Review

Recent insights in the potential role of imaging modalities for diagnosing patients with primary Sjögren's syndrome

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ABSTRACT

Within the last year, interesting developments regarding the assessment of salivary gland involvement in patients with clinical suspicion of, or diagnosed with primary Sjögren's syndrome (pSS) have been performed. In this review various topics will be discussed, starting with the use of salivary gland ultrasonography (SGUS) for the detection of glandular swelling. Furthermore, other imaging modalities, besides B-mode SGUS, which differentiate between pSS patients and healthy controls will be highlighted. Moreover, storage of ultrasonographic images and videos will be discussed briefly, as will be some potential biases and pitfalls. Finally, efforts that have been made to make incorporation of SGUS into the most recent classification criteria possible will be discussed, as well as the important steps that have been taken to develop a new semi-quantitative scoring system for the assessment of salivary gland involvement in patients with suspected or confirmed pSS.

Introduction

Primary Sjögren's syndrome (pSS) is a common, heterogeneous, systemic auto-immune disease, with an estimated prevalence of 0.04% in the general population (1-3). Above all, pSS is characterised by chronic inflammation of the salivary and lacrimal glands (4). The most common symptoms are dryness of the mouth and eyes, resulting in xerostomia and keratoconjuntivitis sicca, respectively. Furthermore, fatigue, arthralgia and various extraglandular manifestations can be present at any time during the disease course (1, 4).

Currently, there is no golden standard to diagnose a patient with pSS, and therefore, diagnosis mainly relies on expert opinion, which is based on the interpretation of several tests and clinical observations. In addition, classification criteria have been developed with the intention to define homogenous study groups, rather than being used for diagnosing a patient, as for diagnosis not only specificity, but also sensitivity should be high (4, 5). Nevertheless, diagnosis and classification often show quite some overlap, as both rely on the same components.

The most recent set of criteria applied for pSS are the American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) classification criteria (6, 7). The ACR-EULAR criteria actually are a new mixture of items that were already integrated in the previously developed 2002 American European Consensus Group (AECG) and 2012 ACR, and, endorsed by both, EULAR and ACR (8-10). The ACR-EULAR criteria assign three points for a positive biopsy (focus score ≥1) and positive anti-SSA antibodies, and one point for a decreased unstimulated whole salivary (UWS) flow, decreased Schirmer's test, or increased ocular staining score (OSS). Patients with a score of ≥4 are classified as pSS (6, 7). An interesting critical note has recently been raised by van Nimwegen et al. (10). As a matter of fact, the authors uncover that these new 2016 ACR-EULAR criteria are not optimally balanced (10). Whereas tear gland involvement is evaluated by the Schirmer's test, a functional test, as well as by the OSS, which is an imaging modality to measure structural ocular involvement, salivary gland involvement is solely evaluated by measuring the UWS flow, which can also be categorised as a functional test (10). An imaging modality to measure salivary gland involvement appears to be missing.

Interestingly, even after many years, salivary gland imaging is still an evolving field within pSS. Previously, the

salivary glands were mainly visualised by sialography or scintigraphy, as both methods were also incorporated in the 2002 AECG criteria (8, 11). Nowadays, these more invasive imaging modalities are, in daily clinical practice, mainly replaced by salivary gland ultrasonography (SGUS). With B-mode SGUS, which is easily accessible in the outpatient setting, repeated measurements can take place, as it is non-irradiating, not invasive, in-expensive, and well-tolerated by patients (10, 12, 13). In this review, we highlight interesting developments within the last year, including studies investigating the use of SGUS for the detection of glandular swelling, the value of other imaging modalities besides B-mode SGUS to differentiate between pSS patients and healthy controls, storage of SGUS images and videos, some biases and pitfalls, the incorporation of SGUS into classification criteria, and the development of a novel semi-quantitative scoring system for the assessment of salivary gland involvement in patients with suspected or confirmed pSS.

The use of salivary gland ultrasonography for the detection of glandular swelling

Besides sicca complaints and reduced salivary flow, another typical manifestation of salivary gland involvement in pSS is glandular swelling. Salivary gland enlargement, which is detected in about thirty percent of the patients, is considered a risk factor for the development of mucosa-associated lymphoid tissue (MALT)-lymphoma, especially in patients with persistent enlargements of the glands (14). Therefore, salivary gland involvement is one of the twelve domains of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), which is nowadays the most frequently used assessment of systemic disease activity (15). The domain measuring glandular involvement contains three levels of activity *i.e.* (i) No: absence of glandular swelling; (ii) Low: small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular (≤2 cm) or lachrymal swelling (≤1 cm) and (iii) Moderate: major glandular swelling with enlarged parotid (>3 cm), or important submandibular (>2 cm) or lachrymal swelling (<1 cm) (15).

