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Ultrasonography of salivary glands in primary Sjögren's syndrome. A comparison with magnetic resonance imaging and magnetic resonance sialography of parotid glands

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***Objectives*. To evaluate ultrasonography (US) of salivary glands in primary Sjögren's syndrome (SS) and to compare US with parotid magnetic resonance (MR) imaging and MR sialography.**
***Methods*. US examination of parotid, submandibular and sublingual glands was performed on 27 patients with primary SS, 27 healthy controls and 27 symptomatic controls without SS. The results were compared with parotid MR imaging and MR sialography and the clinical features of the patients.**
***Results*. Salivary gland abnormalities, parenchymal inhomogeneity or adipose degeneration, were visualized in 21 (78%) SS patients, in one healthy control and in two symptomatic controls by US. Eighteen (67%) patients had changes in the parotid and submandibular glands and 8 (30%) changes in the sublingual glands. In the comparison, MR sialography was found to be the most sensitive method (96%), followed by MR imaging (81%) and US (78%), in detecting glandular changes. The specificity of US was 94%. The US and MR results were related to anti-Ro/SSA positivity but not to saliva secretion. The focus scores were related only to parotid MR imaging findings.**
***Conclusions*. US, MR imaging and MR sialography with modern technology have reached such a good accuracy in visualizing glandular structural changes that they are promising alternatives to the conventional invasive examinations in the diagnostics of SS.**

KEY WORDS: Diagnostics, Submandibular glands, Sublingual glands.

Conventionally, minor salivary gland biopsy and X-ray sialography have been considered the cornerstones of the diagnosis of Sjögren's syndrome (SS) [1–3]. However, they are both invasive examinations that may cause inconvenience and a risk of complications to the patient [1, 4, 5], and therefore new, reliable, non-invasive methods for the detection of diagnostic glandular changes are sought. In the recent years, rapid technical development has improved the accuracy of non-invasive radiological methods, including ultrasonography (US) [6–16], magnetic resonance (MR) imaging [15, 17–23] and MR sialography [23–29]. These methods have been widely replacing conventional invasive examinations in scientific research as well as in clinical practice. According to available data, MR sialography and MR imaging seem to yield quite definitive information of the morphological changes of salivary glands in SS [19–23], while the US results have been more variable and lack data of studies with the most recent technology [13–16].

The purpose of our study was to examine salivary glands in primary SS patients and in healthy and symptomatic controls by using modern US equipment in order to evaluate the diagnostic value of the method. The US results were also compared with parotid MR imaging and MR sialography and the clinical features of the patients.

Subjects and methods

Subject characteristics

Twenty-seven consecutive outpatients with primary SS from the Division of Rheumatology at Oulu University Hospital constituted the patient group. The patients had to fulfil the American–European Consensus Group Classification Criteria for primary SS [30] to be eligible. Fifteen (55%) patients had a new and 12 a previous diagnosis of SS. The healthy control group consisted of 27 age- and sex-matched volunteers, mainly from among the medical staff of the hospital. The symptomatic control group consisted of 27 subjects with suspected SS. They had either sicca symptom ($n = 25$) and/or salivary gland swelling ($n = 6$), but they did not fulfil the international classification criteria for SS [30]. Subject characteristics are shown in Table 1. All patients and controls gave their informed consent. The study protocol was approved by the Ethical Committee of the University of Oulu.

Methods

Interviews and careful physical examinations, including Schirmer's I test (mm/5 min) and unstimulated whole saliva sialometry

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TABLE 1. Characteristics of patients with primary Sjögren's syndrome (SS), healthy controls and controls with sicca symptom or salivary gland swelling without SS

	Patients with SS ($n=27$)			Healthy controls ($n=27$)			Symptomatic controls without SS ($n=27$)*		
Variable	*n*	Mean ± S.D.	Range	*n*	Mean ± S.D.	Range	*n*	Mean ± S.D.	Range
Age		50 ± 14	18–67		50 ± 10	28–67		45 ± 6	29–56
Female/male	26/1			25/2			27/0		
Dry eyes	27			0			22		
Dry mouth	27			0			24		
Schirmer's I test ≤5 mm	21	4.6 ± 5.7 2.5**	0–22	0	15 ± 9 11**	5.5–35	7	13 ± 11 7.5**	0–40
UWSF ≤ 1.5 ml	25	0.9 ± 0.7	0–3.8	0	4.4 ± 3	1.6–14	7	4.1 ± 4.2	0.3–21
Focus score ≥ 1	14/15†	2.3 ± 1.6 2.2**	0.8–5.0				2/16†	0.7 ± 1.3 0.4**	0–5.0
Anti-SSA/SSB	20			0			1		
Disease duration‡		12 ± 8	1–30					5 ± 4	1–15

UWSF, unstimulated whole saliva flow per 15 min.

