Review

Practical guidelines for the early diagnosis of Sjögren's syndrome in primary healthcare

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ABSTRACT

Primary care physicians can play a crucial role by recognising Sjögren's syndrome (SS) in the early stages identifying those patients with the greatest probability of being diagnosed with SS. SS has a very specific epidemiological profile at presentation (female aged 30-50 years), which may aid an early diagnosis. Although the disease may be expressed in many guises, there are three predominant clinical presentations that should be considered as key clues to increased clinical suspicion (multiple symptoms of dryness, asthenia-polyalgia syndrome and systemic organ-specific manifestations). The physical examination may provide important clues to systemic involvement (parotid gland enlargement, skin lesions suggestive of purpura or annular erythema, respiratory crackles, arthritis, neurological sensory or motor deficits). Simple laboratory studies may be very useful in reinforcing the clinical suspicion of SS, and the triad of cytopenia, raised erythrocyte sedimentation rate and high serum gamma globulin levels is a very specific "biological" pattern suggesting SS. A solid clinical suspicion of SS requires both the patient reporting sicca symptoms and objective evidence that these symptoms are associated with dysfunction of the lachrymal and salivary glands. Ultrasonography of the parotid glands, a non-invasive method, may be a major advance in the diagnostic approach to SS in primary care. Primary care physicians must be considered essential members of the multidisciplinary team in charge of the follow-up of SS patients, due to their key role in the continuum of patient care and their cross-sectional knowledge of common diseases that frequently coexist in patients with SS.

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease in which immune-mediated inflammation causes secretory gland dysfunction, leading to dryness of the main mucosal surfaces, together with the involvement of many extra-glandular tissues (1). A sensation of dryness, above all in the eyes and mouth, is the predominant symptom, but is often given little importance by physicians or patients. However, SS is a serious disease, with a substantial impact on the quality of life (QoL) (2, 3), and organ-specific damage may end in chronic failure of internal organs and excess mortality (4), mainly due to lymphoproliferative disease (5). The protean presentation may result in diagnostic delays of up to 10 years with patients often visiting various specialists (6). The distinction between primary and associated (secondary) SS only reflects a clinical situation of coexistence with other autoimmune diseases.

Primary care physicians can play a crucial role by recognising SS in the early stages. Despite the key role of primary care, a PubMed Search crossing the terms "Primary Care" and "Sjogren syndrome" identified only 343 articles and, of the six that seem to be focused on SS in primary care according to the title, only two were reviews of primary care approaches but did not contain specific recommendations for primary care physicians (7, 8). Therefore, we have selected relevant studies and reviews focused on SS searching for clinical information that could be useful for a reliable diagnostic approach by primary care physicians.

This review summarises the main recommendations that may help primary care physicians make an early identification of SS, an approach made ac-

cording to the means usually available in primary care, and whose objective is to select patients with the greatest probability of being diagnosed with SS so they can be referred as soon as possible to a systemic autoimmune disease unit.

Epidemiological clues

SS has a very specific epidemiological profile at presentation, which may aid an early diagnosis. There are three specific epidemiological clues that may aid family physicians to consider SS as a probable diagnosis. First, even though SS is less frequent than the main diseases seen in primary care, it is by no means rare, as it is the most frequent systemic autoimmune disease. Although the frequency of SS varies widely according to the study design and the classification criteria used, a recent population-based study estimated that SS may affect 1 in 400 people (9), with an incidence rate of 7 new diagnoses per 100,000 person-years (10). Secondly, SS is diagnosed overwhelmingly in women and is the systemic autoimmune disease with the most unbalanced gender ratio; a recent Big Data study reported a female/male ration of nearly 10:1 (11). Thirdly, although SS occurs at all ages, it is mainly diagnosed between the fourth and sixth decades of life. SS in children is very rare (around 1% of cases have a childhood-onset), while in older people, the diagnosis is more frequent (around 10% of patients are aged >75 years at diagnosis) (12). Therefore, the closer to the typical epidemiological profile of SS the patient is (female aged 30–50 years), the greater the suspicion of the disease should be.

Identifying the predominant phenotypes of presentation

SS may be expressed in many guises, but three predominant clinical presentations should be considered as key clues to increased clinical suspicion.

