 patients. Analysis of the aggregate data led to the “Preliminary criteria for the classification of SS: results of a prospective concerted action supported by the European Community” [22]. These preliminary criteria include six items, any four of which are sufficient for diagnosis of pSS:

1. positive response to one of three specified ocular symptoms;
2. positive response to one of three specified oral symptoms;
3. Schirmer test $\leq 5$ mm/5 min or ocular rose bengal stain $\geq 4$ [13];
4. LSG biopsy with focus score $\geq 1$ focus/4 mm$^2$;
5. positive results from one of three salivary tests (scintigraphy, sialography, or unstimulated whole flow $\leq 1.5$ ml/15 min);
6. presence of any one of four serum autoantibodies (rheumatoid factor, antinuclear antibody, anti-SS-A, or anti-SS-B) (titers not specified).

These criteria reduce the previous Schirmer test threshold from $\leq 10$ mm to $\leq 5$ mm and slightly lower the LSG focus score threshold from $> 1$ to $\geq 1$. In providing diagnostic alternatives between each of the six numbered items and additional choices within four of the six items, these criteria identify nearly three times as many patients having pSS as the Copenhagen criteria and more than six times as many as the San Diego criteria [22]. These criteria support a pSS definition in which two of the three SS components must be present.

These criteria were prospectively developed and provided extraordinary clinical latitude to clinicians in diagnosing pSS, which can include patients with early or mild SS, but may also include conditions other than SS in which dry mouth and/or dry eyes is a clinical sign or symptom. Calculations of specificity and sensitivity were based on the individual diagnoses of SS and controls that were in use at each of the 26 participating centers. The criteria apply patient symptoms for up to half of the criterion for SS diagnosis and possible alternatives between additional items. The authors of these criteria subsequently modified item number 6 to only include the presence of anti-SS-A and/or anti-SS-B [23]. The between-item alternatives permit diagnosing a patient with pSS who is seronegative and has a negative LSG biopsy. Hence, the diagnosis can rest entirely on subjective data and physiologic tests that have low specificity for SS, leading to the following revision.

**American-European consensus criteria**

During the 6th ISSS in 1997, formation of an ad hoc group was initiated in an attempt to resolve a widening controversy regarding the European classification criteria. The group included European and American colleagues and was called the International Sjögren’s Syndrome Diagnostic Criteria Group. With the support of the Sjögren’s Syndrome Foundation, the group held workshops at subsequent meetings of the American College of Rheumatology (ACR), ISSS, or independently. An initial intent of this group was to develop internationally recognized criteria, but lacking the resources for such an endeavor, the group approved reanalyzing a subset of 180 cases in the European data set, from which the 1993 European criteria were developed [24]. The cases selected, included all those with both serological and LSG biopsy results from the original evaluations. Attempts were made to obtain recognition of the revised criteria by the ACR, but they were willing to do so only for newly developed data.

The consensus report from this group proposes two sets of diagnostic criteria: a “4 of 6” criterion in which item no. 4 and/or no. 6 (from the European criteria described above) must be present along with any three other items (including symptoms); and the rarely cited “3 of 4” criterion using only the objective items (no. 3, 4, 5, and 6). These criteria represent expanded collaboration, utilized a subset of 25% of the previously used multi-center European database, were based on criteria popular with clinicians, and improved specificity of the 4 of 6 criteria by requiring the presence of item number 4 and/or number 6, to represent the autoimmune process. However, there is a strong emphasis on patient symptoms and a relatively narrow ethnic group is represented in the data set.

**The SICCA Project**

In 2002, the NIH issued a request for proposal to develop an International Research Registry Network for Sjögren’s Syndrome. The contract was awarded to an international group of colleagues centered at the University of California, San Francisco for their proposal called Sjögren’s International Collaborative Clinical Alliance (SICCA), and ultimately funded from 2003 to 2013. The alliance includes collaboration and participant enrollment at an academic medical center in Argentina, China, Denmark, England, India, Japan, and three centers in the United States. The SICCA goals include:

- designing and implementing an international clinical data and biospecimen repository;
- providing these resources for future studies of SS;
- developing standardized, universally acceptable classification criteria for SS.

