Primary Sjögren’s Syndrome
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Chapter 3E

Can ultrasound of the major salivary glands differentiate primary Sjögren’s syndrome from other systemic diseases with salivary gland involvement?

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Under submission
Abstract

Purpose: To assess the diagnostic accuracy of ultrasound of the major salivary glands (SGUS) to differentiate primary Sjögren’s syndrome (pSS) from other diseases with salivary gland involvement.

Patients and methods: SGUS was performed in 20 consecutive patients with pSS and 20 consecutive patients with well-established systemic disease, i.e. 5 patients with either sarcoidosis, amyloidosis, HIV infection or HCV infection. Images were scored independently by two blinded observers according to the Hocevar scoring system. Diagnostic accuracy to discriminate between the patient (sub-)groups was explored.

Results: The accuracy of SGUS to differentiate pSS from other systemic diseases was excellent (area under ROC curve of 0.91). The optimal cut-off value to define positive or negative ultrasound for pSS was 15. Sensitivity, specificity, positive predictive value and negative predictive value were high, varying from 85-90%, and diagnostic odds ratio was 51. SGUS was positive in the vast majority of pSS patients (n=18), but also in 2 patients with HIV infection and one patient with sarcoidosis. UTS differed significantly between patients with pSS and other systemic diseases (median 27 vs. 10, p<0.001) as well as between pSS patients and patients with either sarcoidosis, amyloidosis, HIV or HCV infection (all p<0.05).

Conclusion: This pilot study indicates that SGUS has a potentially high diagnostic accuracy to discriminate pSS from associated systemic diseases with salivary gland involvement.

Introduction

The accuracy of B-mode ultrasound to evaluate the involvement of the major salivary glands in primary Sjögren’s syndrome (pSS) and eventually to diagnose the disease continues to be a topic of interest [1,2]. It is generally agreed that salivary gland ultrasonography (SGUS) is a well-tolerated, non-invasive, inexpensive and non-irradiating imaging technique [3]. Thus, there are considerations that in the future, SGUS may be added to the classification criteria for pSS and may even replace more invasive diagnostic tests, like the salivary gland biopsy [2,4-6]. A recent meta-analysis demonstrated that SGUS has a sensitivity, specificity and diagnostic odds ratio of 69%, 92% and 33.9, respectively, to diagnose SS in the major salivary glands [7]. This meta-analysis also detected a considerable variety in the study populations (patient and control groups) used in the included studies. However, none of those studies included a control group of patients with sarcoidosis, amyloidosis, and human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection. These diseases are known to frequently affect the major salivary glands, cause dry mouth or they have similar histopathological features with pSS [8-11]. The aim of this pilot study was to assess the potential diagnostic accuracy of SGUS to differentiate patients with pSS and patients with sarcoidosis, amyloidosis, HIV or HCV infection.

Materials and methods

Patients

Twenty consecutive patients fulfilling the American European Consensus Group Criteria (AECG) criteria for pSS [12] and 20 consecutive patients with well-established systemic diseases mimicking pSS, i.e. 5 patients with sarcoidosis, 5 patients with amyloidosis, 5 patients with HIV infection and 5 patients with HCV infection, were included in this pilot study. The diagnosis of the systemic diseases was made by clinical presentation, histologic proof of granulomatous inflammation, and exclusion of malignancy and infection as alternative cause of granulomas for sarcoidosis, biopsy for amyloidosis and with detection of circulating antibodies and polymerase chain reaction (PCR) for HIV and HCV infection. All patients visited the outpatient clinic of the department of Rheumatology and Clinical Immunology and the department of Internal Medicine, Infectious Diseases Service of the University Medical Center Groningen. All patients with pSS were subjected to SGUS evaluation as part of the routine diagnostic work-up, and patients with sarcoidosis, amyloidosis, HIV infection and HCV infection provided written informed consent in accordance with the requirements of the ethics committee of the University Medical Center Groningen (METC waiver 016/120).
Ultrasonography

All patients were examined with the same ultrasonographic scanner (Esaote MyLab-Se7en, Genova, Italy), equipped with a high resolution linear scanner (4-13MHz). Each patient was scanned in a supine position with the neck slightly extended and the head turned slightly to the opposite side. The parotid glands were examined in both axial and coronal planes, the submandibular glands only in the coronal plane.