Multiple symptoms of dryness

Dryness of the mouth and eyes (xerostomia and xerophthalmia) are the predominant symptoms of SS and must be considered the principal features leading to its suspicion, especially when they present in tandem, as reported by nearly 90% of patients (13); these symptoms have positive and negative predictive values of 54-77% and 94-98%, respectively (12, 13). In people evaluated for dry mouth and/or dry eyes, SS is diagnosed in around 10-15% of cases (14).

Xerostomia is the subjective feeling of oral dryness and is related to reduced salivary volume that interferes with basic functions such as speaking or eating. The absence of the antimicrobial functions of saliva may accelerate local infection, tooth decay, and periodontal disease, and may lead to difficulty with dentures and the need for dental res-

Table I. Non-pharmacological causes of dry eyes.

- Allergic conjunctivitis: burning eyes, mucoid secretion, and conjunctival erythema
- Blepharitis: eyelid margins are erythematous and thickened with crusts and debris within the lashes; usually worse in the morning and improves as the day goes on; does not respond to lubricant drops
- Blepharospasm: uncontrolled blinking due to an increased local neural reflex circuit
- Iritis/uveitis: in most cases associated with pronounced photosensitivity
- Herpetic keratitis: generally, with ophthalmic distribution of shingles
- Environment: dryness caused by prolonged exposure to low humidity, dust, or sun
- Lifestyle: dryness caused by diminished blinking during long periods of reading, driving, or computer use
- Rosacea: ocular symptoms (*e.g.* itchy, burning, dry eyes with eyelid swelling and erythema) occur in 50% of patients with rosacea
- Meibomian gland deficiency
- Neurologic defects: V or VII paralysis
- Eyelid defects: ectropion, hyperthyroidism, proptosis
- Contact lens use
- Deficient nourishment: hypovitaminosis, A avitaminosis
- Conjunctival scarring: Stevens-Johnson syndrome, ocular pemphigoid, trachoma

Table II. Non-pharmacological causes of dry mouth.

- Diabetes: dryness worsens with poor glycaemic control.
- Periodontal gingivitis.
- Head and neck radiation: external beam radiation damages salivary glands.
- Hepatitis C: sialadenitis results in dry mouth in 15% of persons with hepatitis C.
- HIV infection: Oral candidiasis, and HIV-related salivary gland disease exhibits clinical manifestations similar to Sjögren's syndrome.
- Obstructed nasal passages: dryness caused by mouth breathing.
- Sarcoidosis: decreased salivary flow results from noncaseating granulomas in salivary glands
- Dehydration
- Mouth breathing
- Hypoplasia or aplasia of salivary glands
- Surgical gland excision

Table III. Drugs causing sicca symptoms.

- Antihistamines: pseudoephedrine, chlorpheniramine, diphenhydramine.
- Alpha-1 antagonists (terazosin and prazosin)
- Alpha-2 agonists (clonidine)
- Beta blockers (atenolol, propranolol)
- Muscle relaxants: cyclobenzaprine, methocarbamol
- Urologic drugs: oxybutynin, bethanechol
- Parkinson drugs: carbidopa, levodopa, biperiden
- Ant-arrhythmic: disopyramide, mexiletine
- Neuroleptics, sedatives, and hypnotics: benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants, opioids
- Anticholinergics: atropine, scopolamine

toration, particularly in older patients. Other oral symptoms include soreness, adherence of food to the mucosa, and dysphagia.

Ocular dryness often manifests as sensations of itching, grittiness, soreness, and dryness, although the eyes have a normal appearance. Other ocular complaints may include photosensitivity, erythema, eye fatigue, or decreased visual acuity. Environmental factors such as smoke, wind, air conditioning, and low humidity may exacerbate ocular dryness. Diminished tear secretion may lead to damage of the conjunctival epithelia (*keratoconjunctivitis sicca*), with greater susceptibility to ocular infections (15).

Additional sicca symptoms that often coexist with oral and ocular dryness include the involvement of other mucosal surfaces. Reductions in respiratory tract glandular secretions can lead to dryness of the nose, throat, and trachea resulting in persistent hoarseness and chronic, non-productive cough. Likewise, involvement of the exocrine glands of the skin leads to cutaneous dryness (Tables I, II). In female patients with SS, dryness of the vagina and vulva may result in pruritus, dyspareunia, and repeated candida infections (16).

