

**Review Article**

Primary Sjögren's Syndrome and Oral Cavity Disorders

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Abstract: Sjögren's Syndrome (SS) is one of the three most common autoimmune diseases in the world, which affects the exocrine glands, specifically the salivary and lacrimal glands. Primary SS (pSS) particularly affects only the exocrine glands, while secondary SS is associated with other systemic autoimmune pathologies. SS is characterized, histopathologically, by an inflammatory lymphocytic infiltrate that interferes with the normal gland function. It affects 0, 5% of the world population, being more common in women (9:1 versus men), mainly around 50 years old, after the menopause. The medical dentist role is very important in the diagnosis of pSS, as in most cases he is the one who detects the first symptoms, in particular dry mouth or xerostomia. The primary syndrome doesn't have a painful development, being dry mouth and eye dryness the most prominent clinical characteristics. The majority of the oral evidences are consequence of salivary glands hypofunction: dental caries, periodontal disease or fungal infections. Along with hyposalivation and xerostomia communication disorders can occur like dysphagia and pharyngeal dryness leading to difficulties in speech and voice fatigue. These last ones have a negative impact in the patients quality of life although a large percentage don't seek professional help. There is a need for awareness of the voice disorders associate with pSS referring the patients to proper professional help. The treatment of pSS is empirical, symptomatic and aimed at dealing with the complications during the early-stages of the disease consisting of limiting the xerostomia and xerophthalmia damages.

Keywords: Primary Sjögren's Syndrome, Pathogenesis, Voice Disorders, Dysphagia, Oral Infections, Xerostomia

1. Introduction

Sjögren's Syndrome (SS) is a chronic autoimmune disease that affects the exocrine glands, namely salivary and lacrimal glands. Primary SS (pSS) affects specifically the exocrine glands while secondary SS occurs associated with other autoimmune systemic pathologies such as Systemic lupus erythematosus and Rheumatoid arthritis [1, 2].

pSS is characterized by a lymphocyte periepithelial infiltration of the salivary and lacrimal glands causing the destruction of the gland tissue and the decrease of the secretions, hence the mucosal dryness named xerostomia and xerophthalmia [3].

It affects approximately 2% of the adult population in spite

of underdiagnosed in more than half of the cases [4]. There is also a delay of several years between the beginning of the symptoms and the diagnosis [5].

More recent studies confirm it's more common in women than in men (ratio 9:1), mainly between 40 and 60 years, and its more frequent around 50 years old [6].

It's a disease that occurs all over the world, in all ethnics, but is more prevalent in the Caucasian race [7].

Concerning the oral cavity most of the patients with pSS are considered to have a deficient oral health [8]. The more common oral manifestations, result from the hypofunction of the salivary glands: dental caries, periodontal disease and fungus infections [9].

Patients with pSS also present difficulty in chewing, reporting dry mouth sensation or xerostomia, alterations in

taste, burn sensation and pain associated with food swallowing. Clinical evidences of the pSS include hyposialia, cracked and dry lips, dry saburral, erythematous and fissured tongue [10].

Hyposalivation can also cause dysphagia: the tongue sticks to the roof of the mouth impairing the clarity of speech causing chewing difficulties and swallowing alterations that interfere with the adherence of the food to the surface of the teeth [11].

Also the main manifestations concerning voice and speech alterations, as reported by Freeman and colleagues are dysphonia, rhythm and articulation disorders causing these patients a social limitation that should require intervention [12].

2. Primary Sjögren's Syndrome

2.1. Etiology and Pathogenesis

Although complex, pSS etiology is considered multifactorial as most of the autoimmune diseases, involving the interaction of genetic and environmental factors that play a

significant role in the progression of the disease.

Also endocrine factors and immune system disturbances are implied like cellular apoptosis disruption [13]. It's proved that in patients with pSS gland cells begin apoptosis mainly the ductal cells. This alteration in the glands function may precede the inflammatory cell penetration and can be caused by virus like Epstein Barr (EBV) or C Hepatitis (CVH) [14].

