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Ultrasonography of salivary glands in primary Sjögren's syndrome: a comparison with contrast sialography and scintigraphy

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Objective. To compare ultrasonography (US) of salivary glands with contrast sialography and scintigraphy, in order to evaluate the diagnostic value of this method in primary SS (pSS).

Methods. The diagnostic value of parotid gland US was studied in 77 patients with pSS (male/female ratio 3/74; mean age 54 yrs) and in 79 with sicca symptoms but without SS. The two groups were matched for sex and age. Imaging findings of US were graded using an ultrasonographic score ranging from 0 to 16, which was obtained by the sum of the scores for each parotid and submandibular gland. The sialographic and scintigraphic patterns were classified in four different stages. The area under receiver operating characteristic curve (AUC-ROC) was employed to evaluate the screening method's performance.

Results. Of the 77 patients with pSS, 66 had abnormal US findings. Mean US score in pSS patients was 9.0 (range from 3 to 16). Subjects without confirmed pSS had the mean US score 3.9 (range from 0 to 9) ($P < 0.0001$). Results of sialography showed that 59 pSS patients had abnormal findings at Stage 1 ($n = 4$), Stage 2 ($n = 8$), Stage 3 ($n = 33$) or Stage 4 ($n = 14$), and 58 patients had abnormal scintigraphic findings at Stage 1 ($n = 11$), Stage 2 ($n = 18$), Stage 3 ($n = 25$) or Stage 4 ($n = 4$). Through ROC curves US arose as the best performer (AUC $= 0.863 \pm 0.030$), followed by sialography (AUC $= 0.804 \pm 0.035$) and by salivary gland scintigraphy (AUC $= 0.783 \pm 0.037$). The difference between AUC-ROC curve of salivary gland US and scintigraphy was significant ($P = 0.034$). Setting the cut-off score >6 US resulted in the best ratio of sensitivity (75.3%) to specificity (83.5%), with a likelihood ratio of 4.58. If a threshold >8.0 was applied the test gained specificity, at the cost of a serious loss of sensitivity (sensitivity 54.5%, specificity 97.5%, likelihood ratio 21.5).

Conclusions. Salivary gland US is a useful method in visualizing glandular structural changes in patients suspected of having pSS and it may represent a good option as a first-line imaging tool in the diagnostics of the disease.

Key words: Sjögren's syndrome, Salivary glands, Ultrasonography, Sialography, Salivary gland scintigraphy, Diagnosis.

Introduction

Sjögren's syndrome (SS), also known as 'autoimmune exocrinopathy' [1] or 'autoimmune epithelitis' [2], is a chronic inflammatory disease that primarily affects females. It is characterized clinically by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) and histologically by lymphocytic infiltration and destruction of the salivary and lachrymal glands [2]. The term primary SS (pSS) applies to those patients in whom SS is not associated with other autoimmune diseases [2]. In spite of the recently published classification criteria proposed by the American–European Consensus group in 2002 (which also serve as diagnostic criteria) [3], the evaluation of salivary gland involvement in SS is still a matter of debate. In addition to standard tests for assessment of salivary gland involvement, namely the unstimulated salivary flow test, salivary gland scintigraphy and contrast sialography, other methods have been studied such as ultrasonography (US), MRI, CT [4–6]. These diagnostic tools have widely replaced conventional invasive examinations in scientific research as well as in clinical practice. Among them, US of the major salivary glands seem the most attractive as a non-invasive, inexpensive and non-irradiating investigation. According to available data, it seems to yield quite definitive information about the morphological changes of salivary glands in SS. In recent years, also, colour Doppler US has been used to evaluate the vascular anatomy of the salivary glands and to analyse the physiological changes in blood flow that occur during salivary stimulation in the diseased glands of SS patients [7–13].

The purpose of this multi-centre cross-sectional study was to examine salivary glands in pSS patients and in symptomatic controls by using modern US equipment in order to determine whether US can take the place of contrast sialography or scintigraphy as an alternative technique for the assessment of salivary gland involvement in SS.

