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Sjögren's Syndrome: an Update on Diagnostic, Clinical, and Basic Aspects for Oral Medicine Specialists

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Sjögren's syndrome (SjS) is a common autoimmune disorder characterized by lymphocytic infiltration in the salivary and lacrimal glands, resulting in severe dry mouth or eyes. As a result, most of SjS patients suffer from oral dryness and can visit the department of oral medicine with or without diagnosis of SjS. Therefore, oral medicine specialists should know clues, which may indicate the diagnosis of SjS from the clinical and laboratory investigations. By the recent SjS criteria, SjS can be diagnosed by focus score, ocular staining, Schirmer's test, unstimulated whole saliva flow rate, and anti-SSA/Ro antibodies. The aim of this article is to review the diagnostic criteria, clinical investigation, and basic aspect related to SjS and to make oral medicine specialists play an important role in the detection of emerging SjS.

Key Words: Biopsy; Oral medicine; Sjögren's syndrome; SSA antibodies; Staining and Labeling; Xerostomia

INTRODUCTION

Sjögren's syndrome (SjS) is a systemic autoimmune disorder characterized by lymphocytic infiltration in the salivary and lacrimal glands, resulting in severe dry mouth or eyes.[1)] Primary Sjögren's syndrome (pSjS) is distinguished from secondary Sjögren's syndrome (sSjS). pSjS is defined when the exocrinophathy alone encounter without the evidence of other autoimmune issues. sSjS occurs as part of other autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, limited and progressive systemic sclerosis.[1,2)] The underlying etiology remains relatively unclear, although genetic, environmental, and/or immunologic factors appear to contribute to the etiology.[3)]

The main symptoms in SjS are subjective oral and/or eye dryness due to chronic inflammation in the salivary and lacrimal glands.[1,4)] However, more than half of pSjS patients also have extra-glandular manifestations, such as mainly arthralgia, fatigue, and myalgia.[5)] These symptoms have a major effect on quality of life, primarily because of disabling fatigue, with associated loss of work productivity.[6)] Variability of symptoms may make the diagnosis of SjS be delayed up to 9 years after the onset of symptoms.[7)]

Oral dryness is one of the most common symptoms of patients who visit the department of oral medicine.[8)] It is also the most common complaint of SjS patients.[1,4)] However, as it can be seen in patients with hyposalivation from various etiologies (e.g., systemic medications, head and neck radiation, graft versus host disease, and other systemic diseases),[9)] oral medicine specialists should distinguish SjS patients from patients with other etiologies related to oral dryness. For this reason, oral medicine specialists should be alert to clues from the clinical and laboratory investigations, which may indicate the diagnosis of SjS.

The aim of this article is to review the diagnostic criteria, clinical investigation, and basic aspect related to SjS for oral medicine specialists. It also is purposed that oral medicine specialists can play an important role in the detection of emerging SjS and improve their understanding about SjS.

DIAGNOSITC CRITERIA OF SJÖGREN'S SYNDROME

1. The 2002 American-European Consensus Group Classification Criteria

SjS may present with numerous extraglandular manifestations. Such diverse manifestations make SjS a complex pathology to characterize and give rise to variability in disease classification. Therefore, a uniform, standardized set of criteria to classify individuals to have SjS have been needed. There have been 13 classification criteria systems for SjS from 1965 to 2016.[10] Among those criteria, the 2002 American-European Consensus Group Classification Criteria (the 2002 AECG) have been the most widely used classification criteria with over 1,500 citations.[11] This criteria was proposed to overcome objections and broaden the acceptance of the European classification criteria by the European Study Group on Classification Criteria and a group of American experts for SjS on 2002. They revised criteria including two different goals: firstly, assessment of the ocular and salivary components, and secondly, differentiation between the primary and secondary variants of the syndrome. Finally, the 2002 AECG employed six domains of assessment, of which two were subjective (ocular and oral dryness) and four were objective (ocular signs, oral signs, histopathology, and autoantibodies) (Table 1).[12,13] A distinction is drawn between pSjS and sSjS by the 2002 AECG. The diagnosis of sSjS can be established if only 3 of the 6 criteria items are present in addition to the other autoimmune disease.[12]

The 2002 AECG comprise a number of positive features, including their simple application and the stepwise

Table 1. The 2002 revised American-European Consensus Group Classification Criteria for Sjögren's syndrome[12]

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 SGs as an adult?
  3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs : objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
  1. Schirmer's test, performed without anaesthesia (<5 mm in 5 mins)
  2. Rose Bengal score or other ocular dye score (>4 according to van Bijsterveld's scoring system)[13]

IV. Histopathology: in minor SGs (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, 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. SG involvement: objective evidence of SG 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 mins)
  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

For pSjS
  In patients without any potentially associated disease, pSjS may be defined as follows:
    a. The presence of any 4 of the 6 items is indicative of pSjS, as long as either item IV (histopathology) or VI (serology) is positive
    b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, and 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 sSjS
  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 sSjS