The following images were stored from each patient and used: one showing the thyroid gland, one showing the right submandibular salivary gland, one showing the left submandibular salivary gland, two providing an overview of the right parotid gland and two providing an overview of the left parotid gland (Figure 1). Images were anonymized and allocated to a random number.

All images were scored independently by two observers (KD and JFN; for scoring system see below) on the same monitor (MultiSync E231, 23 inches, NEC, Illinois, USA). The observers were blinded for the diagnostic work-up, i.e., salivary gland biopsy, circulating auto-antibodies, salivary gland function tests, tear gland function tests and subjective oral and ocular symptoms. Both observers scored all patients in a random order.

Ultrasonographic assessments

The following ultrasonographic variables were assessed in the parotid and submandibular salivary glands: echogenicity, parenchymal homogeneity, presence of hypoechoogenic areas, presence of hyperechogenic reflections, and clearness of posterior glandular border, according to the Hocevar scoring system [3]:

i. Parenchymal echogenicity was evaluated in comparison with the thyroid gland or when there was coincident thyroid gland disease by surrounding anatomical structures (muscular structures, sub-cutaneous fat). Echogenicity was graded 0 if echogenicity was comparable to the thyroid, and 1 if it was decreased.

ii. Homogeneity was graded 0 for a homogeneous gland, 1 for mild inhomogeneity, 2 for evident inhomogeneity, and 3 for a grossly inhomogeneous gland.

iii. Presence of hypoechoogenic areas was graded 0 for no hypoechoic areas, 1 for a few scattered areas, 2 for several areas, and 3 for numerous hypoechoic areas.

iv. Hyperechogenic reflections in the parotid glands were graded 0 for no hyperechogenic reflections, 1 for a few, scattered, 2 for several, and 3 for numerous hyperechogenic reflections, and in submandibular glands 0 for absent and 1 for present.

v. Clearness of salivary gland borders was graded 0 for clear, regular defined borders, 1 for partly defined borders, 2 for ill-defined borders, and 3 for borders not visible).

Finally, ultrasound total score (UTS) was calculated as the sum of the grades for the five variables described above for all four glands (range 0-48). According to the literature, the cut-off value to define positive or negative ultrasound for pSS was set at 17 [3] and 15 [13]. Discrepancies between the two observers regarding the positivity or negativity of ultrasound for pSS were resolved in a consensus meeting.

Inter-observer reliability in scoring the ultrasonographic images was excellent, with ICC of 0.88 for the UTS. Cohen’s kappa was 0.80 and 0.85 and the percentage of absolute agreement was 90% and 93%, respectively, when cut-off value ≥17 and ≥15 was applied to define positive or negative ultrasound for pSS.
Table 1. Patients’ characteristics.

<table>
<thead>
<tr>
<th>Disease Group</th>
<th>Age median (range)</th>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
<th>Dry mouth &gt;3 months n (%)</th>
<th>Recurrent/ swollen salivary glands n (%)</th>
<th>Need of liquid to swallow food n (%)</th>
<th>Ultrasound total score median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pSS</td>
<td>50 (20-70)</td>
<td>1:1</td>
<td>1:0</td>
<td>0:1</td>
<td>19 (65)</td>
<td>4 (13)</td>
<td>0 (0)</td>
<td>27 (15-40)</td>
</tr>
<tr>
<td>Other systemic diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Sarcoidosis</td>
<td>53 (28-80)</td>
<td>2:3</td>
<td>3 (60)</td>
<td>1 (20)</td>
<td>10 (95)</td>
<td>3 (60)</td>
<td>1 (20)</td>
<td>10 (9-27)</td>
</tr>
<tr>
<td>2. Amyloidosis</td>
<td>74 (53-80)</td>
<td>2:3</td>
<td>3 (60)</td>
<td>0 (0)</td>
<td>4 (60)</td>
<td>0 (0)</td>
<td>3 (60)</td>
<td>10 (6-14)</td>
</tr>
<tr>
<td>3. HIV infection</td>
<td>58 (26-61)</td>
<td>2:3</td>
<td>3 (60)</td>
<td>0 (0)</td>
<td>5 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>10 (6-14)</td>
</tr>
<tr>
<td>4. HCV infection</td>
<td>53 (29-69)</td>
<td>4:1</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>10 (6-14)</td>
</tr>
</tbody>
</table>

