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REVIEW ARTICLE

Sjögren's syndrome: the diagnostic potential of early oral manifestations preceding hyposalivation/xerostomia

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Sjögren's syndrome (SS) is a systemic autoimmune exocrinopathy that affects mainly the salivary and lacrimal glands, leading to progressive reduction in saliva and tear flow. Although the underlying immuno-mediated glandular destruction is thought to develop slowly over several years, a long delay from the start of the symptoms to final diagnosis has been frequently reported. A limited knowledge concerning SS natural history is among the major causes of the actual diagnostic delay. Although very few studies have been focused on the analysis of SS early clinical onset, a series of oral features preceding xerostomia/hyposalivation development in patients eventually diagnosed as having SS have been reported. Sialochemistry alterations, salivary gland swelling, early dental loss and sialorrhea have been observed before the onset of typical signs and symptoms (namely xerostomia and/or hyposalivation), which usually lead to SS clinical presentation and diagnosis. Here we suggest, after evaluating available data, that the traditional 'untouchable' association between SS and xerostomia/hyposalivation might probably be reconsidered, and that astute clinicians should not underestimate the possible presence or development of SS in patients without xerostomia/hyposalivation and presenting these atypical early oral features.

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Introduction

Sjögren's syndrome (SS) is a systemic autoimmune exocrinopathy that affects mainly the salivary and lacrimal glands typically presenting as the 'sicca complex' of dry eyes (xerophthalmia) and dry mouth (xerostomia) (1). In addition, involvement of the exocrine glands of the skin, pancreas, vagina, respiratory and gastrointestinal systems has been described and SS can also present extra-glandular clinical manifestations, which may involve the joints, liver, kidneys, and central nervous system (2, 3). The immune disorder involves a progressive lymphocytic infiltration of the salivary and lacrimal glands, with polyclonal B lymphocyte activation and autoantibody production, especially antinuclear antibodies (ANA), autoantibodies to SS-A (Ro) or SS-B (La) antigen and rheumatoid factor (4). Reduced salivary flow, even if not pathognomonic, is usually considered a hallmark of SS diagnosis, as well as the main clinical presentation and a cardinal clinical and diagnostic feature in daily practice. However, a frequent delay of diagnosis has been underlined by several authors who reported a period ranging from 3 to 11 years from the start of the symptoms to final diagnosis (3, 5, 6). As consequence, the treatment for most SS patients is essentially symptomatic (7), aimed at alleviating the distressing symptom of ocular and oral dryness (8) caused by the irreversible replacement of the glandular parenchyma by the lymphocytic infiltration and other immunologic factors. Unfortunately very little is known about the natural history of the disease and data concerning its onset, including animal models studies, are still scarce. From a theoretic point of view, the progressive nature of SS immunopathogenesis seems to support the feasibility of early diagnosing the disorder, provided that one might be able to identify the events, signs and/or symptoms associated with its onset and early phases. Very few studies have been focused to analyze this issue by now. However, these have clearly reported that some oral clinical features, because of salivary gland dysfunction, could occur long time before the development of symptomatic xerostomia. These manifestations include sialochemistry alterations, non-dry mouth accompanied salivary gland swelling, early dental loss and sialorrhea. Their detection might lead to diagnose earlier the disorder, thus potentially contributing to recent studies which have explored the possible prevention of irreversible

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parenchimal degenerative changes characterizing advanced-stage disease (9, 10). In the present review, the available data are evaluated and, accordingly, it is suggested that the traditional 'untouchable' association between SS and xerostomia/hyposalivation might probably be reconsidered.

