Sjögren's Syndrome: a literature review

Síndrome de Sjögren: uma revisão da literatura

Abstract

Sjögren's Syndrome (SS) is a chronic inflammatory systemic disease. It is auto-immune in nature and likely has a multifactorial etiology. This disease is characterized by lymphocytic infiltration of the exocrine glands, particularly the salivary and lacrimal glands. The disease causes dysfunction and structural damage leading to the classic SS symptoms of xerophthalmia and xerostomia. No clinical findings or immunological markers have yet been accepted as defining a diagnosis of SS or to identify periods of disease activity and remission. It is important that a patient suspected to have SS is evaluated by multidisciplinary teams consisting of ophthalmologists, rheumatologists, otolaryngologists and dentists, among other professionals. Among the clinical manifestations of SS is a notable reduction in salivary flow. Therefore, it is essential that the dentist knows the clinical characteristics, diagnostic methods and treatments for SS. Patients should be properly guided, and preventive measures must be introduced in order to prevent tissue damage, which may arise due to the decrease in salivary flow. This disease affects the individual not only physically but also emotionally and socially, and dentists and health professionals in general must diagnose the disease and apply a therapy in order to provide the best quality of life for their patients.

Key words: Sjögren's Syndrome; xerostomia, manifestations; xerostomia, diagnosis; xerostomia, treatment

Resumo

A Síndrome de Sjögren (SS) é uma doença sistêmica inflamatória crônica, tem uma natureza auto-imune e etiologia provavelmente multifatorial. É uma doença caracterizada por infiltração linfocitária nas glândulas exócrinas. As glândulas lacrimais e salivares são os principais órgãos afetados originando disfunções e prejuízos estruturais que desencadeiam um quadro clássico de xeroftalmia e xerostomia. Nenhum sinal, achado clínico ou imunomarcador descrito até o momento é aceito isoladamente para determinar um diagnóstico ideal de SS ou detectar os períodos de atividade e remissão da doença. É importante que o paciente com suspeita de SS seja avaliado por equipas multidisciplinares compostas por oftalmologistas, reumatologistas, otorrinolaringologistas e dentistas, entre outros profissionais. Entre as manifestações clínicas, salienta-se a acentuada diminuição do fluxo salivar. Portanto, é imprescindível que o dentista conheça as características clínicas, os métodos de diagnóstico e o seu tratamento. Os pacientes devem ser adequadamente orientados, devendo ser introduzidas medidas preventivas para evitar lesões dos tecidos que possam surgir devido à diminuição do fluxo salivar. A doença compromete o indivíduo não só física, mas também emocional e socialmente, cabendo aos dentistas e demais profissionais de saúde a tarefa de diagnosticar e aplicar uma terapêutica para proporcionar uma melhor qualidade de vida aos pacientes.

Palavras-chave: Síndrome de Sjögren; xerostomia, manifestações; xerostomia, diagnóstico; xerostomia, tratamento

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Received: May 5, 2009
Accepted: August 26, 2009

Introduction

Sjögren's Syndrome (SS) was first identified in 1933 by the ophthalmologist Henrik Sjögren (1), although it had been already reported in the 19th century. SS is a chronic, systemic inflammatory disease (2), can be found worldwide and affects 1 to 3% of the world population (3,4). It is auto-immune in nature and likely has a multifactorial etiology, influenced by genetics and environmental factors still under investigation (5). This disease is characterized by lymphocytic infiltration of the exocrine glands (6). The salivary and lacrimal glands are the main organs that are affected by the lympho-plasmocytary infiltration (3), causing dysfunction and structural damage that lead to the classic presentation of xerophthalmia and xerostomia (2,3,6,7). Other exocrine glands may also be affected, including the pancreas, sudoriparous glands and mucous glands of the respiratory, gastrointestinal and urogenital systems (6,7).

SS is also characterize by hyper-reactive B lymphocytes, which become plasmocytes and produce antibodies against antigens of the epithelium of the acini and the ducts of exocrine glands. This activity causes structural damage to and secretory dysfunction of these organs. Suppressor T lymphocytes are also affected, maintaining the activity of active B lymphocytes and tissue aggression (7). The glandular destruction is mainly caused by CD4+ T lymphocytes; however, in the early stages of the disease, the secretory function of the glands is not affected. Primary Sjögren's Syndrome is defined by a loss of glandular elements and muscarinic receptors, the destruction of enervation and a release of inflammatory cytokines by lymphocytes, as well as a gradual and progressive loss of the secretory function of the gland (8).