The diagnostic approach to primary care patients presenting with sicca syndrome starts by ruling out other causes of oral/ocular dryness, including diabetes mellitus, chronic viral infections, dehydration, irradiation of the salivary glands and psychogenic hyposalivation. However, the most frequent cause of sicca features is the chronic use of medications (mainly antihypertensive, antihistamine, and antidepressant agents), especially in older patients (Table III).

Table IV. Parotid enlargement.

- Viral infections: mumps, HIV salivary gland disease, HCV-related sialadenitis
- Chronic recurrent parotitis
- Benign mesenchymal tumour (*e.g.* haemangioma, fibrous histiocytoma, xanthogranuloma).
- Malignant salivary gland neoplasms (*e.g.* pleomorphic salivary adenoma, lymphomas)
- Malnutrition
- Alcoholism
- Long-term diabetes mellitus
- Bulimia
- Drug-induced swelling.
- Hyperlipidaemias (type IV and V)
- Sclerosing sialadenitis (IgG4-related disease)
- Sarcoidosis
- Amyloidosis

Table V. The laboratory evaluation in Sjögren's syndrome.

Test	Typical result
Blood cell count	• Normochromic, normocytic anaemia. Isolated cases of haemolytic anaemia • Mild leukopenia (3-4x10^9/L), lymphopenia, neutropenia • Mild thrombocytopenia (80-150 x10^9/L). Isolated cases of immune thrombocytopenia (10 x10^9/L).
Acute phase reactants	• Elevated erythrocyte sedimentation rate (>50 mm/h) in 20-30% of cases, especially in patients with hypergammaglobulinaemia • Normal values of C-reactive protein • Raised levels of beta2-microglobulin
Proteinogram	• Hypergammaglobulinaemia • Monoclonal band
Liver function tests	• Raised transaminases (discard hepatitis C virus or autoimmune hepatitis) • Raised alkaline phosphatase and/or bilirubin (discard primary biliary cirrhosis)
Renal studies	• Proteinuria, haematuria (glomerulonephritis) • Hypokalaemia, low plasma bicarbonate, and low blood pH (renal tubular-acidosis)

Asthenia-polyalgia syndrome

A large percentage of SS patients may present with a clinical phenotype overwhelmingly dominated by widespread/generalised pain and fatigue/weakness (1, 17), which may be closely related to other non-specific symptoms such as sleep disturbance, anxiety and depression (14). These non-life-threatening symptoms have a serious impact on the QoL (18) and have been reported in > 80% of patients with SS (19). The environment plays a key role in exacerbating these symptoms. Physicians should be alert to women reporting an abrupt onset of these symptoms (14) with a dramatic change in their QoL. Some authors have proposed alternative names for this specific SS phenotype, such as sicca asthenia polyalgia syndrome (20). Careful assessment is essential in these patients, as these symptoms are also characteristic of other processes (hypothyroidism, neoplasia, primary depression) and, above all, of central sensitization syndromes like fibromyalgia and chronic fatigue syndrome, which have a very significant epidemiological overlap with primary SS (21, 22).

Systemic Sjögren's syndrome

SS patients can develop many extra-glandular manifestations (23), which may be the first "visible" presentation of the disease. These features may appear before the onset of the characteristic features of dryness, or in patients reporting mild sicca symptoms that may be neglected by patients and physicians (14). A long list of systemic features that can precede the diagnosis of SS, including palpable purpura, annular erythema, interstitial lung disease, Raynaud's phenomenon, renal tubular acidosis (hypokalaemia, nephrocalcinosis), mononeuritis multiplex, pure sensory neuronopathy (ganglionopathy), cranial nerve involvement, myelopathy, optic neuritis and aseptic meningitis. Two additional presentations are closely linked to SS. First, some patients, especially children and young people, may present with continuing, well-tolerated fever, with no other systemic features (24). Second, foetal congenital heart

block in the baby of a pregnant women may lead to the discovery of underlying maternal anti-Ro antibodies; a significant percentage of these asymptomatic mothers will develop SS (25, 26). Logically, the clinical suspicion of SS is exponentially enhanced when extra-glandular manifestations accompany sicca complaints. Systemic SS is scored using the EULAR Sjögren Syndrome Disease Activity Index (ESSDAI), a systemic activity index to assess systemic complications that includes the main systemic features ordered organ-by-organ (27).