The SICCA registry prospectively enrolls individuals using broad eligibility criteria to establish a cohort ranging from participants with symptoms of possible SS to those with established disease. Participants undergo all tests and data collection,
standardized examination forms and procedures are protocol-directed (publically available on the SICCA website at http://sicca.ucsf.edu). Publications from the SICCA project include: its introduction [25], ocular data analyses [26], associations between labial salivary gland histopathology and phenotypic features of SS [27], and systemic features of the cohort [28]. The ACR reviewed the case selection, data analyses and results that went into development of the SICCA classification criteria, which was based on 1618 members of the cohort. The criteria were then approved, adopted and named by the ACR [29]. These criteria apply to individuals whose symptoms or signs are suggestive of SS, and classification is met with the presence of at least two of these three features:

- 1: positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and ANA titer ≥ 1:320);
- 2: labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥ 1 focus/4 mm² (figure 1);
- 3: keratoconjunctivitis sicca with ocular staining score ≥ 3 (assuming that the individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years) [26].

Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: history of head and neck radiation treatment, hepatitis C infection, acquired immunodeficiency syndrome, sarcoidosis,

**Figure 1**

Hematoxylin and eosin-stained labial salivary glands (LSG) exhibiting focal lymphocytic sialadenitis. A. Approximately 10 focal lymphocytic infiltrates can be seen in this image. Under the Microscope, the entire specimen has a total glandular area of 24 mm² and yields a focus score of 2 foci per 4 mm². B. LSG with 2 prominent lymphocytic germinal centers, indicating localized lymphocytic proliferation, and ductal hyperplasia within a large lymphocytic infiltrate. Note normal-appearing mucous acini immediately adjacent to the infiltrate.

Source: Reprinted with permission from the American College of Rheumatology [27].
amyloidosis, graft versus host disease or IgG4-related disease [29]. The new classification criteria for SS offer improved specificity and objectivity and focus on the autoimmune nature of SS. The American College of Rheumatology Classification Criteria for Sjögren’s Syndrome [29] will better support etiologic and genetic research and therapeutic trials for this prevalent autoimmune disease because they rely on only objective tests, two of which clearly reflect autoimmune mechanisms affecting SS. Criteria used for enrollment into clinical trials need to have high specificity, considering the potentially serious adverse effects and co-morbidities of biologic agents. They utilize multiple objective criteria because there remains no single test or clinical feature that can diagnose or classify SS, as further discussed below. SS is a multidisciplinary disease requiring different specialists to both diagnose patients and to manage their long term care.

Notes on evolving diagnostic concepts affecting Sjögren’s syndrome

Because of the multisystem character of SS, a wide variety of tests and measures have been applied to its diagnosis and classification, but over the years, their associations with each other and with SS are becoming clearer.

Patient symptoms

Symptoms of ocular or oral dryness are an important flag to lead clinicians to include SS in a patient’s differential diagnosis and lead to selecting appropriate objective diagnostic tests. However, such symptoms, no matter how carefully selected, are too subjective and non-specific to be used as diagnostic or classification criteria. Symptoms of dry mouth are often associated with: administration of one or more of a long list of systemic drugs (http://www.drymouth.info/practitioner), depression [30,31], aging [32], IgG4 disease [33], or SS [4]. In the SICCA cohort, symptoms of dry mouth or of dry eyes were not associated with positive serum anti-SS/B or with LSG biopsy focus scores > 1 [29]. Furthermore, among the 4% of the cohort who did not complain of dry mouth or dry eyes, 49% had positive anti-SS/A, 36% had a positive LSG biopsy and 68% had positive ocular staining for KCS (unpublished data). Thus, dry eye and dry mouth symptoms are not significantly associated with objective features of SS and a minority of SS patients are asymptomatic.