Sjögren's Syndrome can appear as a primary disease of the exocrine glands (salivary, lacrimal, vaginal, skin, respiratory and gastrointestinal) as primary SS (8), or it can be associated with other autoimmune diseases such as rheumatoid arthritis, systemic erythematosus lupus, progressive systemic sclerosis, scleroderma, polymyositis or Graves' disease, among others (secondary SS). Patients with this syndrome have a high incidence of non-Hodgkin's malignant B lymphoma (7).

Environmental factors such as previous viral infections (Epstein-Barr virus, cytomegalovirus, human herpes virus, hepatitis C virus among others) or bacterial infections (*Helicobacter pylori*) have already been implicated as potential initiators of the immune response in glandular tissue, due to their frequent presence in patients with this syndrome (7).

The signs and symptoms that affect the oral cavity occur due to a decrease in saliva production. Saliva plays an important role in the protection of oral tissues against physical, chemical and microbial agents and furthermore facilitates functions such as taste, speech, chewing, swallowing and digestion. A reduction in salivary flow, which is usually evident through the feeling of dry mouth, can be observed in patients submitted to radiation to treat malignancies in the head and neck region, elderly people and patients who are taking medication to induce hyposalivation, but may also appear as a manifestation of systemic diseases including primary liver cirrhosis, graft versus host disease, AIDS and autoimmune diseases, particularly Sjögren's Syndrome (2). Recent advances in genetic and molecular methods may help us to understand this complex disease and its physiopathology, which remains obscure (5,7).

Etiology

Sjögren's Syndrome is an autoimmune disease, the cause of which is still unknown (8). This disease is multi-factorial in origin and is influenced by genetics as well as by as-yet unidentified environmental factors (2,5,7).

SS affects about nine times as many women as men (4,7,9), and hormonal effects appear to be part of the physiopathology of the syndrome, especially deficiencies in androgens, estrogens and progesterone (7). It is well-recognized that hormonal and genetic factors influence the development of SS, based on its clear predominance in women and the high incidence of the disease or related autoimmune anomalies in relatives of patients with SS (8). Previously, primary SS has been discussed in small cohort studies, but very little is known about the influence of sexual hormones in the pathological mechanism of the disease (9).

A genetic predisposition for SS was suggested based on gene association and household studies, as well as research in animal models (2,5).

The infectious etiology of SS is probably indicated by retro-viruses, Hepatitis C and the Epstein-Barr virus (2,8). Although viral infection may contribute to the development of SS, no definite relationship has been established between these infectious agents and the development of the disease (8).

Incidence

Several epidemiological studies indicate that primary SS is the most common systemic autoimmune disease and the second most common rheumatic disease worldwide (4), affecting about nine times as many women as men (4,7,9).

SS affects 1-4 million people in the US (approximately 1% of the population) and 90% of SS patients are women. The peak incidence of this disease is between 40 and 60 years (10). In China, a regional study of 26,000 people revealed that the prevalence of SS in this population was only of 0.03% (10). It is believed that the worldwide incidence of the disease is 1/2500 (10).

A cohort study carried out in Spain between 1994 and 2000 followed 400 patients with primary SS. Of these patients, 373 (93%) were female and 27 (7%) were male. The ratio of females to males was 14:1. The average age at diagnosis was 52.7 (±0.85) years, ranging from 15 to 87 years. An additional 422 cases were identified in Greece in a cohort study conducted between 1982 and 2003. This study reported 402 women and 20 men with the disease, for a female/male ratio of 20:1. The average age at diagnosis was 55.4 (±12.5) years, ranging from 18 and 81 years (11).

Contrary to its prevalence in adulthood, SS is a very rare disease in childhood, although more than 50 cases in children have been reported (12). The low number of known childhood cases of SS may be due in part to the non-specific and insidious way this disease presents in this age group (13-15).
This disease occurs in all racial and ethnic groups but preferentially affects women between the ages of 30 and 50 (2-4,7,9).