Red flag signs in the physical examination

A complete physical examination is essential, with a special focus on the mucosal surfaces. Various oral signs may be clues, including a moist mouth, reduced pooling of saliva in the floor of the mouth, with a red, lobulated surface of the tongue with partial or complete depapillation and, in advanced disease, a dry, glazed oral mucosa that tends to form fine wrinkles. Angular cheilitis, erythematous changes in the hard palate, and a red tongue with atrophic papillae strongly suggest *Candida* infection. Reduced tear secretion may lead to chronic irritation of the ocular surface resulting in filamentary keratitis (mucus filaments adhering to damaged areas of the corneal surface). Tears also have inherent antimicrobial activity and SS patients are more susceptible to ocular infections such as blepharitis, bacterial keratitis, and conjunctivitis. Severe ocular complications may include corneal ulceration, vascularisation, and opacification.

Episodic swelling of the major (parotid and submandibular) salivary glands is a highly-specific feature of SS that is reported in 10–20% of patients; it may commence unilaterally, but often becomes bilateral. There are causes of parotid enlargement other than SS that should be ruled out (Table IV).

The physical examination may provide important clues to systemic involvement, (skin lesions suggestive of purpura or annular erythema, respiratory crackles, arthritis, neurological sensory or motor deficits). A specific physical examination focused on signs suggestive of lymphoma (peripheral enlarged lymph nodes, hepatomegaly, and splenomegaly) is always recommended (28).

Laboratory approach

Simple laboratory studies may be very useful in reinforcing the clinical suspicion of SS, including a hemogram, acute reactants, standard biochemical study, urinalysis and proteinogram (Table V). The triad of cytopenia, raised erythrocyte sedimentation rate and high serum gamma globulin levels is a very specific "biological" pattern suggesting SS.

The blood count may show cytopenia (normocytic anaemia, leukopenia, and/or thrombocytopenia) in up to 30% of SS patients; lymphopenia is the most frequent abnormality, closely followed by neutropenia. A raised erythrocyte sedimentation rate (ESR) with normal CRP values is frequent and correlates closely with the percentage of circulating gamma globulins (hypergammaglobulinaemia) (29). Polyclonal hypergammaglobulinemia is another characteristic laboratory abnormality found in primary SS that reflects the polyclonal B-cell activation involved in the disease pathogenesis. Hypergammaglobulinaemia is mainly reported in patients carrying autoantibodies (RF, anti-Ro/SSA and anti-La/SSB). Studies have reported that up to 10% of patients with primary SS may have associated monoclonal gammopathy of undetermined significance (MGUS) that appears in the proteinogram as a band of restricted mobility in the gamma region (30). Other laboratory abnormalities may suggest SS-related renal involvement (hypokalaemia, urine pH >5.5, raised creatinine) or associated organ-specific autoimmune diseases (liver, thyroid) (Table V).

Positive results in immunological tests may be central in differentiating SS from non-autoimmune causes of sicca syndrome. Autoantibodies are the key serological markers of autoimmune disease and, in patients with SS, may be present up to 20 years before the disease diagnosis (31, 32). The autoimmune origin of sicca syndrome may be studied in primary care by readily available immunological data including antinuclear antibodies (ANA), rheumatoid factor (FR) and complement levels. ANA are the most frequently detected autoantibodies in primary SS (>80%) and although they are a useful immunological screening test for further diagnostic referral, their specificity is very low, especially in healthy people or with non-specific symptomatology (33). RF is present in half the patients with primary SS and has a similar sensitivity to ANA but a greater specificity for SS classification and has been associated with the main clinical, histopathological and laboratory features of primary SS (34). Hypocomplementemia (low C3 and/or C4 levels) are found in 10–25% of SS patients and are closely associated with very active disease and a higher risk of the main adverse outcomes of SS (lymphoma and death) (35).