*In the symptomatic control group two patients had sarcoidosis, one had Kartagener's triad, one had chronic idiopathic sialadenitis, eight had fibromyalgia, four had anxiety or depression, and six had medication prone to causing sicca symptoms (β-blocker, diuretic or antidepressant).

**Median.

†Number of biopsies taken for this study. A biopsy was taken for diagnostic purposes only if it had not been taken earlier.

‡Years elapsed since the first symptom; sicca symptom or salivary gland swelling.

(ml/15 min) were performed on all patients and controls. All imaging data were compared with the following clinical features of the patients: salivary and tear flow rates, age, disease duration, presence of anti-Ro/SSA or anti-La/SSB, level of hypergammaglobulinaemia, presence and number of systemic disease manifestations, and the focus scores of the 15 patients with minor salivary gland biopsy taken for this study.

High-resolution US examination was performed on all patients and controls by an experienced radiologist (RT) using a GE Logiq 500 MR3 (GE Medical Systems, Milwaukee, WI, USA) real-time scanner with an 11 MHz linear transducer. The deep lobe of the parotid gland was also examined with a 9.6 MHz linear transducer. The length of the contact surface of the transducer was 38 mm, and resolution 0.3 mm to an axial depth of 0–4 cm.

US images were analysed independently by two radiologists (RT, MP) blinded to the clinical diagnosis and MR results. In cases of discrepancy, consensus was negotiated. The parenchymal structure of the glands was categorized into five stages: stage 0 = normal; stage 1 = mild parenchymal inhomogeneity (PIH) (hypoechoic areas <2 mm); stage 2 = evident PIH (hypoechoic areas of 2–6 mm); stage 3 = gross PIH (hypoechoic areas >6 mm); and stage 4 = adipose degeneration of the gland (adipose tissue echogenicity and parenchymal atrophy). The other features that were registered were hyperechoic bands, the size of the gland, separate cysts (visible as hypoechoic or anechoic lesions) and ducts. MR imaging and MR sialography examinations were conducted on 27 patients and on seven healthy controls as described earlier [23].

Statistical analysis

SPSS 9.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analyses. The associations between continuous and ordinal variables were analysed by Spearman's rank correlation. Cohen's kappa test was used for the analysis of inter-observer variation. *P*-values ≤0.05 were considered statistically significant. Sensitivity, specificity, accuracy, positive and negative predictive values were calculated as described previously [31].

Results

Ultrasonography

PIH and adipose degeneration. Twenty-one (78%) patients had abnormal findings on US examination. Eighteen (67%) patients had PIH or adipose degeneration of parotid glands (Table 2, Fig. 1), 18 (67%) PIH of the submandibular glands, and eight (30%) mild PIH (stage 1) of the sublingual glands. Two patients with PIH of the sublingual glands had normal parotid and submandibular findings. The findings were bilateral in all patients. One healthy control had adipose degeneration (stage 4) in her parotid glands and two symptomatic controls (one with sarcoidosis and one with Kartagener's triad) had evident PIH (stage 2) in their parotid glands and mild PIH (stage 1) in their submandibular glands. Other controls had normal findings.

TABLE 2. Structural classifications of parotid and submandibular glands by ultrasonography in patients with primary Sjögren's syndrome

	Structure of submandibular gland*				
Structure of parotid gland	Normal	Mild PIH	Evident PIH	Gross PIH	Total
Normal	8	1			9
Mild PIH		2	2		4
Evident PIH	1	1	3		5
Gross PIH		1	1		2
Adipose degeneration		2	4	1	7
Total	9	7	10	1	27

*$r = 0.73$, $P < 0.0001$.

Comparison between glands. The parenchymal structural scores of parotid and submandibular glands were associated with each other ($r = 0.73$, $P < 0.0001$), while there was no relationship between the parenchymal stages of sublingual and parotid or sublingual and submandibular glands. There were three patients with normal parotids, but with stage 1 changes in either sublingual (two patients) or submandibular (one patient) glands.

The sensitivity of US was 78%, specificity 94%, accuracy 85%, positive predictive value 88% and negative predictive value 88%, if PIH and adipose degeneration (stages 1–4) were considered as a sign of primary SS. The kappa test for inter-observer variation was very good (0.83). The other salivary gland findings (hyperechoic bands, separate cysts or ducts, and the size of the gland) were not associated with the parenchymal classification and did not give any additional information for the diagnostics.