Materials and methods

Patients

Patients who had been referred to the Department of Rheumatology of the Università Politecnica delle Marche, to the Department of Rheumatology of Sapienza University of Rome, to the Department of Rheumatology of the University of Padova and to the Rheumatology Units of the University of Perugia for symptoms suggesting sicca syndrome were evaluated using the proposed recently criteria revised by the American–European Consensus Group (AECG) [3]. Patients who had been treated during the last 12 months with either immunosuppressive agents or other drugs known potentially to cause a reduction in salivary and lachrymal secretions were not included in the study. Only those patients in whom a minor salivary glands biopsy was available were selected for inclusion in the present research. All subjects gave informed consent to participate in the study, which

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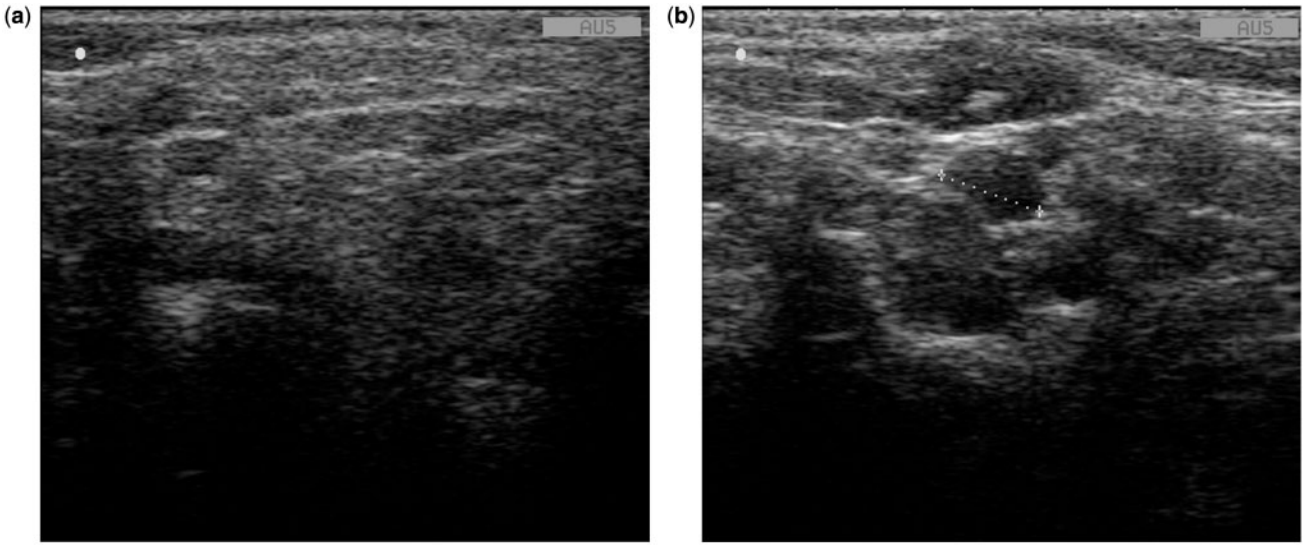

FIG. 1. Sonography of a parotid gland in patients with pSS. (**a**) Gland with irregular echogenicity and multiple hyperechoic bands and hypoechoic areas (grade 3); (**b**) gland with irregular contour, multiple large hypoechoic areas and multiple cysts (>6 mm) resulting in severe damage of the parenchymal architecture (grade 4).

was performed according to the criteria of the Helsinki Declaration and the study was approved by the institutional review boards for human research.

Clinical and histopathological evaluation

A complete SS work-up was available in all patients, including data on whole and gland-specific salivary involvement, level of subjective complaints and disease duration. Disease duration was defined as the time from first complaints related to oral dryness up to the US evaluation stage. All patients were asked to come to four Departments of Rheumatology between 9 a.m. and 11 a.m., having fasted and not brushed their teeth, rinsed their mouth or smoked tobacco for at least 1 h before the examination took place. Six questions to assess both ocular and oral involvement were given to each patient [14]. Information on related treatment was collected at the same time. Besides the questionnaire, all patients were subjected to a Schirmer-I test, Saxon test and serological tests. In these 156 subjects, minor salivary glands (MSGs) were excised through the mucosa of the lower lip within 3 weeks after the imaging studies. A minimum of four minor salivary glands per biopsy was obtained. Focus score was determined on the basis of number of inflammatory cell aggregates containing >50 lymphocytes/4 mm^2 of salivary gland tissue [15]. A diagnosis of SS syndrome was made if at least one focus (focal sialadenitis) was found (Grades 3 and 4) [3]. The MSG biopsy specimens were examined separately by two observers who were unaware of the clinical findings. The differences between the two sets of results were negligible. The inter-observer agreement (k-value) in the evaluation of the MSG biopsy specimens, evaluated in a sample of 31 subjects, was 0.783.