Diagnostic tests in primary care

Solid clinical suspicion of SS requires both the patient reporting sicca symptoms and objective evidence that these symptoms are associated with dysfunction of the lachrymal and salivary glands. Although the study of impaired saliva and lachrymal secretions is not routinely available in primary care, some simple tests may easily be used in primary care.

Salivary flow measurement is the simplest method of confirming major salivary gland involvement, is acceptable to patients and requires no special equipment. Patients should be instructed to spit saliva into a graduated test tube every minute, and unstimulated salivary flow measurement showing <1.5 mL (less than half a teaspoonful) collected over 15 min has a sensitivity of 56% and a specificity of 81% for the diagnosis of SS (28).

Lachrymal gland output can easily be measured using Schirmer's test, which quantitatively measures tear formation via placement of filter paper in the lower conjunctival sac, although this test is not usually available in primary care. The test result is positive when <5 mm of paper is damp after 5 minutes. Analysis of the corneal surface using dyes that stain degenerated or dead cells (corneal staining) is a key diagnostic test but must carried by an ophthalmologist.

Ultrasonography (US) of the parotid glands, a non-invasive method, may be a major advance in the diagnostic approach to SS in primary care, as US is increasingly used in primary care (36, 37). Findings such as parenchymal heterogeneity (due to hypoechogenic areas resembling fluid cysts, increased glandular size, hyperechogenic bands, imprecision of the borders, intraglandular calcification, and/or parenchymal inflammation assessed by power Doppler or vascular abnormalities assessed by colour Doppler are evidence of parotid gland damage (38-41). Recent studies of the potential role of US in the evaluation of parotid involvement in daily practice found it has a potential role in the early non-invasive diagnosis of SS, a correlation with subjective and objective oral and ocular items and systemic features, and an improvement in the diagnostic performance of the SS classification criteria when the salivary gland ultrasonography score was added (42-44).

Specialised workup

All suspected cases of SS should be referred to multidisciplinary teams specialised in the management of systemic autoimmune diseases. According to the 2019 EULAR Guidelines for SS, a multidisciplinary approach involving various health professionals is essential, with a central role for specialists in autoimmune diseases, who should act as the coordinator of diagnostic and therapeutic healthcare processes, and the involvement of primary care physicians was highly recommended in the management of SS patients (45).

Glandular dysfunction should be confirmed by additional tests. A complete ophthalmological assessment should include the Schirmer test and corneal staining using colourants (rose Bengal, fluorescein) for slit lamp examination to detect conjunctival epithelium destroyed by desiccation. Parotid scintigraphy, with a sensitivity of 80% and a specificity of 86% (28), provides valuable information on the prognosis and outcome (46).

The final step in confirming SS should be two diagnostic tests that, although not pathognomonic, are considered the key markers of SS, since they confirm a proven diagnosis according to the 2002 American-European Consensus Group Criteria (sensitivity of 93.5% and specificity of 94%) and the 2016 ACR/EULAR criteria (sensitivity of 96% and specificity of 95%) (Table VI) (47, 48). Anti-Ro/SS-A and/or La/SS-B antibodies, which were detected in 73% of patients in the largest reported series (12), are the key immunological markers of SS, although they are not specific to SS and are found in other systemic autoimmune diseases (mainly SLE, systemic sclerosis, mixed connective tissue disease and inflammatory myopathies) (49). Minor salivary gland biopsy remains a highly specific test for the diagnosis of SS (50): although invasive, it is safe and has few adverse lo-

Table VI. American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome.

The classification of primary Sjögren's syndrome applies to any individual who meets the inclusion criteria, does not have any of the conditions listed as exclusion criteria, and has a score of at least 4 when the weights from the 5 criteria items below are summed.

INCLUSION CRITERIA

1. Patients with ocular and/or oral dryness, defined as a positive response to at least 1 of the following questions:

- Have you had daily, persistent, troublesome dry eyes for more than 3 months?
- Do you have a recurrent sensation of sand or gravel in the eyes?
- Do you use tear substitutes more than 3 times a day?
- Have you had a daily feeling of dry mouth for more than 3 months?
- Do you frequently drink liquids to aid in swallowing dry food?

or

2. Patients with suspected systemic Sjögren's (at least 1 domain with a positive item in the European League Against Rheumatism SS Disease Activity Index questionnaire)

EXCLUSION CRITERIA

Prior diagnosis of any of the following conditions, which would exclude diagnosis of SS and participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:

- history of head and neck radiation treatment
- active hepatitis C infection (with confirmation by polymerase chain reaction)
- AIDS
- sarcoidosis
- amyloidosis
- graft-versus-host disease
- IgG4-related disease

CRITERIA ITEMS (*score*)

1. Labial salivary gland with focal lymphocytic sialadenitis and focus score of >=1 foci/4 mm^2 (*Score = 3*)

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.