Clinical aspects

Sjögren's syndrome may present several *general manifestations*:
Ocular: Dry keratitis or xerophthalmia (2,6,8,16) and ulceration of the cornea (16). These may not be reported until the patient encounters significant difficulties in accomplishing daily activities due to eye irritation, foreign body sensation, burning eyes, photophobia, "crying without tears" and blurred vision. The symptoms usually worsen in dry environments (air conditioning, dust, wind), when reading and with the use of computers (7).
Optic neuromyelitis (17), or photosensitive injury, is the most common symptom of SS in the newborn and is reversible after six months of age (18).
Muscle and skeletal: Arthralgia (5,19), morning stiffness, bone and joint ache, fatigue (7) and joint deformities (rheumatoid arthritis) (6,7,16,19). These symptoms are more frequent in secondary Sjögren's Syndrome (7).
Respiratory: Dry nasal mucous (2,7), shortness of breath (7), pulmonary fibrosis (2,7), frequent infections of the respiratory system (7) and lymphocytic infiltrate and pulmonary nodules. (16)
Genital and urinary: Vaginal dryness and itching (2,7,16), painful coitus (dyspareunia), pain when urinating (7), renal lithiasis (16), renal tubular acidosis and interstitial nephritis (16). Patients with primary Sjögren's Syndrome may present glomerular nephritis (7).
Skin: Xeroderma or xerosis (7,16), depigmentation, erythema, itching and eczema can be observed. These are more frequent in secondary Sjögren's Syndrome. Some cases of alopecia have been reported (7).
Vascular: Raynaud's phenomenon (7,16), deep vein thrombosis, vasculitis (skin, liver and kidneys) (7) and peripheral neuropathies (2). Heart block is sometimes observed in children whose mothers are anti-Ro/SSA positive (5,16).
Psychiatric: Anxiety, depression and personality disorders were more frequently reported in patients with SS than in the general population (7,20). Difficulty in sleeping has also been observed (19).
Gastrointestinal: Primary biliary cirrhosis (2,16), atrophic gastritis (16), celiac disease in adults (16), active autoimmune chronic hepatitis (16), pancreatitis and primary pancreatic insufficiency (16).
Neurological: Peripheral and autonomic neuropathy (16,21) and autoimmune deafness (16).
Cancer: Lymphoma and peripheral lymphadenopathy (16).
Hormonal: Autoimmune diseases of the thyroid (16) and high secretion of anti-diuretic hormones (20).

Sjögren's Syndrome may present several *oral manifestations*:
- Xerostomia (most evident oral symptom) (2,6-9,16). Approximately 20% of patients with SS have symptoms of dry mouth related to sialometry (8).
- High prevalence of caries, especially in the cervical region of the teeth (2,3). Patients exhibit an increased proportion of *S. mutans, Lactobacilli* sp. and *Candida* sp. (8,22).
- Early loss of teeth (10).
- Reduction of salivary flow (the need to moisten the mouth frequently) (7).
- Periodontal disease (greater loss of alveolar bone in patients with rheumatoid arthritis) (10).
- Dry lips, tongue and pharynx (2).
- The need to drink fluids during the night decreases the quality of sleep (19).
- Difficulty in speaking, chewing (3,7), swallowing (7) and in the digestion of solid foods (2).
- Pain when swallowing (7).
- Viscous and foamy saliva (2).
- Fissured and ulcerated tongue, atrophy of tongue papillae and a burning sensation in the tongue. The tissue usually exhibits a lobulated characteristic, often red, with the surface partially or totally atrophic (1,3).
- Decrease in taste due to a decrease in the number of gustatory buttons (3).
- Unpleasant breath (10).
- Thrush and ulcers on the labial mucous (10).
- Mouth infections, especially candidiasis (70% of patients) (2,7). In the erythematous form, the palate and lip co-measure (2,3).
- Increase of the volume of the parotid, sub-lingual and sub-mandible salivary glands (more frequent in primary Sjögren's Syndrome) (7).
- Oral mucous is red and atrophic (1).
- Difficulty in controlling dental prostheses (3).

Diagnosis

No single clinical finding or immunological marker has been accepted as the ideal for establishing a diagnosis of Sjögren's Syndrome or to identify periods of activity and remission of the disease. It is important that the patient suspected of having SS be evaluated by a multidisciplinary team including ophthalmologists, rheumatologists, otolaryngologists and dentists, among other professionals (7).
The association of inflammation with increased levels of autoantibodies in the plasma of patients with the syndrome suggests an autoimmune etiology. Autoantibodies against epithelial duct cells, antinuclear antibodies (ANA), ribonucleoproteins (Ro/SS-A and La/SSB), alphaprodine, calreticulin and rheumatoid factor (RF) are present in a high percentage of patients with the syndrome (8).

The production of autoantibodies and polyclonal hypergammaglobulinemia indicates that abnormalities in humoral immunity play an important role in the pathogenesis of this disease, and its diagnosis is based on a combination of several clinical and laboratory findings (2).