SG, salivary gland; pSjS, primary SjS; sSjS, secondary SjS.
Exclusion criteria: past head and neck radiation treatment, hepatitis C infection, acquired immunodeficiency disease, pre-existing lymphoma, sarcoidosis, graft versus host disease, use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug).
Cited from the article of Vitali et al. (Ann Rheum Dis 2002;61:554-558).[12]

approach to patient classification in a rheumatologist's office without the need for invasive tests because the criteria provide ocular and salivary subjective items along with Schirmer's test and anti-SSA/Ro antibodies.[14]

However, the criteria had been criticized for including subjective tests (symptoms), physiologic measures that lack specificity and alternate objective tests that are not diagnostically equivalent. For example, the Schirmer's test may be used instead of Rose Bengal ocular stain, even though they differ in sensitivity and specificity. Further, the inclusion of symptoms of dry mouth and/or eyes can lead to misclassification of asymptomatic patients. In addition, physiologic measures, such as unstimulated whole salivary flow, unanesthetized Schirmer's test, and salivary scintigraphy, are useful for assessment of salivary or tear function, but lack specificity for SjS. Therefore, it was desirable for new classification criteria for SjS to be endorsed by professional rheumatology organizations across the world to increase their credibility and maximize standardization when enrolling participants into clinical trials.[15]

2. The 2012 American College of Rheumatology Classification Criteria

In 2012, a new classification system known as the American College of Rheumatology Classification Criteria (the 2012 ACR) for SjS was proposed to improve specificity that would consequently limit the exposure of individuals (falsely classified as SjS) to biologics of uncertain safety in clinical trials. This system eliminated symptoms of oral/ocular dryness and the objective sign of hyposalivation and was based exclusively on objective signs of positive focus score (FS), serology, and ocular staining score (Table 2).[15,16]

Compared to the 2002 AECG, the 2012 ACR are simple. However, the criteria have disadvantages to rely only on objective tests, two of which (ocular staining score and lip biopsy) are invasive and cannot be performed in an outpatient setting.[14]

3. The 2016 American College of Rheumatology/ European League against Rheumatism Classification Criteria

The 2012 ACR was replaced by another system proposed by the International Sjögren's syndrome Criteria Working Group, known as the 2016 American College of Rheumatology/ European League against Rheumatism Classification Criteria (the 2016 ACR/EULAR). This set incorporated criteria from both the AECG and ACR sets and give weighted points for the four objective signs. The final classification criteria are based on the weighted sum of 5 items. Individuals who have a total score of ≥4 with signs and/or symptoms suggestive of SjS are classified as having pSjS (Table 3).[13,16-19]

Differences from previous criteria are followed: 1) Objective ocular and oral symptoms have been excluded; nevertheless, they continue to be considered important in evoking the clinical suspicion of SjS and guiding the performance of clinical tests. 2) Ocular staining score threshold was increased to 5 due to the higher specificity[17] compared to the previous score of 3.[15] 3) The immunological profile included only anti-SSA/Ro antibodies, while positivity for antinuclear antibodies (ANA), rheumatoid factor (RF) and isolated anti-SSB/La antibodies were excluded. Compared with the 2002 AECG, exclusionary conditions have also been updated. IgG4-related disease has been

Table 2. The 2012 American College of Rheumatology Classification Criteria for Sjögren's syndrome[15]

The classification of Sjögren's syndrome, which applies to individuals with signs/symptoms that may be suggestive of SjS, will be meet in patients who have at least two of the following three objective features:

1. Positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and antinuclear antibodies ≥1:320)
2. Focal lymphocytic sialadenitis, with focus score ≥1 focus/4 mm^2 in labial salivary gland biopsy
3. Keratoconjunctivitis sicca with ocular staining score ≥3, as described by Whitcher et al.[16] 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.

SjS, Sjögren's syndrome.

Exclusion criteria: past head and neck radiation treatment, hepatitis C infection, acquired immunodeficiency disease, preexisting lymphoma, sarcoidosis, graft versus host disease, use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug), and IgG4 related disease.

Cited from the article from Shiboski et al. (Arthritis Care Res (Hoboken) 2012;64:475-487).[15]

Table 3. The 2016 American College of Rheumatology/European League against Rheumatism Classification Criteria for SjS[17)]

1) Focus score ≥1 foci/4 mm^{2a} (3 points) 1 focus=50 lymphocytes/4 mm^2
2) Anti-SSA/Ro positive (3 points)
3) Ocular staining score ≥5/(or van Bijsterveld score≥4) at least in one eye[bc] (1 point)
4) Schirmer's test ≤5 mm/5 min[b] (1 point)
5) Unstimulated whole saliva flow rate ≤0.1 mL/min[d] (1 point)
A total score of ≥4 points classified someone as having primary pSjS

SjS, Sjögren's syndrome; pSjS, primary Sjögren's syndrome.