2. Anti-SSA/Ro positive (*Score = 3*)
3. Ocular Staining Score –OSS- >=5 (or van Bijsterveld score >=4) in at least 1 eye (*Score = 1*)
4. Schirmer's test <=5 mm/5 minutes in at least 1 eye (*Score = 1*)
5. Unstimulated whole saliva flow rate <=0.1 ml/minute (*Score = 1*)

Table VII. Chronic complications of hyposalivation.

- Tooth demineralisation and caries
- Gingival changes
- Impaired chewing
- Denture use and function impaired
- Swallowing difficulties
- Oral malodour
- Altered taste
- Mucosal dryness and sensitivity
- Oral infections (candidiasis and bacterial sialadenitis)

cal effects (51-53). Focal lymphocytic sialadenitis, defined as multiple, dense aggregates of ≥50 lymphocytes in perivascular or periductal areas in most glands sampled, is the characteristic histopathologic feature of SS. The key requirements for a correct histological evaluation are an adequate number of informative lobules and the determination of a mean focus score (a focus is a cluster of ≥50 lymphocytes), although the focus score assessment may vary between pathologists (50, 54, 55).

Why is it important to reach a diagnosis?

An early, accurate suspicion of SS by primary care physicians may help prevent or ensure timely treatment of many of the complications associated with SS. Untreated dry mouth can result in dental loss, oral candidiasis, and periodontal disease (Table VII), while untreated severe dry eyes may result in corneal ulcers and further perforation, which may eventually lead to loss of the eye. For example, early restoration of salivary function can relieve the symptoms of dry mouth and prevent or slow the progress of oral complications, including dental caries, oral candidiasis, and periodontal disease.

An early diagnosis may aid correct management of non-specific general complaints that are the key contributors to the poor health related QoL (HRQoL) of primary SS patients, including fatigue, chronic pain, and depression. Other features that could contribute to poor HRQoL in undiagnosed patient include inadequate dental and periodontal health (56), the impact of gynaecological involvement on women sex lives (57, 58) and the potential effect of voice disorders and other ENT symptoms on occupational and social activities (59). Specialist evaluation of these symptoms may be of great value. The principal symptoms of SS, namely dryness (particularly oral and ocular), fatigue and pain (of limbs, arthralgia/myalgia) are unpleasant and, often, debilitating. It is hardly surprising, therefore, that many patients report a worsened HRQoL.

Primary SS usually progresses very slowly, with no rapid deterioration in salivary function or dramatic changes in sicca symptoms. The main exceptions are systemic manifestations and the high incidence of lymphoma. An early diagnosis is also mandatory for systemic SS to prevent chronic organ damage by prompt recognition and treatment. Undiagnosed organ-specific involvements may delay appropriate therapy resulting, in some cases, to end-stage organ failure (renal failure, pulmonary fibrosis, progressive neurological disease) and death. Haematological neoplasia is the main complication of SS (60); prospective studies have identified parotid enlargement, purpura, cryoglobulins, monoclonal band and hypocomplementemia as clinical and immunological risk factors (61-64).

Table VIII. Systemic and organ-specific autoimmune diseases associated with Sjögren's syndrome.