A fragment biopsy of the minor salivary gland with evidence of lympho-plasmocytary infiltrate containing 50 or more lymphocytes in 4 mm^2 according to the method of Greenspan and Daniels (23) is one of the most important tests in diagnosing the oral component of SS. However, some patients with a severe dryness of the mouth show only a moderate inflammation in biopsies obtained from minor salivary glands, indicating that mechanisms other than tissue destruction must be related to the dysfunction of exocrine glands (7).

In addition to the classic symptoms, Sjögren's Syndrome can be suggested by findings from a variety of clinical and laboratory methods (3) including anamnesis (the study of the serum proteins), sialochemistry and sialometry (the estimation of salivary flow), biopsy of the salivary gland (3) and sialography (24). An image of the salivary gland can be obtained through several procedures aside from sialography, such as magnetic resonance, computerized tomography, ultrasound and scintigraphy. Although sialography is the oldest of the imaging procedures, it still remains the preferred method to explore/study the system of ducts of the parotid gland as it is less uncomfortable and more accessible for patients than are other methods. Several authors recommend the use of ultrasound, a simple and non-invasive method, for patients who are allergic to iodine-based contrast medium or who exhibit acute infection; these conditions contraindicate the use of the sialography (24).

Table 1 presents the revised international classification criteria for Sjögren's syndrome (2002) (25,26).

Several studies suggest that a change in the electrophoretic profile of salivary proteins occurs in patients with SS. However, the potential diagnostic value of these observations has not yet been completely investigated (3).

Table 2 summarizes the criteria for establishing the diagnosis of Sjögren's Syndrome which are more accepted and used in the European Union.

In sum, according to the European community the most frequently used criteria are (8):

1. Xerophthalmia;
2. Xerostomia;
3. Abnormal ophthalmological examination (Schirmer's test with results under 1 mm/min);
4. Biopsy of the minor salivary gland showing values greater than 1 focus/4 mm;
5. Non-stimulated salivary flow of less than 1.5 mL/5 min (except for patients over age 60 or who are taking anti-cholinergic medicine);
6. Presence of anti-Ro or anti-La antibodies in the blood.

Table 1. Revised international classification criteria for Sjögren's Syndrome (2002) (25,26).

I. Ocular symptoms: a positive response to at least one of the following questions: 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have a recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms: a positive response to at least one of the following questions: 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrently or persistently swollen salivary glands as an adult? 3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs – that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests: 1. Schirmer's I test, performed without anesthesia (<5 mm in 5 min) 2. Rose bengal score or other ocular dye score (>4 according to van Bijsterveld's scoring system)
IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic 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 (18)
V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests: 1. Unstimulated whole salivary flow (<1.5 mL in 15 min) 2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts (19) 3. Salivary scintilography showing delayed uptake, reduced concentration and/or delayed excretion of tracer (20)
VI. Autoantibodies: presence in the serum of the following autoantibodies: 1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Table 2. Revised rules for classification of Sjögren's Syndrome (2002) (25,26).

For primary SS In patients without any potentially associated disease, primary SS may be defined as follows: a. The presence of any 4 of the 6 items is indicative of primary SS, 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, 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 secondary SS 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 secondary SS.

The diagnosis of Sjögren's Syndrome is therefore determined by correlated clinical findings, detailed history and laboratory data. With respect to laboratory tests, the evaluation of serum levels of autoantibodies [*i.e.*, antibodies for SSA (Ro) and SSB (La) associated with SS (6,16)], and to a lesser extent a biopsy of the salivary glands, are recommended (2).

One or more periductal lymphocyte foci (50 lymphocytes/ 4 mm^2) (2,27) must be found in a histopathological examination or the presence of autoantibodies (antinuclear antibody, rheumatoid factor or specific anti-antibodies of Sjögren's Syndrome) must be found in the patient to confirm the diagnosis. Parotid sialography and sialometry, Schirmer's test or the Rose Bengal score are the best tools with which to evaluate the dysfunction of the lachrymal and salivary glands, respectively (2).