The classification of pSjS applies to any individual who meets the inclusion criteria: any patients with at least one symptom of ocular or oral dryness, defined as 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?
4. Have you had a daily feeling of dry mouth for more than 3 months?
5. Do you frequently drink liquids to aid in swallowing dry food?

or in whom there is suspicion of SjS from the European League Against Rheumatism SjS Disease Activity Index questionnaire (at least 1 domain with a positive item).

Exclusion criteria include prior diagnosis of any of the following conditions, which would exclude diagnosis of SjS and participation in SjS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: 1) history of head and neck radiation treatment, 2) active hepatitis C infection (with confirmation by polymerase chain reaction), 3) AIDS, 4) sarcoidosis, 5) amyloidosis, 6) graft-versus-host disease, 7) IgG4-related disease.

[a]The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis and focus score count, using the protocol described by Daniels et al.[18)] [b]Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval without these medications in order for these components to be a valid measure of oral and ocular dryness. [c]Ocular Staining Score described by Whitcher et al.[16)] van Bijsterveld[13)] score described by van Bijsterveld. [d]Unstimulated whole saliva flow rate measurement described by Navazesh and Kumar.[19)]

Cited from the article of Shiboski et al. (Arthritis Rheumatol 2017;69:35-45).[17)]

added, hepatitis C infection requires confirmation by polymerase chain reaction, and preexisting lymphoma is allowable since diagnosis of SjS is sometimes made after a prior lymphoma occurrence.[14,17)]

The strength of the 2016 ACR/EULAR lies in their appropriateness for early identification of SjS, providing patients with the opportunity to be enrolled in clinical trials for new disease-modifying drugs for SjS. These criteria may represent the common language to be used in the future to make the scientific communication easier and more correct, favor the exchange of information, and stimulate the development of collaborative studies.[14)] However, the ACR/EULAR do not discriminate between pSjS and sSjS and define only pSjS.[17,20)]

DIAGNOSTIC INVESTIGATION PROPOSED BY THE 2016 ACR/EULAR

Oral medicine specialists should be aware of the diagnostic investigation proposed by the latest diagnostic criteria for SjS diagnosis. Those are described below.

1. Focus Score

A focus is defined as a cluster of ≥50 lymphocytes when the inflammatory infiltrate is quantified.[12,21)] The FS is the number of focal inflammatory cell aggregates containing 50 or more mononuclear lymphoid cells in each 4 mm^2 glandular section adjacent to normal-appearing mucous acini in the tissue section.[14,18,22)] As described in Table 3, FS ≥1 is considered positive for SjS diagnosis as according to the 2016 ACR/EULAR.[17,21)] For the exact assessment of FS, FS must be determined when a diagnosis of focal lymphocytic sialadenitis (FLS) is made in any specimens. Specimens must have a glandular area of at least 4 mm^2 (preferably 10-20 mm^2 because smaller specimens can overestimate FS) and have lymphocytic foci ≥50 cells. FLS may include hyperplasia and lymphocytic infiltration of ductal epithelium or lymphoid germinal centers. Specimens, exhibiting other patterns of chronic inflammation, are classified as non-specific chronic sialadenitis or sclerosing chronic sialadenitis (SCS) depending on the presence of interstitial fibrosis, atrophic or absent acini, and scattered or focal chronic inflammation. These aggregates should be not counted for a FS

because of the absence of adjacent normal acini. Therefore, specimens must first be diagnosed qualitatively to assess the presence of FLS vs. NS/SCS. If FLS is present, FS assessment should follow. However, if NS/SCS is present, FS is unnecessary and would be misleading. Labial salivary gland (LSG) biopsies with FS ≥1, as compared to FS <1 or with NS/SCS, are strongly associated with phenotypic ocular and serological components of SjS.[17,18,22]

1) Labial salivary gland biopsy technique

LSG biopsy is performed only through normal-appearing mucosa in the lower labial mucosa between the midline and commissure. Under local anaesthesia, a single horizontal incision of around 1.5 to 2 cm is made through the mucosa penetrating the epithelium. The SGs are then released from their surrounding fascia by blunt dissection and are removed separately, avoiding the sensory nerves which can be clearly seen. Five or more glands must be included in specimens.[21]

2. Ocular Test Staining

This test is most commonly used for the evaluation of ocular surface epithelial damage, since vital stains mark cells that are not fully coated by the mucin layer of tear fluid and/or are damaged on the surface of the eye.[21]

1) van Bijsterveld[13] score (Rose Bengal staining)

A quantified version of the original Rose Bengal test is commonly used to quantify the degree of staining. The test is conducted by the application of a 1% solution of Rose Bengal, within the inferior fornix of both eyes. The patient should be asked to make one or two full blinks. The examiner uses white light to assess the amount of staining, in the two exposed conjunctival zones (medial and lateral) and cornea. Each section is scored from 0 to 3 points according to the van Bijsterveld[13] score (1; sparsely scattered spots, 2; densely scattered spots, and 3; confluent spots). The maximum score is 9 and a score of 4 or more is considered diagnostic of SjS.[21]

