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Laryngological manifestations of Sjögren's syndrome

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Abstract

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands and a range of extra-glandular features. The most common and earliest symptoms are oral and ocular dryness. The aim of this study is to present the most common otolaryngological manifestations of SS, their pathomechanism and possible aetiology. The most common oral signs and symptoms are xerostomia, tooth decay, fungal infections, traumatic oral lesions, dysphagia, dysgeusia, and inflammation of the salivary glands. The salivary glands of SS patients are characterised by chronic inflammation. The presence of foci is thus a hallmark of SS. A biopsy can be taken from either the labial or the parotid salivary gland. The most significant complication of SS is the development of lymphoproliferative malignancy, which occurs in about 5% of SS patients. The ultrasonic greyscale scoring system, glandular volume measurement, and intraglandular power Doppler ultrasonography are specific ultrasound parameters of SS.

Key words: Sjögren's syndrome, hearing loss, cranial nerve neuropathy, xerostomia.

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands and a range of extra-glandular features. It affects approximately 1% of the population. The most common and earliest symptoms are oral and ocular dryness. The clinical features involve a wide variety of organs, including skin, eyes, oral cavity and salivary glands, and systems, including nervous, musculoskeletal, genitourinary and vascular, and each of these symptoms may be at times correctly attributed to SS or incorrectly attributed to another disease. Other organs may be involved in more than 30% of cases and, occasionally, extra-glandular manifestations can occur early during the course of the disease [1–9].

Diagnosis of primary SS, approved in 2016 by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) [10, 11], is based on the weighted sum of 5 items: anti-SSA/Ro antibody positivity and focal lymphocytic sialadenitis (FLS) assessed in labial salivary gland biopsy (LSGB) with a focus score of 1 foci/4 mm^2, each scoring 3; an abnormal ocular staining score of 5 (or van Bijsterveld score of 4), a Schirmer's test result of 5 mm/5 minutes, and an unstimulated salivary flow rate of 0.1 ml/minute, each scoring 1. Individuals with signs and/or symptoms suggestive of SS who have a total score of 4 for the above items meet the criteria for primary SS. Because SS affects numerous different areas, many specialists (rheumatologists, primary care physicians, ophthalmologists, and dentists) may be involved in the diagnosis and treatment of SS. Otolaryngological manifestations and hearing loss may be the initial symptoms of SS, and a laryngologist can be the first doctor who diagnoses the syndrome. Sicca symptoms *per se* may occur in a number of other disorders, including rheumatoid arthritis, systemic lupus erythematosus or scleroderma, as well as sarcoidosis or hepatitis C and B infection, but also secondary SS may accompany other rheumatic diseases [12–16].

The aim of this article was to present the most common otolaryngological manifestations of SS, their pathomechanism and possible aetiology.

Oral involvement and xerostomia

The rate of dry mouth in SS ranged from 41% at initial diagnosis to 84% 10 years after diagnosis [17].

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Hyposalivation or xerostomia measured by sialometry is one of the objective clinical criteria in the diagnosis of SS. According to the current classification criteria of SS, an unstimulated salivary flow rate of 0.1 ml/minute in sialometry gives a score of 1 to the weighted sum of 5 items according to the current EULAR/ACR criteria. Dryness is also a subjective symptom of SS and is associated with many clinical implications. The most frequent complaints are dryness of the mouth in the morning and at night, a frequent need to sip water, lip dryness, oral mucosa exfoliation and fissuring, and oral aphthous ulcers. Additionally, some patients complain of a burning sensation in the mouth. The lips are fissured, exfoliative, and bleed easily. The patients report the need to moisten and lubricate the lips frequently [6, 18, 19].

Patients with symptoms of oral dryness are usually referred to a dentist or a laryngologist. A number of hypotheses have been proposed to account for dry mouth in SS, such as destruction of the duct and acinar cells of the salivary glands, and neural degeneration and/or inhibition of nerve transmission. Since in a large proportion of patients almost half of the gland acini remain intact, the possibility of a defect or alteration in nerve transmission could be proposed, though the most decisive factor appears to be the progressive infiltration of mononuclear cells and the consolidation of autoimmune disease [20]. The presence of mononuclear cell aggregates around the ducts and acini of salivary glands results in functional and structural alterations at the level of these glands and impairs their secretory function [15]. In addition to the direct relationship between mononuclear cell infiltrations and secretory function, there are alternative pathways, such as induction of apoptosis of epithelial cells, alterations in aquaporin distribution, or inhibition of neurotransmission by antimuscarinic antibodies, leading to impaired glandular homeostasis [10]. Dry mouth makes talking, tasting and chewing properly difficult, impairing the quality of life of such patients. The most common oral signs and symptoms are hyposialia with or without xerostomia, dental caries, tooth decay, fungal infections, traumatic oral lesions, dysphagia, dysgeusia, and inflammation of the salivary glands [6, 18–21].