Systemic autoimmune diseases

- Systemic lupus erythematosu
- Rheumatoid arthritis
- Systemic sclerosis
- Inflammatory myopathies
- Antiphospholipid syndrome
- Sarcoidosis
- ANCA vasculitides
- Still disease

Organ-specific autoimmune diseases

- Autoimmune thyroiditis
- Primary biliary cholangitis
- Sclerosing cholangitis
- Autoimmune hepatitis
- Multiple sclerosis
- Diabetes mellitus
- Inflammatory bowel disease
- Coeliac disease

Primary SS patients are at a 10-fold higher risk for lymphoma than healthy individuals and patients with other autoimmune diseases (7-fold higher in systemic lupus erythematosus, 4-fold in rheumatoid arthritis) (60). The long-term risk of lymphoma in patients with primary SS is estimated at 5%. Lymphomas in primary SS patients are extranodal in 80% of cases, with the most common site being the parotid glands; persistently-hard glandular enlargement should alert the clinician to a possible lymphoma. Lymphomas in SS may also occur in the gastrointestinal tract or lungs. Studies have identified palpable purpura lymphopenia, cryoglobulinemia and hypocomplementemia as the key risk factors for lymphoma, features that except for cryoglobulins, can easily be detected in primary care.

Follow-up and monitor

Joint, coordinated follow-up between specialist and primary care once the diagnosis of SS is confirmed is highly recommended for the optimal management and care of SS patients. Stable patients with disease limited to mucosal surfaces may require only yearly evaluation in primary care, while those with

Table IX. Organ-specific clinical manifestations of Sjögren syndrome.

Organ	Manifestations
General symptoms	Low-grade fever, generalised pain, myalgias, fatigue, weakness, polyadenopathies
Skin	Cutaneous dryness, palpable purpura, Ro-associated polycyclic lesions, urticarial lesions
Joints	Arthralgias, non-erosive symmetric arthritis
Lungs	Obstructive chronic pneumopathy, bronchiectasis, interstitial pneumopathy
Cardiovascular	Raynaud phenomenon, pericarditis, autonomic disturbances
Nephro-urologic	Renal tubular acidosis, glomerulonephritis, interstitial cystitis, recurrent renal colic
Peripheral nerve	Mixed polyneuropathy, pure sensitive neuronopathy, mononeuritis multiplex, small-fibre neuropathy
Central nervous system	White matter lesions, cranial nerve involvement (V, VIII, and VII), myelopathy
Nose, ear, and throat	Parotid swelling, nasal dryness, chronic cough, sensorineural hearing loss