Sialochemistry alterations

As salivary gland dysfunction is one of the key manifestations of SS, salivary gland function assessment has been widely used as diagnostic tool (11). In addition to the well-known and deeply studied sialometry (11), sialochemistry has been proposed as a useful instrument in diagnosing SS (12) and differentiating various salivary gland diseases. Kalk and colleagues recently reported that, among several components, changes in sodium, chloride and phosphate concentration of submandibular/sublingual (SM/SL) saliva have great potential as diagnostic criteria in SS (11, 12). Furthermore, of more interest, another novel unsuspected finding emerged from their studies: in SS patients with a short duration (<12 months) of oral symptoms, sialometry showed normal flow rates but changes in SM/SL salivary composition were observed by sialochemistry. On the contrary, changes in both sialometry and sialochemistry were significantly related to long duration of oral symptoms (more than 24 months). Accordingly, they concluded that in initial phases of SS, when lymphocytic infiltration has not resulted in significant loss of secreting cells, sialometry might not show any changes in salivary flow rates, whereas its composition may already have been significantly changed by autoimmune inflammation (11, 12). To support this concept, Kalk and colleagues reported labial salivary gland biopsy to be positive in 97 and 96% of their patients with primary and secondary SS respectively (11). Unfortunately, they did not provide data about possible differences in the severity of focal lymphocytic infiltration between early-SS/sialometry-negative patients and advanced-SS/sialometry-positive patients, which might have represented an important evidence of the evolution of the immunopathogenetic process. Besides the usefulness that sialochemistry has in clinical practice toward the definition of non-invasive, simple, safe and sensitive diagnostic tools, it is mandatory to underline its importance in understanding SS natural history. Sialochemical changes, reflecting autoimmune attack on secretory cells (11), may precede by several months salivary gland hyposecretion and, if appropriately recognized, could lead to important clinical considerations. First of all, they could represent an adjunctive and alternative tool among SS diagnostic criteria, allowing early detection of the disorder in patients complaining of xerostomia but without evidence of hyposalivation. In addition, salivary compositional changes could represent an useful diagnostic finding in patients without hyposalivation and xerostomia, but suspected of having SS because of other signs and symptoms (e.g. dry eyes; positive Schirmer's test) or positive diagnostic criteria (e.g. presence of ANA, SS-A, SS-B). In the presence of available preventive treatments aimed at avoiding irreversible advanced-stage replacement of glandular parenchyma, such interventions could then be administered at an early stage. Furthermore, As sialometry has demonstrated to be of little value in SS initial phase, sialochemistry might become an useful tool for screening studies, so that asymptomatic persons incidentally discovered to have sialochemical changes could be monitored or further investigated with SS diagnostic tests, such as presence of autoantibodies or focal lymphocytic infiltration in the labial salivary glands.

Non-dry mouth accompanied salivary gland swelling

Recurrent or persistent swelling of salivary glands is a well recognized oral feature in patients with dry mouth because of SS, although it can occur in several conditions other than SS. Enlargement of parotid and/or submandibular glands is apparent in about 25–66% of the patients during the course of the disease (13) and is an important clinical finding in evaluating the possibility of a retrograde infection and the development of non-Hodgkin's lymphoma (6). However, there are several reports underlying the occurrence of parotid swelling as the presenting symptom of SS, in absence of xerostomia/hyposalivation (6, 14–19).

Nevertheless, non-dry mouth accompanied salivary gland swelling (NDM-SGS) has been categorized as a useful diagnostic criterion only in few cases (8). This situation is probably because of the fact that recurrent parotid swelling is an extremely heterogeneous symptom of varying etiology. Accordingly, some authors have tried to identify clinical factors potentially useful to differentiate patients with benign recurrent sialoadenitis from those with parotid swelling caused by SS. As result, the lack of a history of parotid gland swellings in childhood (20), as well as its onset at a higher age (5 years or over) (21) were found to be associated with SS diagnosis, thus demonstrating the necessity of performing screening for underlying systemic immune disorders mainly in these patient categories.

In general, this atypical onset has been observed almost exclusively in children and adolescents who experienced recurrent parotid swellings for several years before dry mouth occurred. As a consequence, a delay of SS diagnosis, as well a misdiagnosis of recurrent parotitis or sialadenitis, is often reported in these patients (14–19).

With regard to this, some authors have stressed that the classical diagnostic criteria for adult SS are not applicable to a pediatric onset of the disease and, as sicca syndrome seems to develop much later in these patients, have suggested different diagnostic criteria applicable to juvenile SS (14, 18).

Furthermore, the occurrence of parotid swelling in this early SS patients has potential important clinical and prognostic consequences, as both parotid swelling and younger age have been associated in some studies with relevant immunological and clinical features, such as a higher prevalence of sever systemic disease, including lymphoadenopathy, respiratory symptoms, presence of SS-A/SS-B and monoclonal immunoglobulins, and a higher incidence of lymphomas (6, 22).