The user guide, developed in 2015, states that 'parotid, submandibular or lachrymal gland swelling should be assessed by clinical examination and not by ultrasound' (15). Very recently, however, Marteau *et al*. (16) came to a different conclusion by investigating the interobserver reproducibility of parotid and submandibular gland palpation, and comparing this clinical assessment with B-mode SGUS measurements. In this study, 34 patients diagnosed as pSS or non-SS sicca, according to the AECG criteria were included (16).

Swelling of a parotid gland, measured on a binary scale, could reliably be detected by palpation if the gland is at least 3 cm in length. Of note, a low ESSDAI score on the glandular domain is the case when the parotid gland enlargement is up to 3 cm. Reliable detection of submandibular gland swelling, however, is a complete different story, as physical examination appeared not informative (16). Using ultrasonography, cut-off values for defining glandular hypertrophy were arbitrarily set at more than 5 cm^2 for the parotid glands, and more than 3 cm^2 for the submandibular glands. Herewith, for both investigators, a low agreement between glandular swelling measured by palpation and hypertrophy measured by SGUS was found.

Concerning clinical trials, among others, a complementary method to measure glandular swelling, like ultrasonography, might be warranted, as it appears that, even for pSS experts, physical examination regarding mild glandular swelling might be overestimated (16). Interestingly, Milic *et al*. found a significant correlation between B-mode SGUS score and the glandular domain of the ESSDAI in a large group of pSS patients, and suggest that SGUS might be a surrogate item for the glandular domain (17). Further research on the additional value of SGUS examination on top of clinical palpation of the salivary glands is needed, since the ESSDAI is a widely used measurement tool. Moreover, this information is also important for the development of future composite endpoints. The value of SGUS for early detection of MALT lymphomas has not been determined yet.

B-mode ultrasonography in relation to salivary flow

Nowadays, there is sufficient evidence that SGUS enables us, at group level, to differentiate between pSS patients and healthy controls, and patients with other connective tissue diseases (CTDs), and even between pSS patients and non-SS sicca patients (18-22). Within the past year, these topics have been investigated further (23-25).

Inanc *et al*. showed that patients with anti-SSA and/or anti-SSB antibodies, and those with a reduced UWS flow rate on average had higher B-mode SGUS scores in comparison with seronegative patients and patients with a normal UWS flow, respectively (23). The former was also shown by La Paglia et al., who showed that SS patients had higher B-mode SGUS scores compared with other CTD patients with sicca complaints, but without a diagnosis of secondary SS (24).

In a recent review, Devauchelle *et al*. (26) emphasised the need to identify SGUS characteristics caused by glandular damage, and to differentiate between potentially reversible markers of active disease and probably irreversible damage. The importance to differentiate between active disease and disease damage was previously pointed out by Baldini *et al*. (11), and recently underlined by Zabotti *et al*. (25). The latter authors aimed to identify the SGUS component that showed the best association with a decreased salivary flow in pSS patients, and compared 75 established pSS patients with 23 age- and sex-matched healthy controls. Reduced salivary flow showed significant associations with the detection of hyperechoic bands in the parotid and submandibular glands, of which the authors propose that this finding represents glandular damage. In addition, these hyperechoic bands were much rarer in the group of healthy controls, and less prominent (25). More research needs to be done to fill current knowledge gaps, with perhaps also a role for other SGUS modalities.

Imaging modalities other than B-mode ultrasonography

Recently, also other ultrasound modalities or techniques have been investigated in pSS patients, as well as in healthy controls (27-29). Among these modalities are grey-scale histogram analysis, and (two-dimensional shear wave) elastography (27-29). With grey-scale histogram analysis of ultrasonographic images, a more objective method to provide quantitative information about the echogenicity of the salivary glands is applied, as a range of 0–255 grey-level pixels is used. Herewith, subjective, operator-dependent ratings of the normally applied B-mode ultrasound evaluation are eliminated (27). With elastography, another ultrasonographic technique, the stiffness of the organ, in this case the salivary glands, can be evaluated (27) and two-dimensional shear wave elastography (2D SWE) enables a quantitative assessment of this tissue stiffness (in meters per second and kilopascals) (29, 30).

Caraba et al. found that ultrasonography and sonoelastography are valuable tools in assessing salivary glands involvement in pSS, since the ultrasonographic parameters showed significant differences between 32 pSS patients and 32 age and sex matched healthy controls (28). Furthermore, Arslan et al. showed that 2D SWE values differed significantly between 53 pSS patients and 30 healthy controls, and concluded that salivary glands should be assessed by both, B-mode SGUS and 2D SWE (29). Moreover, Sezer *et al*. found that the mean histogram values of parotid glands of 57 female pSS patients were significantly lower compared with the histogram values of 48 female healthy controls, whereas previous studies did not find a significant difference between normal and abnormal glands (27, 31, 32). However, the inclusion of healthy controls rather than non-SS sicca patients, makes it easier to detect differences, as it is expected that healthy individuals have normal salivary glands. It would be of interest to investigate whether these promising results could also be found between pSS patients and non-SS sicca controls. This, since an imaging modality should be able to differentiate between these groups, as both are referred to a rheumatologist, and healthy controls usually are not.