In SS the gingiva and mucosa of the oral cavity are not protected by salivary mucins, leading to less lubrication of the tissues. This can cause signs such as oral mucosal inflammation, mucosal sloughing, erythematous mucosa and traumatic ulcers. In advanced cases depapillation of the tongue may occur. Patients suffering from the disease for a shorter time have a higher level of stimulated saliva than those with a longer disease duration. With time, the concentration of lactoferrin, potassium and cystatin C in saliva grows, while the amylase and carbonic anhydrase concentrations decrease.

Finally decreased secretion of saliva, the loss of its buffer properties and a lower concentration of saliva proteins such as histamine, mucin, IgA, proteins rich in proline and statherin increase the risk of opportunistic infections, mainly fungal infections by *Candida albicans* [18]. Oral candidiasis may be asymptomatic or may show as fissured tongue, rhomboid mid-tongue, non-specific ulcerations, prosthetic stomatopathies, or generalised candidiasis. It most often takes the form of chronic candidiasis, and less often of pseudodiphtheritic candidiasis [6]. *Candida* spp. infections often present as atrophic or erythematous candidiasis and are associated with a burning mouth, which is described by approximately one-third of patients with SS. The prevalence of *Candida albicans* is > 68% in patients with SS, whereas the prevalence in the normal population ranges from 23 to 68% [19]. Apart from *C. albicans*, other species were isolated, namely *C. tropicalis*, *C. glabrata*, and *C. parapsilosis* [6, 19]. Candidiasis accompanies angular cheilitis and exfoliative cheilitis and is very often observed in SS patients. Angular cheilitis may be due to fungal infection, but may also be caused by staphylococcal infection or anaemia. In simple cheilitis, dominant manifestations are bad lip exfoliation and cracking, their proneness to bleeding, periodic swelling and burning. The lesions are mostly limited to lip vermillion, less often labial mucosa or the facial skin around the vermillion is affected. In exfoliative cheilitis, thick brown keratin plaques are also formed. Skin redness over the lip vermillion and swelling are more often observed [6].

Many patients have a history of frequent aphthae and non-specific ulcerations. They may be related to concurrent diseases, not necessarily to SS. Lupus erythematosus predisposes to non-specific oral mucosa lesions and to lichen planus. Typical lupus lesions are whitish, round or discoid plaques with erythema inside and marked keratinisation around. Systemic scleroderma promotes oral mucosa fibromatosis and its paleness due to its improper vascularisation. Anaemia and a low level of ferritin may, in turn, predispose to frequent formation of aphthae and aphthoid lesions [6]. Severe cases of candidiasis in combination with a decrease of immune resistance may lead to oesophagitis or laryngitis.

Salivary gland manifestations

The salivary glands of SS patients are characterised by chronic inflammation, as witnessed by the presence of lymphocytic infiltrates located around the striated ducts. These so-called periductal foci can be seen in both the minor and major salivary glands and are present in

most SS patients. They are mainly composed of T and B lymphocytes with a few other mononuclear cells, including macrophages, myeloid and plasmocytoid dendritic cells, and follicular dendritic cells. They may develop into organised ectopic lymphoid structures resembling secondary lymphoid organs with segregated T and B cell areas, and high endothelial venules. These structures become active centres of an immune response. This is reflected by the presence of germinal centres in the B cell area of the organised periductal infiltrate and the presence of plasma blasts and plasma cells at the border of the infiltrate. Initially, activated lymphocytes and plasma blasts become triggers for the combined action of pro-inflammatory cytokines and chemokines. This action starts the sequential stages in SS [16].

