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Review Article

Sjögren's Syndrome

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Sjögren's syndrome [SS] is an autoimmune disease of mainly exocrine glands. Sicca symptoms are the most common cause of admission to the outpatient clinics. However systemic involvement like lungs, peripheral nervous system, joints, liver, kidney can also be seen. SS is called primary SS [pSS] when SS is not accompanied by another autoimmune disease like rheumatoid arthritis, systemic lupus eritematozus [SLE] [1].

EPIDEMIOLOGY

SS primarly affects females over 40 years of age. The female:male ratio in this age group is 9:1. Studies of geriatric populations revealed that the prevalance is 3% [2].

CLINICAL FEATURES

Dry mouth and/or dry eye are the most common presenting symptom [3]. Lymphocytic infiltration of lacrimal glands and/or salivary leads to diminished basal tear and saliva production resulting in sicca symptoms. Diminished basal tear production results in burning or sandy sensation under the eyelids, grittiness, red eyes, itching, photosensitivity. Decreased salivary production is the cause of difficulty in chewing and swallowing of dry food, speaking contiunously and also burning sensation of the mouth. Physical examination shows a dry, erythematous sticky oral mucosa, red tongue, scanty and cloudy saliva and atrophy of the filiform papillae. Hallitosis, dental caries and periodental disease are also increased as a result of decreased saliva production [4]. Laryngeal dryness leads to hoarseness, dry cough, diminished vaginal secretion results in dyspareunia. Itching, irritation, discomfort are the result of dry skin [5]. Swelling of major salivary glands, chronic or persistant is one of the characteristic features of the disease. Swelling is usually bilateral, although at the initial stages can be unilateral [6].

Systemic manifestations like constitutional symptoms or other organ system involvement are not rare in SS. Extraglandular involvement of SS is related to either periepithetial lymphocytic invasion or extraepithetial immun complex deposition. Interstitial nephritis, liver involvement, obstructive bronchiolitis is related to lymphocytic invasion of the epitelia of extraglandular organs. Periepithelial involvement usually follow a benign course. On the other hand, immune complex deposition is the cause of extraepitelial involvement and palpable purpura, glomerulonephritis, peripheral neuropathy can be seen. Extraepithelial involvement is associated with morbidity and lymphoma as a result of B-cell hyper reactivity [3].

Although artralgia or myalgia is quite frequent, frank arthritis is rare [6]. Raynaud phenomenon as well as palpable purpura are the most common skin manifestations [7].

Non-Hodgkin lymphoma relative risk in pSS is 44 times higher than normal population. [8,9]. Risk factors for lymphoma development in SS include parotid gland enlargement, splenomegaly, lymphadenopathy, low C4 levels, mixed monoclonal cryoglobulinemia and vasculitis. Mucosa associated lymphoma [MALT] is the most common lymphoma in SS patients [9,10].

INVESTIGATIONS

Cytopenias frequently leukopenia and lymphocytopenia rarely thrombocytopenia can be seen in SS. Erythrocyte sedimentation is elevated frequently. ANA and RF is found positive with high titers. Anti-Ro [anti-SSa] and anti-La [anti-SSb] are highly sensitive autoantibodies for SS along with SLE [1].

Schirmer's tear test, wetting of less than 5 mm per 5 minutes with strips of filter paper is objective finding of dry eyes, however is not diagnostic of SS. Rose Bengal staining which stains devitalized or damaged epithelium of the cornea and the conjuctiva also reveals decreased tear secretion. Tear film break up time which is overly rapid in SS is another usefull assessment for decreased tear secretion [11].

Sialometry, sialography and scintigraphy are methods of evaluation of salivary gland function. Sialometry measures salivary slow rates in SS however decreased salivary slow rate is not diagnostic for SS [12]. Sialography shows increased incidence of sialectasis in SS which is highly specific and sensitive for the diagnosis [13]. Scintigraphy provides a functional evaluation of all salivary glands. 99m-Tc pertechnetate uptake by salivary glands and secretion in the mouth is delayed or absent in SS [14].

Minor salivary gland biopsy is the cornerstone for the diagnosis of SS. The key requirement of SS is focal lymphocytic sialoadenitis. Minor salivary gland biopsy including 5-10 glands which demonstrates FLS in most of the glands in the specimen and a focus score above 1 has a diagnostic threshold [>1 according to Chilsom] [15, 16].

DIFFERENTIAL DIAGNOSIS

Among other causes of sicca syndrome the most important is age-related glandular atrophy since SS is the disease of this age group. Also dehydration, previous irradiation to the head

Table 1: American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: The classification of primary Sjögren's syndrome (SS) 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 ≥ 4 when the weights from the five criteria items below are summed.

Item	Score
Weight/score Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4 mm^2 ‡	3
Anti-SSA/Ro-positive	3
Ocular Staining Score ≥ 5 (or van Bijsterveld score ≥ 4) in at least one eye§¶	1
Schirmer's test ≤ 5 mm/5 min in at least one eye§	1
Unstimulated whole saliva flow rate ≤ 0.1 mL/min§**	1

and neck, salivary gland trauma, salivary gland tumor, hepatitis C or HIV infections, diabetes mellitus, sarcoidosis, IgG4-related disease, amyloidosis, psychological factors, Alzheimer's disease, drugs such as opioids, trycyclic antidepressant drugs, anticholinergics should be included in the differential diagnosis [17].

CLASSIFICATION CRITERIA

ACR/EULAR classification criteria for pSS applies to any individual who meets the inclusion criteria [patients with objective dry mouth and/or dry eyes] and does not have any other cause of sicca syndrome with a score of at least 4 when the weights from the 5 criteria items are summed can be classified as SS [17] (Table 1).

TREATMENT

SS treatment involves treatment of sicca symptoms as well as systemic involvement. Dry eyes should be lubricated with artificial tears when necessary. Cyclosporin-A topical forms are also effective in alleviating dry eye symptoms. Punctal cauterization can also be used in severe cases. Treatment of dry mouth is usually palliative like carrying water or chewing gum. Adequate oral hygiene is the prerequisite for prevention of dental carries. Pilocarpine or cevimeline can also be used if the salivary hypofunction is severe with caution, especially cevimeline in patients with cardiovascular diseases [18].

Hydroxychlorine or methotrexate can be given for arthritis, cyclophosphamide for vasculitis or interstitial lung disease, biologics like rituximab, belimumab and abatacept showed their effectiveness in open studies for some extraglandular features of SS [19].

CONCLUSION

SS is one of the most common connective tissue disorders among postmenopausal women. ACR/EULAR proposed in 2016 a classification criteria which showed good performance in when compared with other sets of SS classification criteria [20]. Sicca symptoms can severely deteriorate life quality but the treatment is only paliative. Remission can be induced in extraglandular manifestations by immune suppressives or by off-label usage of biologics.

*These inclusion criteria are applicable to any patient 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 three 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 Sjögren's syndrome [SS] from the European League Against Rheumatism SS Disease Activity Index questionnaire [at least one domain with a positive item].

†Exclusion criteria include 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: [1] history of head and neck radiation treatment, [2] active hepatitis C infection [with confirmation by PCR], [3] AIDS, [4] sarcoidosis, [5] amyloidosis, [6] graft-versus-host disease, [7] IgG4-related disease.

‡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. [21].

§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.

¶Ocular Staining Score described by Whitcher et al. [22]; van Bijsterveld score described by van Bijsterveld [23]

**Unstimulated whole saliva flow rate measurement described by Navazesh and Kumar [24].

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