Also non-specific organ autoantibodies can be found in 60% of the patients. The autoantibodies include rheumatoid factor and antinuclear anti-Ro/SS-A and anti-La/SS-B and contribute to tissue destruction, by immunocomplex deposition before the inflammatory reaction is evidenced [15].

The T and B lymphocytes that infiltrate the glands cause its disruption by several forms (Figure 1), including:

1. Destruction of the gland cells
2. Cytokine secretion like IFN- γ that also continues the inflammatory response
3. Production of autoantibodies that block muscarinic receptors
4. Metalloproteinases secretion (MMP) that degrade the cells and matrix of the gland [43].

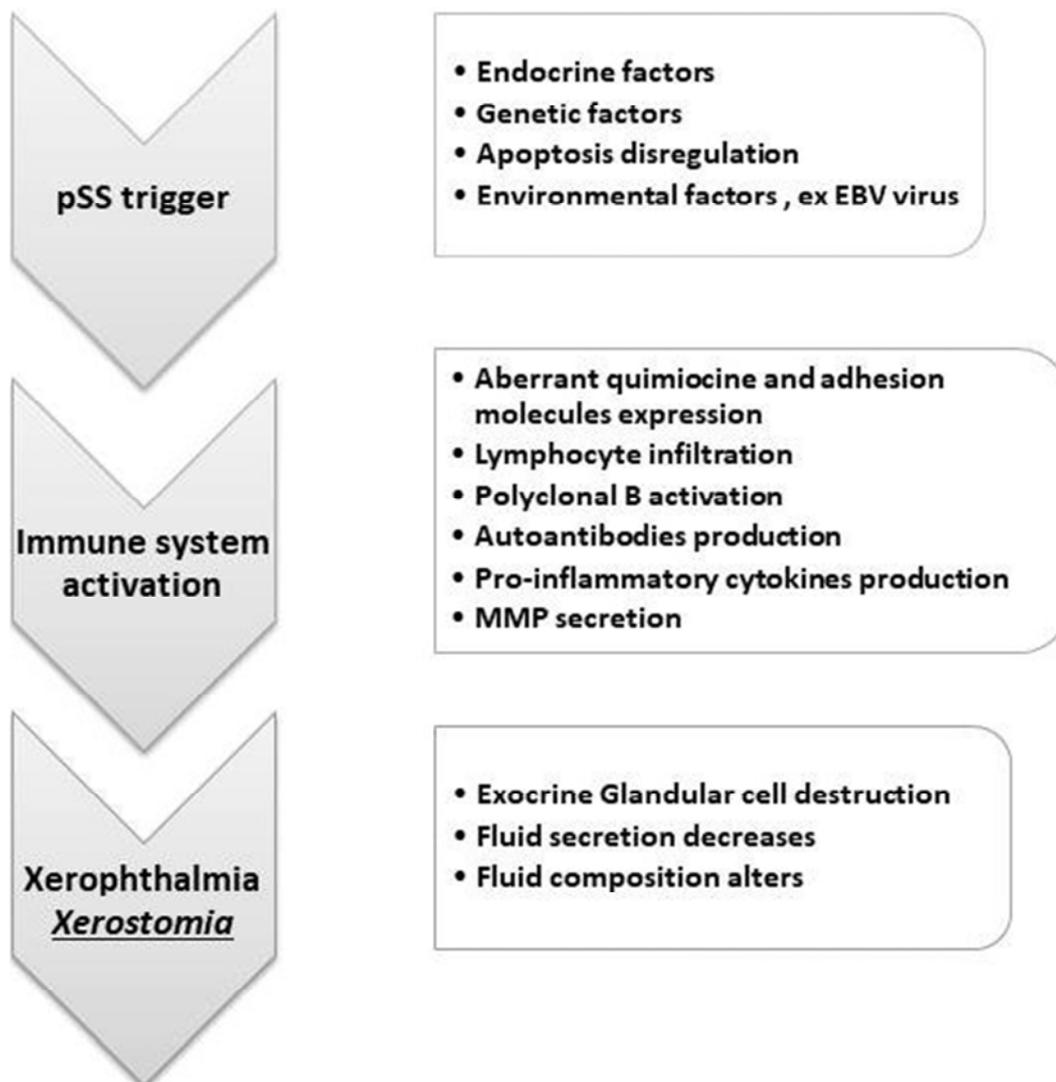


Figure 1. Etiology and pathogenesis of pSS.

2.2. Oral Manifestations and Communication

Oral dryness is normally the first symptom to be reported by pSS patients and it impacts in their quality of life [16].

The decreased salivary flow has a great impact in the oral cavity due to the loss of lubrication, tamponing and antimicrobial capacity. Salivary fluid is colorless, transparent with small viscosity and is composed by 99, 5% of water [17]. It also has electrolytes, proteins and glycoproteins, enzymes like defensins, proteases, histatins and lysozymes and other molecules essential to maintain the normal physiology of the oral cavity [18].

Salivary fluid forms a fine layer that covers soft and hard tissues as well as provides protection to the oral mucosa, oropharyngeal and esophagi structures. Its organic and inorganic components can modulate PH alterations and the salivary proteins are adsorbed in to the dental surface creating a biofilm [19]. Thus, the main function of the salivary fluid is to protect from outside aggressions the oral mucosa and the teeth [17].

Besides mucosal lubrication and tamponing effect it helps to taste the food and to form the alimentary bolus, starting the digestion process [10]. Thus hyposalivation is associated with oral function, nutrition, and oral health- alterations in tasting, speaking, swallowing and chewing and also a higher risk for dental caries development and periodontal disease [20].