Differential diagnosis

Patients submitted to radiation therapy (2,4) to treat malignancies in the head and neck region, elderly people [progressive dryness of the mucous membranes is frequently associated with age, characterized by the degeneration and liposis of the exocrine glands (4)], patients who take medicines that reduce saliva (2), patients with burning mouth syndrome (2,4), infections, tumors, metabolic disorders, sarcoidosis, hypoproteinemia (type II, IV and V), lymphoma, amyloidosis or infections of the hepatic routes (4) may show symptoms of dry mouth; however, Sjögren's Syndrome involves a variety of clinical and laboratory signs and is characterized as a systemic disorder (Table 3) (2).

overnight) (2,8). These will prevent oral infections (7) as well as dental caries and periodontal disease (2).

Frequent deontological consultations are recommended (8).

- **Salivary replacement**: Artificial saliva (Salivan®/ Pharmaceuticals APSEN S/A) (2,7,29), sugarless gums (7,8), water with few drops of lemon (7,8), *mucolytic* agents (*e.g.*, *bromhexine*) (2) or vitamin supplements based on LongoVital herbs (30) (Amarillo Biosciences, Amarillo, TX) can be used to increase salivary flow (8). Abundant ingestion of fluids is recommended (28).
- **Stimulation of salivary secretion**: Muscarinic agents such as pilocarpine and cevimeline (29) act on the muscarinic receptors to stimulate salivary and lacrimal secretion. These compounds objectively and subjectively improve the clinical status of the patient and do not have many associated side effects (7).
- **Complementary treatment**: The results obtained from the previous stages can be complemented with several additional therapies, for example the use of topical anti-inflammatories (corticoids) or systemic anti-inflammatories (7), topical immuno-modulators or systemic immuno-modulators (diet rich in foods such as fish and olive oil that contain Omega fatty acids) (7), α-interferon or corticosteroids. In cases that are more serious and difficult to control, hydroxychloroquine, methotrexate and cyclophosphamide may be used (7,31).

  Treatment with α-fodrin has been shown to reduce lymphocytic infiltrate and also auto-immunity (32). Cases of oral candidiasis can be controlled through anti-fungal medications and the use of chlorhexidine (8). Several studies have reported that acupuncture has helped to reduce the feeling of dry mouth (8).

Table 3. Differential diagnosis of idiopathic primary SS from SS-like disorders that are associated with infection by HIV, HCV or sarcoidosis (4).

	Primary SS	HIV infection with SS	HCV infection with SS	Sarcoidosis with SS
Age	Middle age	Young	All ages	Middle age
Sex Predilection	Female	Male	No difference	No difference
Anti-Ro (SSA) and Anti-La (SSB) autoantibodies	Frequently present	Absent	Absent	Absent
Predominant T-cell in lymphoid infiltrates	CD4	CD8	CD4	Granuloma
Diagnostic viral serologic test	None	HIV Tests	HCV Tests	None
HLA-association	DR3, DRw53, DQA1*0501	HLA-DR5	Unknown	Unknown

Treatment of oral manifestations

The treatment of Sjögren's Syndrome manifestations in the oral cavity is mainly a treatment of symptoms. (2) Treatment can go through several stages depending on the severity of the symptoms and their response to the different phases of the treatment:

- **Oral health**: Oral hygiene must be strict (2,7,28) and requires the topical application of fluoride (fluoride varnish may be useful in the prevention of subgingival caries and dental trays can be used to apply fluoride gel

Conclusion

Sjögren's Syndrome (SS) is a systemic inflammatory disease that is auto-immune in nature and chronic in development, causing several stereotypical symptoms in affected individuals. Xerostomia is considered to be the main oral symptom and clinical sign of the disease. Therefore, it is essential to stress the importance of otorhinolaryngologists, rheumatologists and dentists in the early diagnosis and treatment of this disease, as well as the importance of their ability to recognize this condition in clinical practice.

The most common reason that patients with SS choose to see a dentist is the presence of xerostomia. The dentist may be the first professional to diagnose the disease based on the patient's complaints about the symptoms in the oral cavity. Therefore, it is essential that the dentist knows the clinical characteristics, diagnosis guidelines and treatments available for this disease. Patients should be properly guided and preventive measures should be introduced in order to prevent the tissue damage that may arise due to decreased salivary flow. The disease affects the individual not only physically but also emotionally and socially, and it is the duty of dentist and health professionals in general to identify the disease and administer therapy to provide the best overall quality of life for the patient.

Measures to compensate for the decrease of salivary flow (fluids, artificial saliva etc.) must be taken, allowing the patient to improve his quality of life, *i.e.*, to improve speech and swallowing and to protect oral tissues. Because of its systemic character, a multidisciplinary treatment of SS involving several health professionals must be provided to address the diverse manifestations of the disease.

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