Early dental loss

Dental loss, because of increased caries activity, is a well-known complication of several conditions associated with long-term xerostomia/hyposalivation, including SS. In 1994, the European study group on diagnostic criteria for SS (EEC COMAC), analyzing a group of 39 SS patients, reported the occurrence of early dental loss (before the age of 45) in 40% of them. Interestingly, in 11 of these 16 patients dental loss preceded the first symptom of xerostomia by more than 9 years on average (23). Although the authors did not perform sialochemistry, they concluded that early dental loss might reflect a silent infraclinical involvement of the salivary glands resulting in changes in saliva biochemistry long before development of hyposalivation. These changes, involving pH and buffer capacity of saliva, could have led to increased caries activity and subsequent early dental loss in these patients. However, further studies were not performed toward this issue and other opportunistic conditions generally associated with reduced salivary defenses, such as oral candidosis, which could also be considered as early manifestation of SS in patients without xerostomia/hyposalivation. Actually, it is intriguing how the above mentioned recent studies on sialochemistry changes in early SS (11, 12) seem to give new importance to this clinical report. Accordingly, early dental caries-induced teeth loss might represent a useful clinical feature to suspect early SS in patients without the complaint of xerostomia. However, it should be stressed that dental loss because of caries is highly influenced also by xerogenic medications and other non-salivary factors, such as dietary and behavioral factors. As consequence, in every patient with sudden increased caries activity and absence of dry mouth-inducing drugs, altered oral hygiene behavior or incorrect dietary regimen, the possible presence of SS should be investigated.

Sialorrhea

In a previous paper we described four patients, whose histopathological features and laboratory data suggested that they were suffering from SS but with initial clinical findings which did not fulfill European diagnostic criteria and did not allow us to make a prompt and early diagnosis (24). For each one of them, we observed, in association with SS-A (Ro), SS-B (La), ANA antibodies and focal sialoadenitis of minor salivary glands (focus score ≥ 1), the presence of an excessive salivary flow causing soiling of clothes and bed linens at night and embarrassing dysfunction and distortions in speech and swallowing. After a mean time of 8 months, they all developed gradually the traditional symptoms of dry mouth and dry eyes and in two cases enlargement of the parotid glands occurred, allowing us to make a definitive, even if delayed, diagnosis of SS (24).

We concluded that sialorrhea might represent, in certain cases, an early clinical feature of SS. We hypothesized that the lymphocytic infiltration, in its early phases, might cause via cytokines secretion an alteration of the salivary gland function, which clinically might be expressed as an increased salivary flow. The destruction of the glandular acinar units might occur subsequently, leading to the traditional clinical feature of xerostomia with a reduction of salivary secretion. Thus, we have argued that also patients affected by the complaint of sialorrhea, if not related to none of its common causes, should be carefully investigated for ANA, SS-A (Ro) and SS-B (La) antibodies, and focal sialoadenitis in order to early detect SS.

Discussion

It is generally accepted that SS diagnosis should be based on several clinical and laboratory findings; nevertheless, none of these is specific for SS (25) and, although different diagnostic criteria have been proposed, the question continues to be controversial (26). Nowadays, there are five different sets of criteria which are commonly used worldwide (8) for the diagnosis of SS: the Copenhagen criteria (27), the Californian criteria (28), the Greek criteria (29) the Japanese criteria (30) and the recently revised European criteria (31). Even if some differences distinguish one from each other, the presence of oral dryness, either subjectively or objectively evaluated, is usually considered a cardinal feature. Nevertheless, SS diagnosis still remains a challenge for the clinicians, and delays from the start of the symptoms to final diagnosis have been frequently reported. This fact probably reflects the slow progression of the disease and the lack of knowledge concerning its natural course and etiopathogenesis. As a consequence, at present treatment for most patients is essentially symptomatic (32). However, early diagnosis could be important in order to potentially initiate preventive treatment and avoid the irreversible lymphocyte-mediated destruction of the salivary glands.

Nevertheless, clear data about this issue still lack, thus leading to the common concept that, as preventive tools are not available at the present time, early recognition is not able to influence SS prognosis.

However, it is our opinion that further considerations should be made about this issue. Firstly, the burden of a chronic disease, such as SS, should be evaluated not only in terms of mortality, but also with regard to patients' quality of life. This latter has been reported to be significantly decreased in patients affected by SS and, in general, xerostomia (33–35).

Furthermore, the recently reported reversibility of abnormalities in sublabial salivary gland biopsy specimens following treatment with corticosteroids seems to demonstrate that prevention of permanent degenerative glandular changes is possible in SS (36).

In addition, it is important to underline that more recent reports have suggested and indicated the molecular mechanism by which it might be possible to protect the salivary glands of SS patients against the destruction of acinar structure (9, 10). In fact, suppression of tumor necrosis factor alpha (TNF-alpha) pathway, either by anti-TNF-alpha antibodies (infliximab) or cephatanthine treatment, has been showed to be crucial in restoring *in vivo* proper localization of aquaporin-5 (10) and inhibiting *in vitro* the production of TNF-alpha-induced matrix metalloproteinases-9 in

acinar cells (9), which is believed to be a major determinant of acinar tissue disruption during SS pathogenesis (9).