Xerostomia or dryness of the mouth relates to the salivary fluid in the oral cavity none stimulated when 50% of the fluid is below normal levels [21]. However, in patients with pSS, xerostomia is also associated with alterations in the composition of the decreased salivary fluid, like less mucins [22].

As a result of the decrease in the volume of fluid and the subsequent loss of the antibacterial properties in pSS the process of caries accelerate [23]. On the other hand these patients also present a decrease in the secretion of IgA, the main neutralizing antibody in the oral mucosa, again, causing more caries development [10].

The increase in the number of teeth affected by caries causes frequent visits to the dentistry clinic and usually they have more tooth loss or restored comparing to healthy individuals [24]. The use of prosthesis due to tooth loss is also impaired due to xerostomia and the number of teeth restored is frequently very high and expensive, especially in older patients [4].

It's also documented that patients with pSS have a higher risk of developing periodontal disease but the number of studies are less as the ones relating caries and pSS. Although periodontal disease is not very frequent in patients with pSS there are studies that show that the risk of developing it is 2, 2 times higher than in healthy patients [25].

Mainly dental caries and periodontal disease leads to tooth loss, especially in elderly people, leading to difficulties in eating and interference in communication- speaking and smiling, thus also impairing the self-esteem [26]. Also tooth loss induces changes into the anatomy of the oral cavity and,

again, swallowing problems are more likely to appear, like poor masticatory ability [27].

It's documented that oral Candidiasis occurs in 80% of the patients with pSS commonly in the form of angular cheilites (extra-oral) or erythematous acute candidiasis, pseudo membranous candidiasis and sub-prosthetic, inside the oral cavity [28, 29]. Thus it affects mainly the tongue, palate and lip commissures [30].

Patients with pSS can also have dry and fissured lips and loss of taste buds in the tongue. The tongue due to the hyposalivation as the aspect of minced meat, dry, fissured and sticky [10].