Data analysis

Statistical analyses were performed using IBM SPSS Statistics 23 (SPSS, Chicago, IL, USA).

Diagnostic accuracy of SGUS to discriminate between pSS and other systemic diseases was explored using area under the ROC curve (AUC), sensitivity, specificity, Youden’s index, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio (DOR). AUC was interpreted as no discrimination (0-0.5), poor accuracy (0.5-0.7), fair (0.7-0.8), good (0.8-0.9) or excellent (0.9-1.0) [14]. Furthermore, differences in UTS between the patient (sub-)groups were analyzed using the Mann Whitney U test. P values <0.05 were considered statistically significant.

Figure 2. Ultrasonographic images of the major salivary glands of patients with systemic diseases who had positive ultrasound for pSS: a. parotid gland of patient with HIV infection; b. parotid gland of patient with sarcoidosis; c. submandibular gland of patient with HIV infection; d. submandibular gland of patient with sarcoidosis.
Table 2. Ultrasound of major salivary glands versus classification diagnosis (pSS or other systemic disease). The cut-off points to define positive or negative ultrasound for pSS was set at 15 [13] and 17 [3].

<table>
<thead>
<tr>
<th>Cut-off point</th>
<th>15</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>Specificity</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Youden's index</td>
<td>0.75</td>
<td>0.70</td>
</tr>
<tr>
<td>PPV</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>NPV</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>LR+</td>
<td>6.0</td>
<td>5.7</td>
</tr>
<tr>
<td>LR-</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>DOR</td>
<td>51.0</td>
<td>32.1</td>
</tr>
</tbody>
</table>

PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; DOR = diagnostic odds ratio.

Results

Of the 20 included patients with pSS, the median age was 50 years (range: 20-71), 19 were female, and the median UTS was 27 (range: 11-40). Of the 20 included patients with systemic diseases or infectious, the median age was 53 years (range: 25-80), 14 were male, and the median UTS was 10 (range: 6-29; Table 1). Regarding the oral symptoms, 95% of the patients with pSS reported to have daily complaints of dry mouth longer than 3 months, 85% needed liquid, e.g. water, to swallow food and 70% reported recurrent or persistent swelling of the major salivary glands. Interestingly, in the group of patients with systemic diseases, 45% of the patients reported to have daily complaints of dry mouth longer than 3 months, 20% reported recurrent or persistent swelling of the major salivary glands, and 30% needed liquid to swallow food. Table 1 summarizes the patient characteristics of all disease (sub-)groups.

The accuracy of SGUS to discriminate pSS from other systemic diseases was excellent, with area under ROC curve of 0.91 and the optimal cut off value was 15, in accordance with Zhang et al. [13]. The agreement between SGUS positivity and positive diagnosis for pSS was good (κ=0.75 and percentage of absolute agreement was 87.5), with sensitivity of 90%, specificity of 85%, PPV of 86% and NPV of 89% (Table 2). When the cut-off value was set at 17, the sensitivity, PPV, NPV, LR+, LR- and DOR slightly deteriorated (Table 2). UTS was positive in 2 patients with HIV infection and one patient with sarcoidosis (Figure 2), whereas UTS was negative in 2-3 patients with pSS (depending on the cut-off value).