2) Ocular staining score

(1) Corneal fluorescein staining pattern (step 1 of the ocular Sjögren's International Collaborative Clinical Alliance grading): Each cornea is examined at the slit lamp using the cobalt blue filter. Corneal epithelial staining is a dynamic and time-sensitive process. Therefore, to insure reproducibility, grading of the fluoresence in pattern is initiated consistently between 4 and 8 minutes after instillation. Punctate epithelial erosions (PEEs) that stain with fluorescein are counted and scored. If there are no PEEs, the score is 0; If 1 to 5 PEEs are seen, the corneal score is 1; 6 to 30 PEEs are scored as 2; and more than 30 PEEs are scored as 3. An additional point is added if: (1) PEEs occurred in the central 4 mm diameter portion of the cornea; (2) 1 or more filaments are seen anywhere on the cornea; or (3) 1 or more patches of confluent staining, including linear stains, are found anywhere on the cornea. The maximum possible score for each cornea is 6.[16]

(2) Conjunctival lissamine green staining pattern (step 2 of the ocular Sjögren's International Collaborative Clinical Alliance grading): One drop of 1% lissamine green dye (Leiter's Pharmacy) is applied to the inferior conjunctival fornix of both eyes. In the ocular grading system (OSS), grade 0 is defined as 0 to 9 dots of lissamine green staining of the interpalpebral bulbar conjunctiva (nasal and temporal bulbar conjunctivae graded separately); grade1 is defined by the presence of 10 to 32 dots; grade 2 is defined by the presence of by 33 to 100 dots; and grade 3 is defined by the presence of more than 100 dots. Fourth grade consisting of totally confluent staining initially is considered, but later was determined not to add quantitatively to the diagnostic grading scheme, although it could be qualitatively meaningful for monitoring treatment in patients with keratoconjunctivitis sicca (KCS). Nasal and temporal areas of the conjunctiva are graded separately with a maximum score of 3 for each area or a total maximum score of 6 for each eye (nasal plus temporal). The total OSS for each eye is the summation of the fluoresence score for the cornea and the lissamine green scores for the nasal and temporal bulbar conjunctiva. Therefore, the maximum possible score for each eye is 12.[16]

3. The Schirmer's Test

The Schirmer's test (without anesthesia) is carried out before any drops are instilled in the eye. Standardized Schirmer's strips are bent at the notch and placed carefully

over the lower lid margin as far toward the temporal angle of the lids as possible. The patient is instructed to keep their eyelids closed during the test. Strips remain in place for 5 minutes, or until they are completely saturated with tears. After 5 minutes, wetting of the strips is measured using the millimeter scale on each strip.[16] Normal tear production usually results in wetting of 15 mm or more of the strip over a 5 min period.[23] The Schirmer's test ≤5 mm/min is considered as SjS.[11]

4. Unstimulated Whole Saliva Flow Rate

Saliva is composed of approximately 99% water and 1% proteins and salts. The normal daily production of saliva is between 0.5 and 1.5 liters. The submandibular glands are the major contributors to resting (unstimulated) saliva, and the parotid glands are the major contributors to stimulated saliva.[19] The 2016 ACR/EULAR recommend the guidelines of the University of Southern California School of Dentistry (USCSD) for measuring unstimulated whole saliva salivary flow rate.[17] The guidelines of USCSD are shown in Table 4.[19]

5. Anti-SSA/Ro and Anti-SSB/La Antibodies

Reichlin and associates identified two cytoplasmic proteins which were termed Ro and La from sera of SLE patients in 1969 and 1974.[24,25] Later Alspaugh and Tan[26] reported the occurrence of antibodies to two cellular antigens, termed SS-A and SS-B, from sera of SjS patients. In 1979, Alspaugh and Maddison[27] showed agreement between Ro and SS-A, and La and SS-B. Since then, it is known that the SSA/Ro antigens are nuclear and cytoplasmic polypeptides which serve as autoantigens in SLE and SjS. They contain two major isoforms of 60 kD and 52 kD and one protein of 46 kD, while the SSB/La antigen consists of a 48 kD protein.[28,29] The 52 kD protein of Ro is a major autoantigen in its denatured form and the 60 kD protein of Ro is the native antigen. Although the third protein of 46 kD termed

Table 4. The guidelines of the University of Southern California School of Dentistry for Unstimulated and stimulated whole saliva collection[19]

1. Collection of unstimulated whole saliva

The patient is advised to refrain from intake of any food or beverage (water exempted) one hour before the test session. Smoking, chewing gum and intake of coffee also are prohibited during this hour. The subject is advised to rinse his or her mouth several times with deionized (distilled) water and then to relax for five minutes.