Other studies focus the association between pSS and the presence of oral lesions of autoimmune etiology like lichen planus, recurrent aphthous stomatitis, mucosal pemphigoid and pemphigus [31].

The more serious complication of pSS is the development of lymphomas in the parotid gland: about 5% of the patients develop Non- Hodgkin lymphoma [32].

2.3. Other Communication Disorders and Dysphagia

There are several authors that report voice disorders in patients with pSS that go from mild to moderate range and relate to the severity of the disease, independently of the age, sex or medications used [33].

The communication problems already established include difficulty in the articulation of words with difficulty to perform a clear speech, and production of "click" sounds when speaking, due to the adhesion of the tongue to the roof of the mouth [34].

Studies of voice disorders report difficulties in projecting voice, discomfort while using it, chronic throat soreness and frequent throat clearing, reducing the quality life of these patients [35]. All this problems are exacerbated with vocal use causing vocal fatigue and strain, but can be improved by avoiding dry environments and increased intake of fluids [36].

Speech problems and dysphonia usually appear before the diagnosis is established and although dysphonia is rare it can occur, not associated directly with xerostomia, but with nervous system impairment [37]. Between 20 and 25% of patients with pSS can have peripheral nervous system lesions: the more frequent is trigeminal neuropathy. Sensorial neuropathies are more frequent than motor dysfunction but if these last one occurs, it can affect the facial nerve [38].

Although the difficulty of speech is a parameter with a subjective classification, studies like the one of Tanner and colleagues introducing tools like Voice-Related Quality of Life (V-RQOL) and its relation with disease severity should be broader [35]. Other studies show that patients with pSS may have dysphonia and articulatory imprecisions, from a mild to moderate range [39]. It's important to detect the patients with problems in speech to seek the correct treatment and refer them to the wright professionals and hence increase their quality of life.

Also, the use of removal prosthetics can be an alternative to teeth restauration in tooth loss. However in patients with pSS

due to xerostomia there is a difficulty in the prosthesis retention causing mucosal pain and irritation. Thus the speech is less noticeable [24].

The swallowing disorders or dysphagia of patients with pSS range from 32 to 71% although the prevalence studies are rare, especially the ones that correlate dysphagia with the life quality of the patients [12].

Studies conducted by Allec and colleagues refer over 90% of cases of patients with pSS with swallowing disorders, most of them not presenting lingual and dental alterations. They presented dryness of the oropharyngeal mucosa with food adhering to the roof of the mouth which creates difficulties in swallowing. Thus there is a significant risk of malnutrition as well as negative impact in the quality of life, namely social

limitations [11].

More recent studies show that dysphagia is associated with increase severity of SS, either primary or secondary. The swallowing disorders were associated with dry mouth, solids ingestion and having to take smaller bites to swallow safely. All of this reports excluded a possible medication impact in the nature and severity of swallowing. Also the swallowing disorders were associated with some risk factors like tobacco smoke, post-nasal drip, frequent sinus infection and esophageal reflux. Thus these risk factors are also associated with the severity of the swallowing symptoms. The swallowing disorders reported caused a reduction in the quality of life, although of the 64% participants only 27% asked for professional help [33]. (Figure 2)