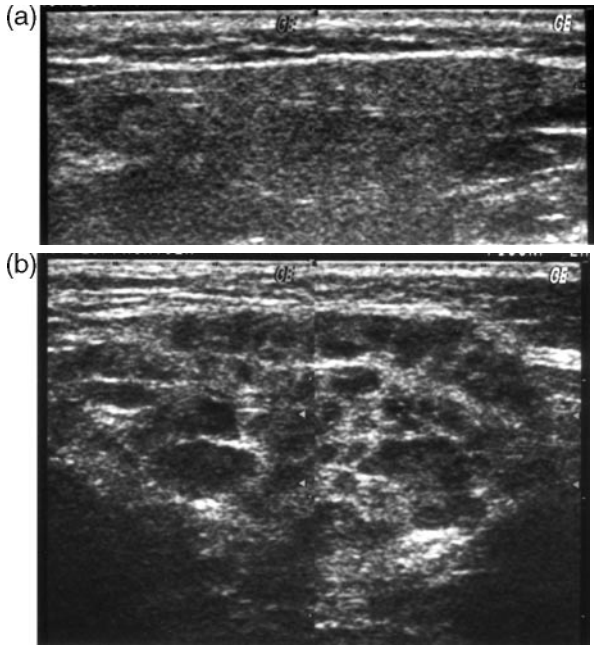

FIG. 1. Ultrasonographic images of parotid glands with (a) normal parenchyma and (b) gross parenchymal inhomogeneity (grade 3).

US compared with MR

Twenty-two (81%) patients with primary SS had abnormal parenchymal findings (nodular parenchyma or adipose degeneration) on MR images and 26 (96%) on MR sialography (ductal system changes or cavities) of parotid glands, while all the seven healthy controls had normal findings. These results have been described in more detail earlier [23]. The parenchymal scores of parotid glands on US and MR images were closely related to each other ($r = 0.76$, $P < 0.0001$).

Clinical associations

The presence of anti-Ro/SSA and/or anti-La/SSB antibodies was associated with the parenchymal findings on parotid MR imaging ($P < 0.01$) and US ($P < 0.05$), but not with submandibular or sublingual US. The focus scores of the 15 SS patients with a recent minor salivary gland biopsy were related to the parotid changes on MR imaging ($r = 0.6$, $P < 0.05$), but the association with the US findings was not significant. The results of neither US nor MR examinations were related to tear or saliva secretion, age, disease duration, the presence or number of systemic disease complications or hypergammaglobulinaemia in the patients.

Discussion

Abnormal findings (either PIH or adipose degeneration) were found in 21/27 (78%) patients, and in 1/27 (4%) healthy and 2/27 (7%) symptomatic controls in US of salivary glands. The findings of parotid and submandibular glands were in concordance with each other and were equally frequent, though adipose degeneration was only seen in parotid glands. The sublingual glands seemed to be less severely affected, although two patients with mild PIH of the sublingual glands had normal parotid and submandibular findings. Thus, to achieve the best sensitivity of US, all salivary glands should be examined. In a comparison of the US and MR methods, MR sialography seemed to be the most sensitive method (96%), followed by MR imaging (81%) and US [23]. The specificity of US was 94%. We could not assess the definitive specificity of MR methods reliably because they were only performed on seven healthy controls, although all controls had normal findings [23].

Heterogeneous, or nodular, parenchyma is considered the most accurate finding of SS patients' salivary glands in both US and MR imaging. The finding of adipose degeneration differs significantly from the stages of PIH and cannot be graded by the same criteria. There are some previous data to show that this finding may be unspecific, as the amount of fat tissue increases in salivary glands with age [22, 32, 33] and in serum hyperlipidaemia [34, 35]. On the other hand, it has also been related to SS [21, 22], higher grades of X-ray sialography and focus score, and decreased saliva secretion [19, 21, 22]. Although we found one healthy control with adipose degeneration of parotid glands on US (MR imaging was not performed on her), the SS patients with such findings clearly showed features of advanced disease. They were all anti-Ro/SSA-positive and had manifestations of active systemic disease. Their focus score levels were higher (3.8 ± 1.7 *vs* 2 ± 1) and disease duration longer (8 ± 4.5 *vs* 3 ± 2.8), and they were younger (43 ± 10 *vs* 50 ± 14 yr) than the other patients. All these features together suggest that, although this finding is somewhat unspecific, it may also reveal the most advanced glandular disease stage in SS.