The patient is then told the following: "I will first obtain measures of saliva flow while you are at rest. This means that before and during the collection you should make every effort to minimize movement, particularly movements of your mouth. To begin a collection trial, I will ask you to swallow to void the mouth of saliva. Then you should lean your head forward over the test tube and funnel (demonstrate)."

"Keep your mouth slightly open and allow saliva to drain into the tube. Keep your eyes open. At the end of the collection period, I will ask you to collect any remaining saliva in your mouth and spit it into the test tube. This movement should be done very quickly and should be done in the same manner from trial to trial. This is very important. Do you understand the procedures?"

When you start a trial, tell the subject:

1) Swallow to begin a trial (begin timing).
2) Make as little movement as possible. Do not swallow, and keep your eyes open during collection periods.
3) At the conclusion of the trial, collect the remaining saliva and spit it out.

For each subject, collect saliva for one minute of practice trial and discard it. A plastic or paper cup may be used for this trial. The actual trial should last for five minutes, and the sample should be saved for further analysis if indicated.

2. Collection of unstimulated whole saliva with gum

1) Instruct the subject to sit motionless.
2) Instruct the subject to lean the head forward over the funnel.
3) Instruct the subject to swallow to void the mouth of saliva (starting time).
4) Instruct the subject to chew the inert gum base according to the pace of the metronome (approximately 70 strokes per min).
5) Every one minute, ask subject to spit saliva into the tube without swallowing. Tell subject, "Spit out, keep chewing" (after first minute), "Spit out, keep chewing" (after second minute), etc. Discard the first two-minute collection. A plastic or paper cup may be used for this collection. Proceed with another three-minute collection. Save this sample for further analysis if indicated.
6) Ask the patient to spit everything (that is, both saliva and gum base) into the tube.
7) Remove the gum base from the funnel before weighing the tube and funnel with saliva.
8) If the patient is too dry (that is, has dry mouth), it is possible to add the weight of the gum base to the pre-weight measure with the gum base in the funnel of the test tube of saliva.

Cited from the article of Navazesh et al. and the University of Southern California School of Dentistry (J Am Dent Assoc 2008;139 Suppl:35S-40S).[19]

'calreticulin-Ro' is an autoantigen found in the sera of some patients with SLE, it is probably unrelated to the SSA/Ro system.[29]

Anti-SSA/Ro and anti-SSB/La antibodies are the most common autoantibodies in SjS and are directed towards the autoantigens Ro/La ribonucleoprotein complex. These have been incorporated into the classification criteria for SjS for a long time[16,30] and associated with an earlier disease onset, glandular dysfunction and extraglandular manifestations as well as with other B cells activation markers.[31]

Anti-SSA/Ro and anti-SSB/La antibodies were found in approximately 50%-70% of pSjS patients. Anti-SSA/Ro antibodies were detected either solely or concomitantly with anti-SSB/La antibodies, whereas exclusive anti-SSB/La antibodies positivity was rare.[30] Finally, the ACR/EULAR decided to exclude anti-SSB/La antibodies from diagnostic criteria of SjS as an item based on group discussions and on a study demonstrating that the presence of anti-SSB/La antibodies without anti-SSA/Ro antibodies had no significant association with SjS phenotypic features, relative to seronegative participants.[17,32]

ADDITIONSAL CLINICAL INVESTIGATION

1. Additional Diagnostic Markers in Serum/Plasma

Several autoantibodies can also be found in SjS in addition to anti-SSA/Ro and anti-SSB/La antibodies. However, these biomarkers have not become validated diagnostic markers as they have not provided improved descriptive power over the biomarkers already established in SjS diagnosis.[16]

1) Antinuclear antibodies

ANA, along with RF, are parameters commonly measured in SjS as clinical and diagnostic tools.[16] ANA is positive in up to 90% of cases although it is not specific for SjS. ANA-positive SjS patients are more frequently of female sex and have a younger mean age than males, as well as a higher prevalence of recurrent parotidomegaly. They also have an increased frequency of extraglandular features, such as Raynaud's phenomenon, cutaneous vasculitis, articular and renal involvement, fever, adenopathies, cytopenias, and elevation of acute-phase proteins.[30] Furthermore, ANA in pSjS have been associated not only with a greater number of involved organs, but also with a higher prevalence of hypergammaglobulinemia, positive RF, anti-SSA/Ro and anti-SSB/La antibodies, and antiphospholipid antibodies.[33]

2) Rheumatoid factor

RF is present in up to 70% of SjS patients and its positivity has been associated with younger age, female predominance, positive SG biopsy, and extraglandular manifestations. Several studies showed RF might be associated with an active serological profile characterized by markers, such as anti-La/SSB and anti-Ro/SSA antibodies, cryoglobulins, ANA, hypocomplementemia and hypergammaglobulinemia. Both the presence and the concentration of RF have been positively correlated to the number of extraglandular manifestations found in SS.[30]