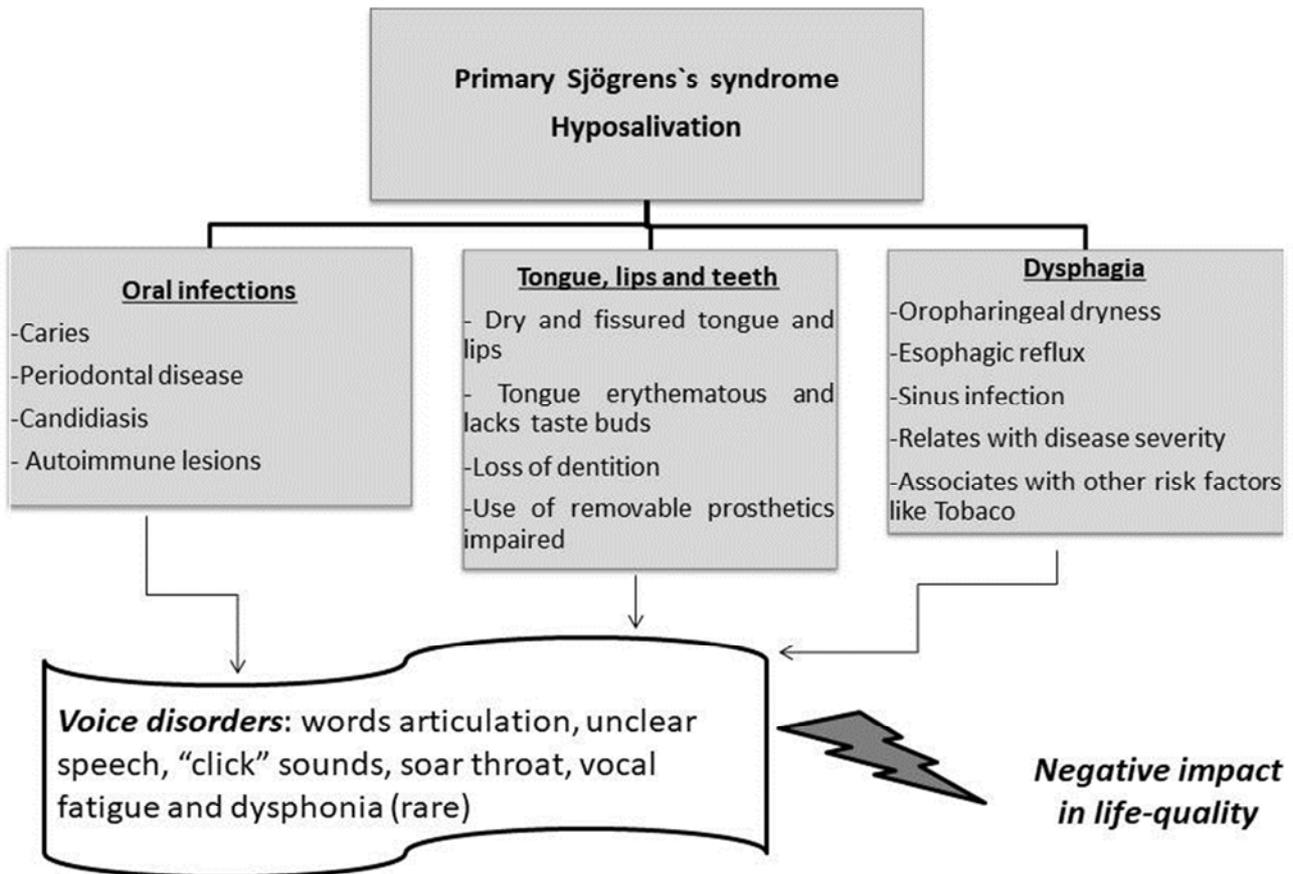


Figure 2. Consequences of hyposalivation and relation with voice disorders.

2.4. Prevention of Symptoms in Oral Cavity and Treatment

Patients with pSS should avoid the use of irritant agents like alcohol and tobacco and the medical dentist should encourage them to have a good oral hygiene using tooth pastes with fluor to prevent caries progression. They are also advised not to ingest products with sugar, like drinks or sweets [40]. They should drink water in a regular basis to help lubrication and increase the salivary fluid, helping with the PH and again diminishing caries risk [4].

To avoid adhesion and growth of bacteria the chemical control more commonly used is chlorohexidine, xylitol and fluor in the form of spray, gel, varnishes, shewing gums, paste

and mouthwashes [24].

In patients with removable prosthetics due to the increased risk of *Candida* infections they are advised not to use it during the night and should wash them with 2% chlorohexidine [41].