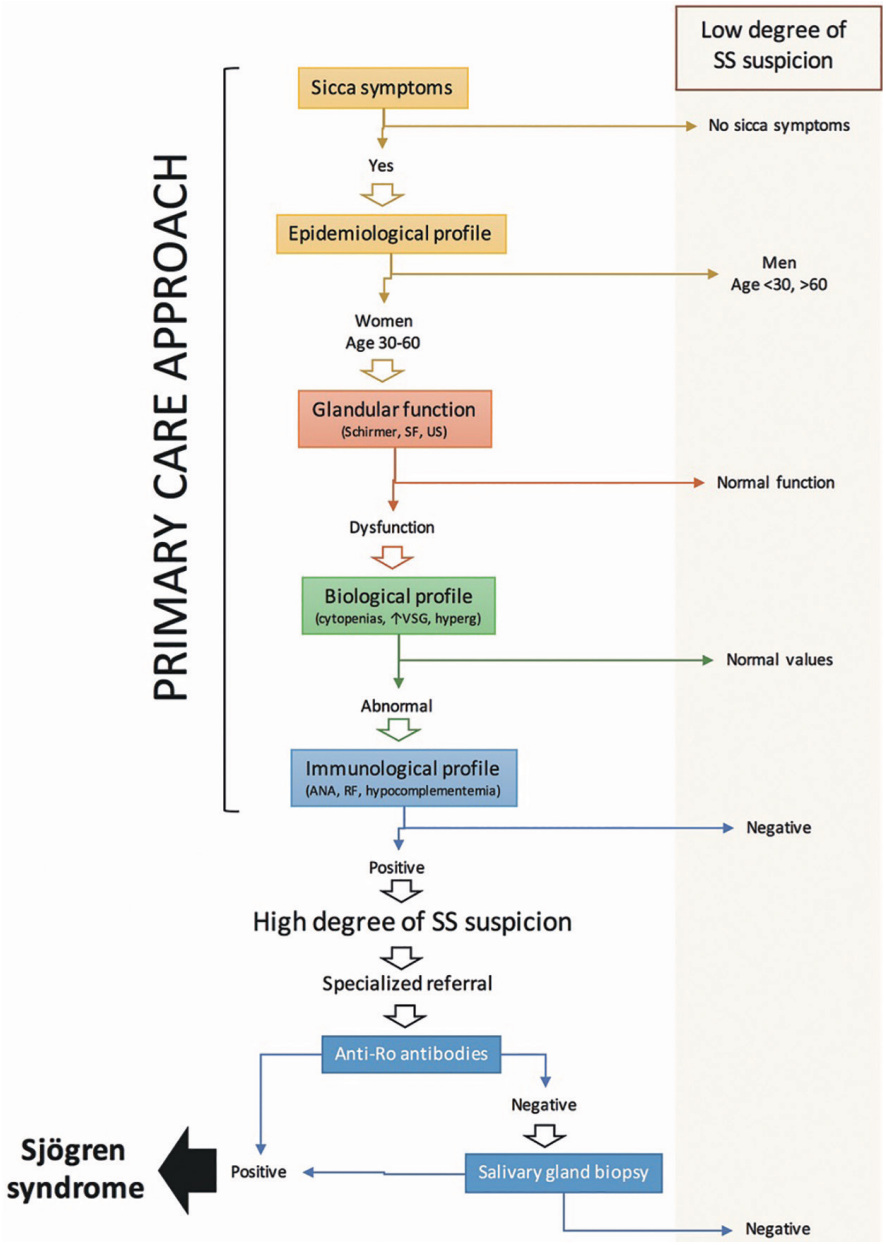

Fig. 1. Diagnostic algorithm for SS in primary care.

extra-glandular manifestations should be evaluated every 6 months and patients with end-organ damage every 3 months (65). Routine physical examination should include the evaluation of mucosal surfaces to rule out local complications and examination for peripheral adenopathies, and enlargement of parotid glands, the liver and spleen. Annual routine laboratory tests should include a complete blood count, ESR, and renal and liver tests. Immunological tests should not be included in the routine follow-up of SS patients with two exceptions: markers associated with a poor prognosis and a clinical suspicion of a concomitant systemic or organ-specific autoimmune disease (Table VIII).

During the follow-up, specific symptoms that merit referral to the appropriate specialist may be encountered (Table IX). With respect to mucosal involvement, these include dental loss, oral candidiasis, and periodontal disease (odontologist), acute red eye and eye pain suggestive of corneal ulcer (ophthalmologist) and severe dyspareunia and vaginal candidiasis (gynaecologist). Extra-glandular involvement requires organ-specific specialist referral for the diagnosis of the main systemic complications. Patients with recurrent respiratory infections or dyspnoea should be evaluated by a pulmonologist through pulmonary function tests and pulmonary scan. Neurological symptoms such as paraesthesia, ataxia or diplopia should be evaluated by a neurologist searching for peripheral neuropathy or central nervous system disease. Patients with raised serum creatinine or recurrent renal colic should be referred to a nephrologist for a complete renal study including renal biopsy, while those with altered liver function tests should be referred to a hepatologist who may indicate a liver biopsy. Patients with persistent high fever, polyadenopathies and/or increased parotid swelling should be referred to a haematologist to rule out haematological neoplasia.

SS is a chronic disease that has no cure, and the therapeutic management has not changed significantly in recent decades with the use of agents locally applied to the mucosal surfaces involved (as the key approach for treating sicca symptoms) and corticosteroids and immunosuppressive agents (in patients with systemic disease (45). Unfortunately, current evidence remains very limited, without solid results that could change the SS management (66), although novel targeted therapies may open new therapeutic options (67).

Conclusions

Current evidence on the source of the inequality of clinical care of SS patients is scarce and of limited generalisability in different countries (68), especially about the role of primary care. Primary care physicians can play a crucial role when a diagnosis of SS is suspected, by reducing the time from symptom onset to a confirmed diagnosis. Although primary care physicians may think SS is an uncommon, complex disease that is very difficult to diagnose, most symptoms, signs, laboratory data and diagnostic tests are familiar in the primary care ambit and permit a reliable diagnostic approach (Fig. 1). In addition, primary care physicians must be considered essential members of the multidisciplinary team in charge of the follow-up of SS patients, due to their key

role in the continuum of patient care and their cross-sectional knowledge of common diseases that frequently coexist in patients with SS and which may have a significant impact on the prognosis and quality of life.

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