Serology

No single serological test has yet been identified that is present exclusively in SS. Elevated anti-SS/A or/and SS is most prevalent in SS, but can also be present in systemic lupus, RA and polymyositis. Furthermore, a minority of patients having clear objective evidence of the ocular and salivary components of SS are anti-SS/A-B negative, but have high ANA titers and positive rheumatoid factor, which led to the latter being included as a serological alternative in the recent ACR classification criteria [29].

Keratoconjunctivitis sicca

While the ophthalmology community is currently reassessing the classification and diagnosis of dry eye conditions [34], we have continued to use the term originated by Sjögren of keratoconjunctivitis sicca (KCS), but its naming may change in the future. In the context of diagnosing SS with only its ocular component, it has been known for some time that KCS can occur independently of SS [35]. In addition, recent data from the SICCA Project confirms that 27% of SICCA participants had KCS without either positive serology or LSG biopsy [29]. Analysis of SICCA follow up data shows that few of the participants having KCS-only at base-line examination developed objective features of SS two years later (data not yet published).

Dry mouth symptoms and salivary flow rates

There are three physiologic salivary flow rates: resting and awake (unstimulated), stimulated (gustatory, masticatory, olfactory, or cholinergic stimuli) which is about 5 x the resting rate, and sleeping, which is approximately 10% of the resting rate [36]. In the context of dental health, the resting and sleeping rates are the most critical because they maintain the homeostatic environment for the teeth during about 90% of the 24 hour day. Therefore, unstimulated resting salivary flow is the most relevant physiologic indicator of dental and oral health and studies show strong negative correlation of dental caries indices with unstimulated flow rates [32].

Several aspects of salivary physiology need to be considered in interpreting flow rate measurements. The range of “normal” parotid or submandibular salivary flow in groups of healthy adults is about 10 x from lowest to highest, whether stimulated or unstimulated [37]. Age is another variable. In unmedicated healthy adults, unstimulated whole salivary flow rates decrease by 40 to 70%, between the ages 20 and 80 [32,38,39] while there is little or no change in the range of stimulated salivary flow rates in the same age groups. These wide ranges of normal salivary flow, differences in stimulated and unstimulated flow rates and age-related changes make defining a single abnormal threshold problematic.

Experimentally, symptoms of dry mouth in young healthy subjects began when each individual’s baseline salivary flow rate was reduced by 40 to 50% [40], but not at any arbitrarily defined level, such as < 0.1 ml/min. A clinical extension of this observation is seen in some SS patients with unstimulated whole salivary flow < 0.1 ml/min, but who did not complain of dry mouth (unpublished SICCA data).
Salivary scintigraphy
This technique has been available since the 1960s and first methodically applied to patients with SS in 1971 [15]. Results from salivary scintigraphy, in that and subsequent studies, demonstrate this technique’s ability to assess salivary gland function while simultaneously imaging the four major glands and oral cavity. In comparing scintigraphic scoring results with salivary flow rate measures, there is correlation between it and the flow rates, but there is little or no correlation with LSG lymphocyte scoring [15], which reduces its disease specificity. When applied in SS, scintigraphy may not provide sufficient diagnostic specificity to offset its monetary expense, placement only in tertiary medical facilities and needed intravenous radiation.

Sialography
X-ray contrast sialography assesses anatomical changes in the ducts of one major salivary gland at a time. It requires cannulation of the duct and can distinguish duct obstruction from diffuse inflammatory changes. It can be helpful in distinguishing inflammatory from neoplastic causes of parotid or submandibular gland enlargement, but it usually cannot distinguish the various causes of glandular inflammation. It is used with decreasing frequency and largely replaced by magnetic resonance sialography, whose value in diagnosing SS has not yet been validated.