The presence of foci in labial salivary glands is thus a hallmark of SS and their histopathologic analysis is an important item in the diagnosis and classification. A biopsy can be taken from either the labial or the parotid salivary gland, but currently according to the diagnostic criteria only labial salivary gland biopsy (LSGB) is recommended to confirm the diagnosis of SS. It is the natural operative area for a laryngologist, who may be the first doctor to diagnose SS. Both types of biopsy have a similar predictive and diagnostic value in SS [15, 22, 23]. Parotid gland biopsy is more recommended for detection of lymphomas and for evaluation of the progression of SS. They are scalpel biopsies and are based on taking the most representative and pure glandular tissue. The histopathological confirmation of SS in LSGB is based on the presence of focal lymphocytic sialadenitis (FLS). Although the lymphocytic infiltrations are similar in labial salivary glands and in parotid glands, only LSGB is used with scoring and the diagnosis of SS. Parotid gland biopsy is treated as an additional diagnostic tool and as an alternative diagnostic method, especially in monitoring of SS progression and the detection of lymphomas accompanying SS. According to the current classification of SS only a positive LSGB is included in the diagnostic process [16, 22].

The term FLS refers to the presence of one or more foci in the biopsies, while the tissue surrounding the foci is composed mainly of unaffected parenchyma. A focus is defined as an aggregate of ≥ 50 mononuclear cells (lymphocytes) and the focus score (FS) is the total number of foci per 4 mm of the salivary gland tissue. In both labial and parotid glands, an FS of ≥ 1 is considered as a positive biopsy and used for the classification of SS [15, 22, 23].

In addition to the FS, two scoring systems are in use for diagnosing SS. Moreover, these scoring systems are based on the presence of foci. Grading according to Tarpley takes the destruction of acinar tissue and fibrosis into account, and for Chisholm and Mason, so does the presence of diffuse infiltrates, when the FS is lower than 1. Besides FS, lymphoepithelial lesions (LELs) and a relative decrease of IgA+ plasma cells appear to be characteristic for SS. Both features may be an additional tool in the assessment of salivary gland biopsies for diagnosing SS, especially when the FS in the biopsy is < 1. In SS patients, LELs are present in 93% of parotid gland biopsies, compared to 33% of labial gland biopsies [16]. A parotid gland biopsy is more recommended for assessment than a labial salivary gland biopsy. LEL development is associated with hyperplasia of the epithelium by the infiltrated lymphocytes. A relative decrease of < 70% IgA+ plasma cells is a specific and sensitive diagnostic test in SS. In daily clinical practice, an evaluation of salivary gland biopsy for the presence of LELs and < 70% IgA+ plasma cells, in addition to FS, may aid in the correct diagnosis of SS. The lymphocytic infiltrations are representative for all salivary glands and have other possible consequences [16].

Although the sicca syndrome prevails in the clinical presentation, a bilateral parotid swelling induced by progressive lymphocyte infiltration leads to both ductal inflammation and acinar destruction in about 50% of patients. Recurrent swelling and inflammation of the parotid or submandibular glands in SS are well documented. Slow salivary flow, acinar destruction and lymphocytic infiltrations predispose to inflammation and salivary gland enlargement. This enlargement should be distinguished from lymphomas. The most significant complication of SS is the development of lymphoproliferative malignancy, which occurs in about 5% of SS patients [16].

Malignant lymphoma, particularly mucosa-associated lymphoid tissue (MALT) lymphoma, is a relatively frequent complication of SS with an incidence ranging between 5 and 10% and a median time from SS to lymphoma diagnosis of 7.5 years. Potential explanations for this incidence variation include differences in the criteria used for the diagnosis of SS and the variable duration of follow-up. The emergence of lymphoma is signalled by persistently enlarged parotid glands, regional or general lymphadenopathy, hepatosplenomegaly, pulmonary infiltrates, vasculitis, and hypergammaglobulinaemia [24–28]. None of these features is specific, but any should raise the index of suspicion, particularly if accompanied by serological features such as a falling packed-cell volume, high sedimentation rate, or the presence of monoclonal immunoglobulin. Further investigations include the lymph nodes, bone marrow, and salivary gland biopsy [8].