Laboratory investigations

An indirect immunofluorescence procedure using Hep-2 cell substrates was employed to detect the presence and titre of ANA. The serum levels of RF were evaluated by laser nephelometry. ANA titres >1 : 160 and RF levels >40 IU/ml in at least two consecutive determinations were considered positive. Anti-SSA/Ro and anti-SSB/La were detected by counter-immunoelectrophoresis.

Ultrasonographic examination

On the same day of the clinical examination, all patients underwent a US assessment by a rheumatologist or radiologist experienced in US and blinded to the results of the clinical assessment. US examinations were performed using an TECHNOS MP (ESAOTE Biomedica, Genoa, Italy) equipped with two broadband linear probes (7.5–10.0 MHz). Each patient was scanned in the supine position with the neck hyperextended and the head turned a little to the opposite side. The parotid glands were examined in both axial and coronal planes and the submandibular glands only in coronal ones. The following US parameters were recorded: parenchymal homogeneity, echogenicity, size of the glands and posterior glandular border. Each of these parameters was scored according to previously described scoring system [13]. A sonographic score, ranging from 0 to 16, was obtained from the sum of the scores (0–4) for each parotid and submandibular gland. A US pattern was considered abnormal if both parotids or both submandibular glands exhibited a minimum score of 1. The characteristic sonographic pictures on score 3 and 4 in SS are depicted in Fig. 1a and b. Each patient evaluation took <10 min, and representative images were archived. Inter-observer reliability was determined by comparing the findings obtained by one of the rheumatologists experienced in US (A.I.) and those of an experienced radiologist (M.C.) who examined 48 parotid and submandibular glands in a random subset of 12 patients. Each examiner performed the US assessments independently and sequentially while blinded to all other study data. Intra-observer reliability was assessed by blinded rescoring of the archived US images in the same subset 2 months after the original US assessment.

Sialographic evaluation

Conventional sialography was performed by using standard X-ray equipment for skull imaging. Before contrast-enhanced images, conventional radiographs were obtained in lateral projection to detect grossly radiopaque sialoliths. Patients were in orthostatic position, sat on a chair, with head in rest position and mildly hyperextended. After identification of the orifice of the Stensen or Wharton duct, the orifice was incannulated with a 24 Gauges catheter [Gallini, Medical Devices, Mirandola (MO), Italy] or with a Manashil catheter (COOK, Bjaeverskov, Denmark). In patients whose ducts were difficult to identify, salivation was stimulated by using a lemon mouth swab (especially for cannulation of the Wharton duct). Conventional films were obtained after manual injection of 0.5–2 ml of non-ionic contrast medium (Iopamiro 300 mgI/ml, Bracco, Milano, Italy). The sialographic patterns obtained were classified in different stages, determined on

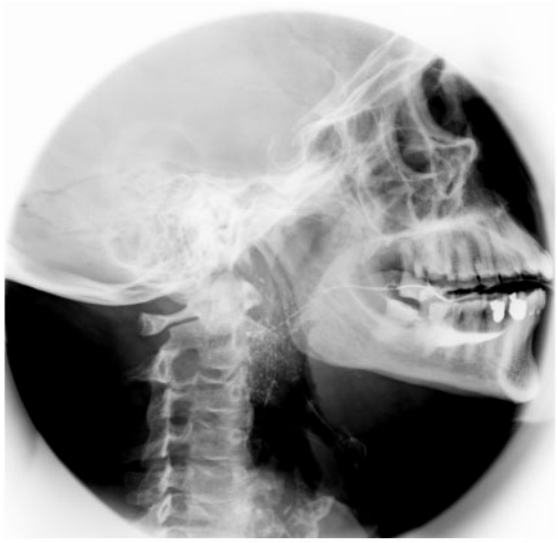

FIG. 2. Sialography of a parotid gland in lateral view shows chraracteristic globular pattern of sialectasia in a patient with pSS.

the basis of lateral views, according to the criteria of Rubin and Holt [16]: Stage 0 = normal; Stage 1 = punctuate, diffuse contrast material collection ≤1 mm in diameter; Stage 2 = globular, contrast material collection 1–2 mm in diameter (Fig. 2); Stage 3 = cavitary, contrast material collection >2 mm in diameter; Stage 4 = destructive [16].