As well as to prevent, in the treatment of oral infections in patients with pSS the salivary substitutes and local salivary stimulation are the main lines of action aiming to diminishes xerostomia [4, 42]. There is no treatment for pSS that can reduce or restore the damages of the glands [43].

Pilocarpine is one of the agents commonly used to prevent xerostomia although until 30% of the patients can have adverse reactions, in the first hour after its administration [40]. Frequent symptoms include nausea, sweat, headache and

gastrointestinal pains that, usually, disappear 2-3 weeks after abandoning the treatment [44].

Concerning salivary stimulants pilocarpine hydrochloride is a natural alkaloid that acts in the muscarinic receptors M3 and M2 of the exocrine glands; its use can improve fluid secretion in 75% thus decreasing xerostomia. Cevimeline is another muscarinic agonist (not commercialized in Europe) with affinity to the M3 and M2 receptors that causes only minor sweating [45].

There are also other salivary substitutes like methylcellulose's, carboxyl methylcelluloses and hydroxide methylcellulose's [17].

Patients with pSS should also have forms of improve the environment humidity like using humidifiers and should avoid warming air systems that cause more dryness of the mucosa. The use of nebulized isotonic saline in these patients also helps with the hydration and decreases the vocal effort that can aggravate voice disorders [46].

The treatment for pSS can also be systemic using anti-inflammatory agents, corticoids and immunosuppressors, but, again, there is no cure for the disease, only ways to soften the symptoms.

Life prognosis for patients with pSS is not very different from the overall population, and the mortality rate increases, only if the syndrome is associated with other auto-immune disease [47].

3. Conclusion

SS is an autoimmune disease with a slow progression and specific symptoms of the exocrine glands, that can present itself in the primary or secondary forms according to how it appears- alone or associated with other autoimmune diseases like Systemic lupus erythematosus.

It affects approximately 2% of the world population and is the third autoimmune disease more common in the woman gender. Its etiology is multifactorial, complex and still not very clear with genetic, hormonal, and environmental factors involved.

Primary SS is characterized by an epithelial lymphocytic infiltration of the lacrimal and salivary glands that causes the gland tissue destruction producing dryness of the mucosa-xerostomia and xerophthalmia. The continuous activation of B cells in these patients causes autoantibodies production that, together with activated T cells, contribute to the gland destruction.

The role of the medical dentist in pSS diagnosis is very important because in most of the cases they are the first ones to detect the oral cavity symptoms.

Patients with pSS present common oral signs like: swallowing and speech difficulties, taste alterations, fissured lips, fissured, dry and erythematous tongue. Concerning infections they have a higher risk of caries disease, periodontal disease and Candidiasis all that causing tooth loss. The risk of developing oral lesions of autoimmune etiology like pemphigus is higher and a small percentage of these patients can develop malignant lesions like Non-Hodgkin

lymphoma.

Also, the use of removal prosthetics can be difficult due to hyposalivation, causing ulceration, irritation of the mucosa and pain, so, in spite of the cost, its preferable rehabilitation with dental implants, to replace the teeth.

The decreased salivary flow and xerostomia additionally cause difficulties in the communication and dysphagia. The dryness of the oropharyngeal mucosa causes voice and speech alterations as well as difficulties in swallowing food and drinks. The dysphagia, associated with vocal disorders as a negative impact in the life quality of these patients. Although dysphonia is rare it affects the speech articulation from a mild to moderate range, and again these findings should be referred to professional help.

Most of them don't seek professional help to improve their voice by lack of awareness regarding all these alterations. Thus it is necessary to educate these patients to predict and prevent voice and speech disorders.

The patient with pSS will need not only a medical dentist but also other professionals that can address dysphagia and difficulties with speech, a multidisciplinary team managing their health-related quality of life.

Abbreviations

SS: Sjögren's Syndrome; pSS: Primary Sjögren's Syndrome; MMP: Metalloproteinases

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