Storage and scoring of ultrasonographic images and videos

Recently, Hammenfors *et al*. investigated the preferred projection, gland and storage format for post-examination evaluation of SGUS in a group of 32 pSS patients (33). The authors concluded that there was a trend favoring longitudinal videos of the parotid gland, and that storing enables later image evaluation for diagnostics, second opinion and disease progression. Furthermore, the authors recommend regular calibration exercises among ultrasonographers, because in daily clinical practice, observer differences may not be detected easily (33). These potential observer differences might be overcome with the use of image segmentation analysis, providing automatically scored SGUS lesions based upon computer algorithms (11). The application of artificial intelligence is also one of the aims of the HarmonicSS project of joint European Research, the Horizon 2020 project (34). Unfortunately, it is not clear yet what different SGUS features truly represent in terms of histopathological parameters. Therefore, a study comparing SGUS evaluations with major salivary gland biopsies is eagerly awaited.

Incorporation of salivary gland ultrasonography into classification criteria

Previously, it had already been suggested to add B-mode SGUS to the 2002 AECG criteria or ACR criteria, or to replace one of the current items by SGUS (22, 35-39). Unfortunately, SGUS was not considered as a potential criteria item in the development of the ACR-EULAR criteria, as its methodological properties were not fully known (10, 40).

It may be clear from the various efforts that have already been made to investigate incorporation of B-mode SGUS into the 2016 ACR-EULAR classification criteria, that this is eagerly awaited. Within the last year, two independent studies have been published (10, 40), both investigated this topic, bringing the total number up to four (41, 42). Despite the methodological differences, there are a few lessons can be learned to ensure that SGUS will become part of the classification criteria anytime soon. First, to keep the ACR-EULAR criteria applicable and easy to use, the weight of the original criteria items should stay the same (10, 40). Furthermore, like the other items to measure tear- and salivary gland involvement, a positive SGUS should be assigned a weight of one point. Even though, consensus about the amount of points that are necessary to classify a patient must still be obtained, there is consensus that a patient should not be classified as pSS patient if only the minor criteria items are fulfilled (10, 40). Replacement of serology or histopathology by SGUS resulted in a significant decrease in the performance of the criteria (10). However, SGUS can be added to the other minor items UWS, the OSS or the Schirmer's test (10, 40). This improves feasibility in clinical practice, as not all individual tests may be accessible in every outpatient clinic. Previously it has been shown that presence of anti-SSA antibodies in combination with a positive SGUS is highly predictive of classifying a patient with pSS (18). Therefore, for classification purposes, the first steps could be determination of antibody status and performing an SGUS. Though for clinical diagnosis, a full work-up is advised, in order to make the best possible risk assessment for the individual patient (10, 18).

However, before worldwide implementation of SGUS into classification criteria can take place, a few problems need to be solved. International consensus regarding which SGUS scoring system to use, with a validated cut-off point to differentiate between pSS patients and other CTD or non-SS sicca patients has main priority. Necessarily, a high level of inter- and intra-observer reliability should be pursued. Within the past years, a sub-taskforce of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) working group, created in 2016, has taken important steps in this procedure, as one of the main goals was to develop a standard-

ised SGUS scoring procedure (43). The first step was to achieve agreement on defining normal and abnormal SGUS findings is patients with probable or confirmed pSS. This resulted in the development of a new semi-quantitative scoring system for the assessment of the parotid and submandibular salivary glands, with excellent intra- and good inter-observer reliability (43). During the development process, attention was also given to fatty replacement and fibrosis, both initially not included as potential items in the new scoring system, and it was suggested that both should be considered when the semi-quantitative system cannot be applied (43). Herewith, significant progress has been made in the development of a reliable, semi-quantitative scoring system that can be used worldwide.

To conclude, there are a few key points to keep in mind. First, detection of mild glandular swelling by palpation appears to be overestimated. Therefore, a potential role for SGUS, especially when the ESSDAI is used as outcome parameter in clinical trials, warrants further investigation. Second, grey-scale histogram analysis and elastography should be evaluated in the target population, to further explore their potential value in diagnosing pSS patients. Third, important steps have been taken to develop a novel SGUS scoring system for the assessment of salivary glands in suspected or confirmed pSS. Herewith, inclusion of SGUS into the classification criteria seems even more justified, as this would rebalance the current classification criteria. SGUS examination should be part of the diagnostic work-up of potential pSS patients.

Take home messages

- SGUS examination should be part of the diagnostic work-up of potential pSS patients.
- Inclusion of SGUS into the classification criteria would rebalance the current criteria.
- Important steps have been taken by a sub-task force of the OMERACT working group to develop a novel semi-quantitative SGUS scoring system.
- Regular calibration exercises should be held among ultrasonographers to overcome potential observer bias.
- Grey-scale histogram analysis and elastography should be evaluated in the target population in order to explore their potential value.
- Detection of mild glandular swelling by palpation appears to be overestimated, a potential role for SGUS warrants further investigation.

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