Methodology

Conventionally, X-ray sialography, scintigraphy and labial gland biopsy are used in the evaluation of salivary glands in the diagnostics of SS. The sensitivity of X-ray sialography has ranged from 66% to 95% in different studies [5, 36, 37], while false positive results have been observed in up to 30–40% of controls [7, 37]. Also, the experience of an observer may be crucial to the results [37]. Sensitivity of scintigraphy has been 73–80% [38, 39] and specificity quite poor in several studies [38–43]. In the validation process of the European criteria, the sensitivity and specificity of X-ray sialography, scintigraphy and labial gland biopsy were assessed in patients with primary and secondary SS, in patients with connective tissue disease without SS, and in patients with oral or ocular symptoms simulating SS. A total of 66 subjects were examined with X-ray sialography, 105 with scintigraphy, and 182 with labial gland biopsy. The sensitivity and specificity were 72 and 92% respectively for X-ray sialography, 82 and 62% for scintigraphy, and 82 and 86% for labial gland biopsy (focus score ≥ 1) [44].

Since 1988, a growing number of studies evaluating the salivary glands of SS patients with non-invasive radiological methods has been published. The equipment used in these studies has markedly improved in resolution over the years. US was the first method of interest. The results of US studies have been variable, showing sensitivities of 47–91% and specificities of 82–94% [6–16]. In recent years, more attention has been given to MR imaging and MR sialography. According to the available data, MR sialography seems to give quite accurate information about glandular morphology in primary SS (accuracy 83% and good correlation with X-ray sialography) [27, 29], followed by MR imaging (sensitivity 71–100%, specificity 93–100%) [15, 18–20], although the number of symptomatic controls has been quite limited in these studies. To the best of our knowledge, there is one previous study in the recent literature comparing US and MR imaging in the diagnostics of SS [15]. In this study, the two methods were equally accurate in diagnosing SS. Our results are not directly comparable with those obtained earlier because we used a newer technology with an 11 MHz transducer in US and a higher magnetic field strength and a surface coil instead of a head coil in MR [23], which yields better resolution. Also, several different classification criteria in the diagnostics of SS and variable gold standards for the definition of the diagnostic value of findings have been used in these studies.

Limitations of the study

As one of our main goals was to examine the findings of major salivary glands in primary SS with modern US technology, we included both previously (45%) and newly (55%) diagnosed patients in the patient group, which may have affected the sensitivity results of our study. We also included all subjects with suspected SS in the symptomatic control group if they did not fulfil the American–European classification criteria for SS. This kind of selection leads to a heterogeneous control group, although it represents the clinical circumstances at a rheumatological outpatient clinic. In clinics, the main role of labial gland biopsy is in patients newly presenting with possible SS who are anti-Ro/La negative and have three out of the four criteria of dry eyes and mouth. These would be the cases where a salivary gland biopsy, or an imaging examination, would determine the diagnosis. We had only seven control subjects with this kind of picture, so we could not test US against labial biopsy in this setting.

Roles of US, MR imaging and MR sialography in the diagnosis of SS

US, MR imaging and MR sialography visualize the salivary gland in its physiological state without artefacts caused by intraductal contrast media or biopsy procedures, not to mention the lack of inconvenience and risk of complications to the patient. With modern equipment, they can yield such a definitive picture of the glandular structural changes that they are promising alternatives to conventional examinations, and their use is likely to increase both in clinical practice and in scientific research in the near future. However, comparative multicentre studies should be conducted to confirm their diagnostic value and cost-effectiveness in SS before they can be widely accepted and included in the classification criteria of SS.

According to the available data, US is a good candidate for a first-line radiological examination in the diagnosis of SS, because it is much cheaper and more widely available than MR and gives an opportunity to evaluate all salivary glands easily at the same time. However, it should be kept in mind that US is operator-dependent, and the examinations should be centralized to radiologists who are experienced in soft tissue US. MR sialography and MR imaging, especially in combination, can yield comprehensive information on both parenchymal and ductal system changes of the gland and seem to have better sensitivity and specificity compared to US, and could thus also be considered as the first choice methods, if they are available.

Rheumatology	Key messages
	• US, MR imaging and MR sialography with modern technology yield definitive picture of glandular structural changes in SS. They are promising alternatives to the conventional invasive examinations in the diagnosis of primary SS.

The authors have declared no conflicts of interest.

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