3) Anticentromere antibodies

The prevalence of anticentromere antibodies (ACA) ranges from 4 to 27% in SjS utilizing indirect immunofluorescence. ACA-positive SjS patients have a higher prevalence of Raynaud's phenomenon, peripheral neuropathy, and concomitant autoimmune disorders. However, prevalence of anti-SSA/Ro and anti-SSB/La antibodies, rates of RF positivity, and frequency of leukocytopenia were lower. Therefore, ACA-positive patients may represent a different subset of the disease in SjS population.[30]

4) Muscarinic type 3 receptor

Muscarinic type 3 receptor (M3R) is one of the new promising biomarkers with direct biological and functional links to exocrine secretion. It is suspected that antibodies towards M3R may potentially inhibit saliva secretion and some have reported a 60%-80% concordance of anti-M3R antibody with SjS. However, as the usage has been hampered by reproducibility issues, anti-M3R antibody is not widely used as a biomarker in clinical settings.[16]

5) Calprotectin

Calprotectin is a complex of the S100A8 and S100A9 proteins found abundantly in neutrophils. In the presence of calcium, calprotectin has inflammatory and antimicrobial activities. Salivary, but not blood, calprotectin has shown

strong correlation with clinical signs of SjS.[16]

2. Salivary Gland Test

1) Sialography

Sialography is a traditional radiographic imaging based on the cannulation of the main salivary ducts and the subsequent injection of iodinated contrast medium.[34] Medium is distributed through the duct system, allowing the analysis of the architecture and configuration of the glandular ducts' organization. A dilatation and twisting of the ducts, with an uneven distribution of the contrast medium, originating the appearance of a branching pattern of the ducts are found in SjS.[21] Golder et al.[35] reported that the peripheral ducts were more affected than the main excretory duct and there was a tendency for asymmetric involvement of the parotid glands in pSjS and of the submandibular glands in sSjS. Parotid glands were globally more involved than submandibular glands.[35] Sialography is considered a reliable and accepted method for pSjS diagnosis.[34] Song et al.[36] summarized the diagnostic power of sialography in pSjS patients with an interesting meta-analysis. The authors showed that sialography had an overall sensitivity of 80% and a specificity of 89%. However, it has limitations in terms of invasiveness and radiation exposure. In fact, cannulation of the salivary duct might cause complications, such as sialadenitis and sialectasia; furthermore, sialography is contraindicated in patients with infection, inflammation or allergy to iodine.[34] For these reasons, sialography has been excluded from the 2016 ACR/EULAR as well.[15,34]

2) Salivary gland Scintigraphy

Salivary gland scintigraphy (SGS) is a non-invasive method to evaluate the function of salivary gland (SG) s by addressing the uptake and secretion of a radioactive labelled substance (sodium pertechnate of ^{99m}Tc). Normally, a rapid uptake and increased concentration of the radioactive probe is attained in the SGs (it can normally be seen within 10 minutes following intravenous administration). After 20-30 minutes, the substance is rapidly secreted into the mouth. Salivary flow may be stimulated with the use of a sialogogue (e.g., diluted lemon juice) administered to the dorsal tongue. Time-activity curves are calculated using manually drawn oval regions-of-interest around both the parotid and the submandibular glands.[21]

According to the 2002 AECG, a positive scintigraphy was defined as a test characterized by delayed uptake, reduced concentration and/or delayed secretion of tracer.[12,34] Angusti et al.[37] reported that SGS may be an accurate and reproducible tool for the diagnosis of pSjS although SjS disease activity index was not shown to be correlated with SGS data. They recommended that SGS should be the first-line imaging technique in patients with suspected pSjS. Aksoy et al.[38] evaluated the diagnostic value of quantifying SGS in correlation to the labial biopsy findings of SjS. With progression in histopathologic grades from 0 to 4, the excretion fraction decreased in all SGs. They also suggested that SGS may be a sensitive and valid method for evaluation of the function of the SGs. However, the value of SGS in the diagnosis of SjS remains controversial. The accuracy of scintigraphy parameters for the diagnosis of SjS among patients with xerostomia was low.[39] A high sensitivity but a low specificity of SGS in SS diagnosis were reported.[21] SGS is also no longer part of the recent classification criteria for pSjS.[17,34] However, it is possible that this technique, monitoring SG functioning over time, may still have some potential indications during patients' follow-up to objectively evaluate changes of their secretory function after treatment.[34]