Both high-resolution CT and MRI are helpful. Recent advances in MRI have shown that use of gadolinium imaging with fat-subtraction views (MRI contrast sia-

lography) allows excellent identification of the ductal structures as well as cystic changes or lymphoma. Another option is parotid ultrasonography, especially in centres where the radiologists have experience of this technique [8]. Lymphomas accompanying SS can be confirmed by histopathological examination of salivary gland biopsy. The detection of germinal centres (GC) in salivary gland biopsy can be a very sensitive and predictive feature for lymphogenesis. Antigen-driven B cell selection normally takes place in GC within secondary lymphoid organs, but there is conclusive evidence that also ectopic GC in the salivary glands of SS allow affinity maturation of GC B cells with somatic Ig gene hypermaturation. Parotid gland biopsy is more recommended for diagnosis of lymphomas than labial salivary glands. Laryngologists are appropriate specialists to correctly diagnose lymphadenopathy and salivary gland enlargement and monitor SS patients with risk of lymphoma development [16, 24–27].

Ultrasonography of salivary glands

In addition to the clinical and histopathological manifestations of SS in salivary glands, laryngologists can apply other diagnostic tools for SS diagnosis. In recent years, the use of salivary gland ultrasonography (US) has increasingly been performed to identify glandular involvement in primary SS. Many studies have highlighted the diagnostic accuracy of this non-invasive, easily performed and feasible tool, and increasing evidence has recently suggested a potential role for patient stratification and monitoring over time [29].

There is a grading system based on the degree of salivary gland inhomogeneity for the diagnosis of primary SS. The results were encouraging and showed a sensitivity of 88.8% in primary SS and a specificity of 84.6% and of 92.2% with respect to controls. A group of ultrasound abnormalities in primary SS patients is proposed and the different echographic parameters to consider in routine practice are also listed. The parameters identified include echogenicity, homogeneity, the number of hypo- or anechoic areas, measurements of the biggest hypo- or anechoic area, the location of the hypo- or anechoic area in the gland, the number of lymph nodes in the glands, calcification, the visibility of the posterior border, and measurements of glands. The assessment of vascularisation is based on the resistive index of the transverse facial artery of the parotid gland before and after stimulation with lemon juice. The first anomaly in SS is salivary gland enlargement. It is a typical primary SS manifestation, detected in almost one third of primary SS patients, and is considered as a risk factor for poor prognosis, including lymphoproliferative complications. Ultrasonography of major salivary glands in primary SS has made it possible to identify a subgroup of patients with subclinical involvement of major salivary glands, with no clinically evident salivary gland enlargement. On the other hand, other patients present normal glands in the US and do not present any change in their sonographic pattern over time. There is no single specific ultrasound parameter of SS [29, 30].

According to Luciano et al. [31], the most valuable diagnostic method in SS is the accuracy of three US parameters: the US greyscale scoring system, glandular volume measurement, and intraglandular power Doppler US (PDUS). The semi-quantitative scoring system consists of parenchymal echogenicity, parenchymal inhomogeneity, the presence of hypoechoic areas, the presence of hyperechoic foci, and clearance of salivary glands' posterior borders. Parenchymal echogenicity is evaluated in comparison with the thyroid parenchyma and surrounding soft tissue (muscle, subcutaneous fat). Selected ultrasonic features and the diagnostic parameters in SS are presented in Table I.

Finally, the US salivary gland score is calculated by summation of the grades of the 5 first parameters described above for all 4 glands. The US salivary gland score ranges from 0 to 48. The volumes of the salivary glands and intraglandular PDUS are additional diagnostic parameters. The volumes of the submandibular and parotid glands are calculated as longitudinal diameter (cm) × transverse diameter (cm) × sagittal diameter (cm) × 0.5 and expressed in ml. Combined evaluation of submandibular and parotid glands shows better diagnostic accuracy than evaluation of a single gland. Therefore, a salivary gland US examination of all four salivary glands is necessary to make a correct diagnosis of primary SS. A new method of US, real-time tissue elastography, is more helpful in diagnosing SS. Various sonoelastographic modalities, including real-time tissue elastography, Virtual Touch imaging and quantification, have provided promising results [31].