UTS differed significantly between patients with pSS and patients with systemic diseases mimicking pSS; (median 27 vs. 10, p<0.001) as well as between patients with pSS and the subgroup of patients with either sarcoidosis, amyloidosis, HIV or HCV infection (p<0.05; Figure 3).
Discussion

The present pilot study explored the use of SGUS in a representative population of consecutive patients diagnosed with pSS or sarcoidosis, amyloidosis, HIV infection and HCV infection. The latter are systemic diseases that could also affect the major salivary glands, cause dry mouth or have similar histopathological features with pSS. These diseases are considered exclusion criteria for the classification of patients according to the AECG [12], American College of Rheumatology (ACR) [15] and the newly published American College of Rheumatology – European League Against Rheumatism (ACR-EULAR) [16] classification criteria, because patients with these diseases can mimic pSS and thus lead to a false positive diagnosis. This pilot study indicates that SGUS has a potentially excellent diagnostic accuracy to discriminate pSS from associated systemic diseases with salivary gland involvement, viz. area under ROC curve of 0.91. The optimal cut off value was 15 and showed DOR of 51. Furthermore, the median UTS was significantly higher in patients diagnosed with pSS compared to patients with these systemic diseases or infectious diseases.

Interestingly, UTS was positive in 2 patients with HIV infection. The first one (UTS=27) reported having both dry mouth for longer than 3 months and recurrent/swelling of the major salivary glands. The second patient (UTS=18) did not report having any oral clinical symptoms that could point towards SS, i.e. neither dry mouth, nor need of liquid to swallow food nor recurrent/persistent swelling of the major salivary glands. Benign lymphoepithelial cysts (BLEC) are a common manifestation in the HIV-positive patient [10], and it is speculated that they might result in ultrasonographic characteristics resembling pSS. UTS was also positive in one patient with sarcoidosis (UTS=29), who presented at the time of the SGUS examination persistent swelling of the parotid glands. Possibly, the presence of non-caseating granulomas in the parotid glands [11] might have led to this ultrasonographic appearance.

In accordance with our study, Luciano et al. showed that SGUS is a highly specific tool for distinguishing pSS from undifferentiated connective tissue diseases [17], a set of unclassifiable systemic autoimmune diseases that shares clinical and serological manifestations with definite connective tissue diseases, which, however, do not fulfill over time, any of the foreseen classification criteria [18]. Similarly, Simizu et al. investigated SGUS in patients with IgG4-related sialadenitis and whether it can differentiate them from pSS [19]. They concluded that changes in the submandibular glands affected by IgG4-related disease could be easily detected using SGUS and that SGUS could also differentiate IgG4-related disease from pSS [19].

The most important strength of the current study is that we included consecutive patients diagnosed with pSS or another systemic disease, avoiding possible selection bias. Moreover, we focused on the Hocevar scoring system [3]. We chose to use this extensive scoring system as it is one of the most detailed ultrasound scoring systems used today and it can easily be transformed to almost any of the existing ones [7].

As with any pilot study, the number of included patients was limited and, thus, the interpretation of data should be done cautiously. Patients with a systemic disease were at different stages of the disease, i.e., some were just diagnosed while others were being in a long term follow up, and additionally patients were treated with different medications. However, it should be kept in mind that pilot studies are a necessary first step in exploring novel applications, and their principal role is to examine the feasibility of a research enterprise [20], and therefore such limitations are up to some extent expected.

Conclusion

This pilot study indicates that SGUS has a potentially high diagnostic accuracy to discriminate pSS from associated systemic diseases with salivary gland involvement, like sarcoidosis, amyloidosis, HIV infection and HCV infection. Further studies including more patients with different stages of systemic diseases are required to confirm and elucidate these preliminary findings.

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Funding: None
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Effectiveness of imaging modalities for screening IgG4-related dacryoadenitis and sialadenitis (Mikulicz’s disease) and for differentiating it from Sjögren’s syndrome (SS), with an emphasis on sonography. Arthritis Res Ther 2015;17:223.


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