3) Magnetic Resonance Imaging

In the 1990s, the role of magnetic resonance imaging (MRI) in the diagnosis of SjS was assessed in great detail.[34] Characteristically, in SjS, MRI reveals an inhomogeneous internal pattern on both T1 and T2 sequences with multiple hypo- and hyper-intense nodules of different sizes. MRI quantitative analysis for the standard deviation of the signal intensity was found to be useful in SjS diagnosis. The signal intensity in T1-weight parotid MR images was found to increase proportionally to the severity of the disease.[21,34] To date, other MR modalities in the SjS assessment have been used including MR sialography, functional MR sialography, and dynamic contrast-enhanced MRI. MR sialography has largely replaced conventional sialography and can produce sialographic images similar to those of conventional sialography without the use of contrast media or radiation.[21] Ogura et al.[40] investigated the correlation between

conventional MRI and MR sialography of parotid glands in SjS patients. They found that MR sialography of the parotid glands may be a useful noninvasive tool for evaluating the decrease of SG excretion in SjS. Others suggested that the presence of multiple high-signal-intensity spots on a MR sialography in the parotid gland should be considered the best diagnostic indicator for SjS and the presence of spots, heterogeneity, and the change to smaller volumes in the submandibular gland were also helpful because of their high specificity, particularly, in advanced cases.[41]

4) Ultrasonography

Major salivary gland ultrasonography (SG-US) represents a noninvasive, non- irradiating imaging modality for evaluation of the major SGs in the diagnosis and follow-up of SjS compared to sialography.[42] Structural changes can be visualized as hyperechogenic and hypoechogenic areas, inhomogeneity, and altered echogenicity in general.[43] However, the reliability of SG-US is poorly investigated and the definition of US abnormalities varies in previously published studies.[42] However, other authors suggested that SG-US may be a useful tool for diagnosis, prognostic evaluation, and response to treatment in SjS, as the evidence supporting its sensitivity in the assessment of SGs in SjS have been increase and this imaging technology have been still under development.[43]

CLINICAL MANIFESTATIONS

SjS affects 0.5%-2% of the entire population and is predominant in women with a female to male ratio of 9:1. Typically, SjS is detected around 30 and 50 years of age, while being rare in children.[44,45]

pSjS patients also have various extraglandular manifestations as well as oral and ocular dryness.[1,4,5] Clinical manifestations are described below.

1. Sicca Syndrome

Lymphocytic infiltration of salivary and lacrimal glands by SjS leads to immune-mediated secretory dysfunction resulting in dryness of the mouth and eyes which is termed "sicca syndrome". Dry eye often leads to KCS, with chronic eye irritation and destruction of the corneal conjunctival epithelium. SjS Patients presenting with KCS frequently have red eyes, itching, and grittiness, a burning or scratchy sensation under the eyelids, and photosensitivity. SjS Patients with xerostomia complain with difficulty in chewing and swallowing dry food, difficulty in speaking continuously, and a burning sensation in the mouth. Dryness of airway mucosa can result in hoarse voice, recurrent bronchitis, and pneumonitis. Reduced vaginal secretion leads to dyspareunia and impaired sexual function.[23]

2. Orofacial Manifestations

1) Oral mucosal manifestations

Oral dryness and hyposalivation are the most important data of patients with SjS. These result in several subjective and clinical manifestations because of the loss of salivary secretion and the products by the result of alterations in SGs secretion.[46]

Angular cheilitis is clinically manifested as erythema with or without painful fissures and sores at the corners of the mouth.[47] It was reported as the second most frequent sign followed by dry mouth in a recent study investigating lesions of the oral mucosa in SjS.[48] Dry and erythematous oral mucosa, a lobulated or depapillated red tongue and gum recession with cervical tooth erosions were also present as physical signs.[23] Increased lip dryness, non-specific ulcerations, aphthae and aphthoid conditions might be occurred in SjS.[48]

2) Oral complications

SjS patients are more prone to have dental caries occurring in areas that are not usually caries-prone.[49] Pederson et al.[50] reported that patients with FS ≥1 or the presence of anti-SSA/SSB antibodies in serum had a significantly higher Decayed-Missing-Filled (DMF) Teeth/DMF surface score than patients without these two factors. Intraoral and extraoral Candida infections are often found.[49] Several studies have demonstrated higher plaque index, gingival bleeding, probing depth, and periodontal index in SjS patients with elevated risk of periodontal disease. However, the evidences about increased prevalence of periodontal disease in SjS patients is controversial.[51] A review reported that incidence and severity of periodontal disease were not increased in SjS although it was presumed that decreased salivary flow

may lead to increases in periodontal disease.[49] Oral lesions by poor lubrication and subsequent trauma from dentures, food, or mucosal tissue contact with teeth may occur in SjS patients. Burning mouth, glossodynia, and neuropathies in SjS patients can be increased. However, there is no increased incidence of temporomandibular disorders.[49]

3) Enlargement and Lymphoma of the Parotid glands

Bilateral parotid gland enlargement has been found in 25% to 60% of SjS patients. The enlargement of the parotid glands can be acute or chronic. Acute bilateral or unilateral swelling associated with pain can be caused by obstruction of the SGs by mucous plugging, which form when acinar cells stop producing serous saliva. This situation can result in obstructive sialoadenitis and SG infection by retrograde contamination from the oral cavity.[45]