Another recommended method of US elastography is acoustic radiation force impulse imaging. This technique provides an objective numerical evaluation of tissue stiffness by measuring the propagation of shear waves emitted during induced tissue displacements [32]. The speed of the shear waves is measured as shear wave velocity (SWV) and it is expressed in metres per second (m/s). Stiffer tissues are characterized by higher SWV. This method can be applied in SS diagnosis. The mean SWV values of parotid and submandibular glands are usually higher in primary SS patients [32]. Acoustic radiation force impulse imaging is useful in the detection of glandular impairment in early primary SS stages. The SWV values indicate a symmetrical distribution of the elastic-

Table I. Grading system for selected ultrasonic salivary gland parameters in Sjögren's syndrome

Ultrasonographic salivary gland features/ parameters in Sjögren's syndrome	Grading system
Parenchymal echogenicity	0 – echogenicity comparable to thyroid 1 – decreased echogenicity in comparison to thyroid
Parenchymal inhomogeneity	0 – for a homogeneous gland 1 – for mild inhomogeneity 2 – for evident inhomogeneity 3 – for a grossly inhomogeneous gland
Presence of hypoechoic areas	0 – absent 1 – few scattered 2 – several 3 – numerous hypoechoic areas
Presence of hyperechoic *foci*	0 – absent 1 – few scattered 2 – several 3 – numerous hyperechoic foci 0 – absent (only for submandibular glands) 1 – present (only for submandibular glands)
Clearance of salivary glands' posterior borders/ delineation of salivary glands	0 – well-defined borders 1 – slightly less defined borders 2 – ill-defined borders 3 – borders not visible, blurred
Volume of submandibular/parotid glands	Longitudinal diameter (cm) × transverse diameter (cm) × sagittal diameter (cm) × 0.5 and expressed in ml
Intraglandular power Doppler ultrasonography	0 – no parenchymal flow 1 – up to three single spot signals or up to two confluent spots or one confluent spot plus up to two single spots 2 – flow signals in less than half of the cross-section of a gland (≤ 50%) 3 – flow signals in more than half of the cross-section of a gland (> 50%)

ity changes in both parotid and submandibular glands [32]. The SWV values correlate with the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and non-stimulated whole salivary flow rate [33]. Increased elasticity in SS does not correspond with ultrasonographic changes in involved salivary glands and fibrosis [34].

Laryngological manifestations

Involvement of the upper respiratory tract may occur in SS. Dryness of mucosa of the upper respiratory tract is a predominant symptom and results in nasal, oropharyngeal, nasopharyngeal, laryngopharyngeal, and vocal cord dryness and dryness of the skin of the external auditory meatus. A laryngological examination (ear, nose and throat – ENT) can reveal the viscid secretions on the posterior pharyngeal wall and tenacious mucus over the vocal cords, dry wax and a „milky" appearance of the tympanic membrane. Dry nose is common and may lead to inflammation with subsequent congestion, crusting, and epistaxis. Iron-deficiency anaemia may appear in SS and predispose to epistaxis. An examination of the nose under direct vision detected dryness, crusting, or atrophy of the nasal mucosa. Severe nose dryness may affect the nasal septum and result in septal perforation. Soreness and/or dryness of the throat, dysphagia, hoarseness, otalgia and tinnitus were the most common complaints in SS patients with dryness symptoms. Trachea dryness may result in a chronic dry cough and may predispose to bronchial mucosa dryness. Due to mucosa dryness SS patients may have an increased risk of pharyngeal-tracheo-bronchial infections. The most frequent respiratory symptoms such as chronic cough and dyspnoea may occur in primary SS [35].

Another important factor in the oropharynx of patients with SS is gastrotracheal reflux. Since saliva has a high pH that normally neutralises acid refluxed from the stomach, the patient can be predisposed not only to gastro-oesophageal reflux but also to reflux into the trachea, which can mimic upper respiratory tract infection [8]. Otalgia in SS can recur in cycles that are parallel to a worsening and improvement of the symptoms and signs of SS. Reddened and dilated capillaries in the left auditory meatus and eardrum can be found, resulting

in otitis externa and myringitis. Steroid therapy relieves the pain, as well as the otitis externa and myringitis [36].

Otological manifestations and hearing loss

Uncommon events include early and progressive hearing loss and symptoms related to neuropathy of the eighth cranial nerve. Approximately a quarter of patients suffer from high frequency hearing loss of cochlear origin, as detected by impedance audiometry or auditory brainstem procedures. Otological symptoms may occur in autoimmune diseases. Sensorineural hearing loss (SNHL) is commonly reported in granulomatosis polyangiitis (GPA), polyarteritis nodosa, Behçet's syndrome, rheumatoid arthritis, and systemic lupus erythematosus. Sensorineural hearing loss is observed in approximately 8% of GPA cases, but in primary SS hearing loss as the primary manifestation is not well known and there are only limited reports. Hearing loss is believed to be the first otologic manifestation of SS.