Thus, the studies we encompassed in this brief review have highlighted some early oral clinical features of SS that might occur long time before the development of symptomatic dry mouth, and might help in targeting patients with early SS to potentially plan future preventive studies.

As symptoms of dry mouth (xerostomia) have been reported to appear only when the salivary flow is reduced to about 50% (37), and SS natural history is accompanied by a progressive loss of salivary acinar tissue, it is plausible that xerostomia could be absent at the early stages of the disease.

Similarly, as the role of salivary phosphorus in dental remineralization as well as the association of low salivary flow rate with augmented dental caries activity are well recognized (38, 39), we hypothesize that the association between asymptomatic hyposalivation and low salivary phosphate concentration in early SS (11, 12) carry the potential to increase caries activity, leading to early dental loss.

Salivary gland hyperfunction, as manifested by increased flow-rate, has been already described in familial dysautonomia, because of denervation supersensitivity of the partially denervated salivary glands (40). As neurological impairment, including denervation and autonomic dysfunction, have been observed in SS (41–43), paradoxical sialorrhea could be an early manifestation of the initial neurological alterations in this disease. In the SS patients with sialorrhea we have described, the eventual occurrence of dry mouth symptom was initially not associated with a decreased salivary flow; however, afterwards all the patients developed gradually hyposalivation, thus underlining the dynamical and progressive nature of SS immunopathogenetic process, with complex interactions and cross-talking among cytokines, nervous system, autoantibodies, lymphocytes and glandular cells.

Furthermore, the reported changes in saliva composition, non-dry mouth accompanied salivary glands swelling (NDR-SGS), early dental loss and temporary sialorrhea, which occurred before the development of hyposalivation, seem to support the hypothesis that autoimmune mechanisms may impair salivary gland function before replacing acinar tissue by lymphocytic infiltration. The identification of autoantibodies that act as antagonists at M3-muscarinic receptors (44) may support this theory. Also the observations about the lack of correlation between the degree of glandular destruction/focal lymphocytic infiltration and the severity of sicca symptoms suggest that other pathogenetic mechanisms are involved, including cytokines release and abnormalities in parasympathetic neurotransmission. Similarly, previous efforts in demonstrating that the presence of lymphocytic infiltration might be used as SS predictor, and thus considered an early disease manifestation, were not successful, because of its relatively common presence in healthy individuals.

Furthermore, as we reported in our four patients with sialorrhea (24), the evidence of an ongoing immunologically active disease was given by the presence of positive labial salivary gland biopsy and positive Ro/La serology results.

Other supporting evidences could be also found in the current literature. It has been recently shown that systemic lupus erythematosus (SLE)-autoantibodies are typically present many years before the symptomatic phase and thus the diagnosis of SLE (45): this have demonstrated that, at least in SLE, the pathogenetic process usually starts long before the development of typical signs and symptoms, and that it could be detectable by early serological changes. Similar laboratory studies in SS patients are very scarce, with only one prospective study reporting of asymptomatic women with positive tests for anti-Ro antibodies who after 5–10 years of follow-up developed Sjögren's syndrome (46). However, we suggest that the clinical features we reviewed, resulting from early salivary gland dysfunction, might represent, at least in some patients, the clinical counterpart of the underlying SS pathogenetic process, before the onset of typical advanced-stage clinical features.

If further studies will confirm this hypothesis, we should take into account that the current diagnostic criteria might be reconsidered, to include also atypical/early oral clinical features occurring in absence of xerostomia/hyposalivation, and to emphasize serologic and histopathologic findings. With regards to this, it is interesting to note that European and American SS research groups have recently proposed a new set of classification criteria, underlying the main role of positive labial salivary glands biopsy and/or positive Ro/La serology as indispensable criteria for the diagnosis of primary SS (31).

Conclusions

Although further studies are needed to better understand the early onset and natural history of SS, it seems that some oral clinical features could occur long time before the development of hyposalivation. Astute clinicians should not underestimate the possible presence or development of SS in patients without xerostomia/hyposalivation and presenting these atypical early oral features. Their detection could lead to diagnose earlier the disorder and potentially contribute to prevent irreversible parenchymal degenerative changes which characterize advanced-stage disease and make SS often incurable.

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