A rapidly enlargement of an individual gland should prompt a search for other causes. Fine-needle aspiration or biopsy of the gland should be considered as it may be related to the emergence of malignant B-cell lymphoma.[23] pSjS have an increased risk of lymphoma or lymphoproliferative disease compared to the general population. Lymphadenopathy, parotid enlargement, palpable purpura, low C4 serum levels and cryoglobulins were the most consistent non-Hodgkin´s lymphoma (NHL)/lymphoproliferative disease predictors. Additionally, some of the studies identified splenomegaly, low C3 serum levels, lymphopenia and neutropenia as significant prognostic factors. The detection of germinal center-like lesions in diagnostic salivary biopsies of pSjS patients was also proposed as highly predictive of NHL. In contrast, anemia, anti-SSA/SSB antibodies, ANA, RF, male gender, and hypergammaglobulinemia were not associated with lymphoma or lymphoproliferative disease.[52] Lymphomas in turn can develop into more aggressive lymphomas and be the leading cause of death of SjS patients.[45]

3. Systemic Manifestations

The clinical hallmark of SjS is exocrine gland dysfunction, resulting predominately in dry eyes and dry mouth. However, the disease often extends beyond the exocrine glands to seriously affect other organs systems, such as the lungs, kidneys, and nervous system.[53] Systemic involvement can be occurred with or without sicca symptoms. Other autoimmune diseases (organ-specific autoimmunity, SLE, systemic sclerosis, antiphospholipid syndrome, systemic vasculitis, sarcoidosis, and IgG4-related disease) and non-autoimmune processes, such as cardiovascular disease, diabetes mellitus, neurodegenerative diseases, and malignancy, should be excluded.[23]

1) Pain and fatigue

Many middle-aged women with pSjS present with a clinical triad comprising dryness, pain, and fatigue, which has a serious negative impact on their quality of life, and may be associated with sleep disturbance, anxiety, and depression.[23] These symptoms may also affect loss of work productivity.[7]

2) Arthralgia and arthritis

Arthralgia is a symptom characterized by joint pain without inflammatory signs in the involved joint(s). Joint involvement (including either arthralgia or arthritis) was reported in 2,784 of 5,268 (52.8%) patients with SjS.[54] Arthritis is the inflammation of one or more joints characterized by joint pain, heat, redness and swelling during the physical examination. It was characterized in detail in 84 patients: arthritis was reported predominantly as symmetrical (60 patients [71.4%]) while 14 patients (16.7%) presented with monoarthritis. Although the number of joints involved varied, it was fewer than five in 144 of 163 (88.3%) patients.

3) Cutaneous involvement

Cutaneous involvement in SjS is relatively common and various manifestations may be present, in particular cutaneous vasculitis, annular erythema, xeroderma, and eyelid dermatitis.[47] The common cutaneous manifestation of SjS is cutaneous vasculitis characterized by the inflammation of the blood vessels. It is associated with other extraglandular manifestations and the presence of autoantibodies and cryoglobulines.[54,55] The clinical expression of vasculitis depends on the location of the vessels affected, with the skin being the organ predominantly involved. Annular erythema is an erythematous, photosensitive rash characterized by a wide elevated border and central pallor (annular polycyclic lesions) and are mostly found in the face, upper arms, neck

and were less frequent in the lower arms and hands.[54]

4) Raynaud's phenomenon

Raynaud's phenomenon has a prevalence of 10%-37% in pSjS patients. Its clinical course is milder than in systemic sclerosis, which can mimic pSjS.[23]

5) Pulmonary involvement

Pulmonary involvement is defined by the presence of respiratory symptoms (mainly persistent cough and/or dyspnea) associated with altered pulmonary diagnostic tests (pulmonary function tests and/or high-resolution computed tomography scan). A significant percentage of patients with pSjS may present with chronic respiratory symptoms (mainly non-productive cough) associated with mucosal dryness of the upper respiratory tract. Clinical features were detailed in 206 patients and included dyspnea in 129 (62.6%), cough in 112 (54.4%), sputum/rales in 29 (14.1%), chest pain in 11 (5.3%), and fever in 7 (3.4%).[54]

6) Nervous system

The types of neuropathies seen in SjS syndrome include: a) pure sensory which presents with distal symmetric sensory loss due to axonal degeneration of sensory fibers; sensory ataxia due to loss of proprioceptive large fibers (ganglionopathy); or with painful dysethesias (small fiber sensory neuropathy) due to degeneration of cutaneous axons. The latter appears to be the most common neuropathy in SjS and requires skin biopsy for diagnosis to document loss or reduction of nerve fiber density; b) sensorimotor polyneuropathy affecting sensory and motor axons, often associated with severe systemic or pro-lymhomatous manifestations, such as palpable purpura and cryoglobulinemia, and c) rare types that include autoimmune demyelinating neuropathy, mononeuropathy, mononeuropathy multiplex and autonomic neuropathy.[56]

7) Renal system

Chronic tubulointerstitial nephritis is the main renal involvement associated with pSjS. Glomerulonephritis is less common, which often comes to light when routine analyses are abnormal (proteinuria, renal failure).[54]

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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