In a study by Calzada et al. [37] on 40 female SS patients, 22.5% of the patients demonstrated cochlear SNHL, mainly in the high frequencies, and it was associated with disease duration. The immunologic theory of SNHL is based on antibody activity and cytotoxic T cell-mediated apoptosis in the inner ear. It has been suggested that these autoantibodies induce thrombosis in the labyrinthine vessels, thereby causing damage to the inner ear, resulting in SNHL. The majority of primary SS patients exhibit hearing impairments of cochlear origin, principally at high frequencies. Autoantibodies of both cardiolipin and M3 muscarinic receptors in the sera are suspected to play a pathogenetic role in the progressive hearing loss of primary SS patients. Sensorineural damage may be attributable to vasculitis or neuritis, or may represent an ototoxic effect of the drugs used to treat primary SS. Increased expression of anti-cardiolipin, anti-endothelial cells and anti-neutrophil cytoplasmic antibodies may correlate with clinical manifestations of hearing loss.

Although there is no evidence of damage to the central auditory pathways in SS, these patients tend to have a higher prevalence of sensorineural hearing impairment compared with the general population. Idiopathic hearing loss may represent the initial manifestation of systemic vasculitis, including primary SS. Therefore, early referral to a rheumatologist should be considered for prompt diagnosis of underlying autoimmune disease and subsequent initiation of therapy [37–39].

Cranial nerve involvement

A variety of neurological symptoms are described in SS. Disease-associated neuropathy is one of the major neurological complications of SS. Neurological manifestations are reported in about 20% of patients with SS [8]. In patients with SS, neurological manifestations may occur, such as peripheral neuropathy and other forms of neuropathies, including sensory ataxia, painful sensory neuropathy without sensory ataxia, multiple mononeuropathy, multiple cranial neuropathy, autonomic neuropathy, radiculoneuropathy and intra- and extraoral paraesthesias, facial hypaesthesia and trigeminal nerve neuropathy [6].

Screening for SS should be systematically performed in cases of acute or chronic myelopathy, axonal neuropathy or cranial nerve involvement. Many cranial nerves can be affected in SS, but multiple cranial neuropathy is a relatively rare complication. Trigeminal and oculomotor nerve palsies are the most common in SS. The occurrence of Bell's palsy resulting from SS has been documented [40]. Cranial neuropathy is an infrequent manifestation of SS. Any cranial nerve from II to XII can be affected, with trigeminal sensory neuropathy being the commonest. Tonic pupils with light-near dissociation have been described in patients with peripheral neuropathy due to SS (Adie pupil). This may be an isolated occurrence or part of generalized autonomic neuropathy. Trigeminal neuropathy may represent local ganglionitis affecting the gasserian ganglion and may be a limited form of pure sensory neuronopathy [41].

The pathomechanisms underlying cranial neuropathy in SS have not yet been explained, except for trigeminal neuropathy due to ganglionopathy. Two possible mechanisms, vascular origin with damage to the vasa nervorum and an immunologic cause inducing lymphocytic infiltration of the nerve, have been suggested in nerve palsies related to SS. Vasculitis in peripheral neuropathy and ganglionopathy in trigeminal or ataxic neuropathies have been reported as the main pathogenic aetiologies. The rapid and almost complete recovery from nerve palsy after therapy with corticosteroids and azathioprine suggests that lymphocytic infiltrate, rather than a vasculitic process, was the cause of cranial neuropathy in SS [41–43]. Birnbaum [44] reported a new, previously unrecognized neurological disorder in rheumatic diseases, characterized by facial weakness, otalgia with neuropathic features, hemifacial spasm, and with both otalgia and hemifacial spasm persisting after the extinction of mild facial weakness.

Conclusions

Dryness is the main manifestation of SS affecting many organs. It can result in clinical symptoms in the oral cavity and in the upper respiratory tract. Salivary gland involvement is a common manifestation of SS and should be included in the routine examination in patients with suspected SS. The appropriate and early detection of dryness may be very helpful in the compre-

hensive diagnosis of SS. Nerve involvement, especially cases of cranial nerve palsy, polyneuropathy, and hearing loss, can be an early manifestation of SS.

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