Minor salivary gland biopsy
The principle of scoring focal lymphocytic infiltrates in salivary glands, in the context of SS, was first applied to major glands [41], then to minor glands [6] and then as SS diagnostic criteria [10]. In a later study of a large group of LSG biopsy specimens, 25% exhibited patterns of chronic inflammation other than focal lymphocytic infiltrates, which were not associated with other objective features of SS [42]. In an analysis of 600 patients, to which the San Francisco SS criteria had been applied, the presence and severity of a particular pattern of lymphocytic infiltration in LSG biopsy specimens (focal lymphocytic sialadenitis) were highly correlated with the presence and severity of KCS, but showed only weak or no correlations with reduced stimulated parotid flow [43]. While assessing LSG focal lymphocytic infiltrates are very useful diagnostically, they are also an accessible site to observe and study the autoimmune-related organ destruction characteristic of SS from early T-cell infiltration, to B-cell proliferation, to development of B-cell lymphoma. Labial salivary glands can also exhibit nonspecific chronic inflammatory changes in patients with AIDS, with or without parotid enlargement [44,45]. Sarcoidosis can cause a SS-like clinical presentation, but with lymphocytic and granulomatous inflammation in LSG specimens [46,47].

Salivary ultrasonography
This new method of examining major salivary glands holds the possibility of non-invasively providing important diagnostic information about major salivary glands in SS, without radiation or surgery. Studies have shown that the presence of hypoechoic areas may be associated with other features of SS. However, it is not yet clear what the composition of these hypoechoic areas is. Do they represent the focal lymphocytic infiltrates characteristic of SS; or do they represent areas of parenchymal atrophy and sclerosis, commonly seen in minor salivary glands, but not associated with objective features of SS? The nature of these hypoechoic areas should be studied by preoperative ultrasound examination of major salivary glands, which will undergo surgery, in order to compare the ultrasound and corresponding histopathological images.

Primary vs. Secondary Sjögren’s syndrome
The distinction between primary and secondary forms of SS was based on its initial definition, which included “rheumatoid arthritis or other connective tissue diseases,” as one of the “two of three” diagnostic criteria [4]. Patients who developed the ocular and salivary components of SS without developing RA were initially labeled as having the “sicca syndrome” and later called “primary SS,” while those with RA who usually developed the dry eye/mouth components after the onset of their joint disease were labeled “secondary SS” [11]. Subsequently, it became clear that various organ-specific (e.g., thyroid, liver, kidneys, and lungs) autoimmune conditions can occur in SS patients, in patients with other autoimmune connective tissue diseases, or independently.

While the details of autoimmune pathogenesis remain elusive, many diseases have now been identified as having autoimmune mechanisms, mostly distinguished by the target organ(s) affected. Extraordinary activity in multiple genetic loci, mostly in the HLA region, has been identified in patients with RA, systemic lupus and other CTDs. Furthermore, individuals with one autoimmune disease seem to have enhanced susceptibility to develop others, and different autoimmune diseases may affect different members of the same family. Therefore, it seems of little use, and risks potential confusion, to distinguish in a given patient one autoimmune disease as secondary to another. The distinction between primary and secondary SS now appears to be obsolete. Accordingly, patients fulfilling the new ACR classification criteria for SS should be given that diagnosis in addition to any other concurrent or subsequent autoimmune disease, without defining either as primary or secondary [29].

Sjögren’s syndrome Heterogeneity
In the last few years, the heterogeneity of SS seems to be increasing. This may come from a wider range of specialists...
becoming aware of SS, who in turn may apply different diagnostic criteria. However, an initial study comparing large groups of patients and controls found the systemic manifestations of primary SS are mainly specific immunologic and hematologic abnormalities, and the occurrence of various extraglandular manifestations (e.g. thyroid, kidney, liver and neurological disease) is relatively uncommon [28].

Conclusion

The answer to the title question is clearly “yes.” The new ACR classification criteria are composed of only objective measures, including those representing autoimmune processes, to create a more uniform and disease specific cohort of SS patients on which to carry out the next phase of research and clinical trials. The research will include identifying genetic differences between SS patients and controls and learning how those differences affect patients’ immune responses. The treatment trials will be focused on improving life for SS patients.

References

[28] Malladi AS, Sack KE, Shiboski S, Shiboski C, Baer AN, Banushree R et al. Primary Disclosure of interest: the author declares that he has no conflicts of interest concerning this article.

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