Scintigraphic measurements

Patients were injected intravenously with 110 MBq technetium pertechnetate (^{99m}Tc) and images were obtained immediately after injection to follow the accumulation phase. The patient lay supine and the camera was positioned frontally. A dynamic study of 40–45 min with 30 s per frame was carried out. Stimulation with citric acid was performed 25 min later, after which the secretory phase was followed for over 20–25 min. Salivary gland scintigraphic data were gathered with a gammacamera with a low-energy general purpose collimator. In the dynamic image sets, the four major salivary glands (submandibular and parotid glands) were followed and the mouth and a background region on the brain were outlined to generate background curves for subtraction. The scintigraphic stages were determined according to the criteria proposed by Schall *et al.* [17] and Daniels *et al.* [18]. The criteria comprised five stages: Stage 0 (normal)—rapid uptake, progressive increase in concentration and prompt excretion into the oral cavity within the first 10 min; Stage 1 (mild)—relatively normal salivary dynamics but a delay in the entire time sequence and absence of excretion into the oral cavity by 10 min; Stage 2 (moderate)—decreased uptake and concentration and absence of excretion into the oral cavity by 20 min; Stage 3 (severe)—markedly decreased uptake and concentration and absence of excretion into the oral cavity by 60 min; Stage 4 (very severe)—complete absence of active concentration and the oral cavity may even appear as a negative defect at 60 min. Decreased uptake and concentration and delayed excretion on salivary gland scintigraphy (Stage 1 or more) were considered abnormal.

Statistical analysis

Data were submitted for statistical analysis using MedCalc (version 9.3 for Windows XP) in order to calculate receiver operating characteristic (ROC) curves, and the Statistical Package for the Social Sciences (SPSS) version 11.0 was used for the remaining statistical procedures. Parametric techniques may be applicable for certain ordinal level data; however, our data was generally not normally distributed (Kolmogorov–Smirnov test for normal distribution), and therefore, the use of non-parametric techniques provided a more conservative estimate of statistical significance. Where appropriate, median and interquartile ranges are given, as well as mean and S.D. The differences among the groups were computed by the Mann–Whitney U-test and Kruskal–Wallis one way analysis of variance for continuous variables or ordinal scaled scores and Fisher's exact test for categorical variables. Inter-observer reliability was determined by the unweighted κ-statistics. Discriminant validity was assessed by ROC curve analysis to compare the ability of US to discriminate between pSS and control patients, in comparison with conventional contrast sialography and scintigraphy of the salivary glands. ROC curves were plotted for each model to determine the area under the curve (AUC) and the sensitivity (probability that a test result will be positive when the pSS is present), specificity (probability that a test result will be negative when the pSS is not present) and positive likelihood ratio (LR) [19]. The LR combines information about the sensitivity and specificity. An LR expresses the addition that a given level of a diagnostic tests results would be expected in a patient with (as opposed to someone without) the target disorder. The AUC was used to evaluate the diagnostic performance of the test. The non-parametric Wilcoxon's signed-rank test was used for calculation and comparison of the areas under the ROC curves (AUC-ROCs) derived from the sample of patients, as suggested by Hanley and McNeil [20].

Results

Patients

Using the AECG classification criteria for SS [3], 77 patients were classified as pSS (male/female ratio 3/74; mean age 54 yrs, S.D. 12.1, range 30–78 yrs) and 79 patients as negative for pSS (male/female ratio 6/73; mean age 53 yrs, S.D. 12.3, range 24–81 yrs). This control group complained of dry mouth due to other diseases, such as diabetes mellitus ($n = 14$), fibromyalgia ($n = 19$), hyperlipidaemic states ($n = 10$), chronic liver diseases ($n = 8$), hypothyroidism ($n = 5$) and anxiety and/or depression ($n = 14$). In the other nine patients in whom pSS was excluded, histopathological findings showed no inflammatory infiltrate (grade 0 or 1); therefore, the cause of xerostomia in these patients remained undiagnosed. Therefore, none of them fulfilled the aforementioned AECG criteria for the diagnosis of pSS [3]. The mean duration of subjective xerostomia in the pSS patients was 2.9 yrs (range 6 months–10 yrs), which was similar to that of the controls (mean 2.8 yrs, range 4 months–12 yrs). In addition, there was no statistically significant difference between these two groups in the use of anti-cholinergic drugs, and smoking. On the other hand, the difference between the pSS and symptomatic controls was statistically significant for objective features of dry eyes ($P = 0.003$) and dry mouth ($P < 0.001$) and for presence of anti-Ro/SSA and/or anti-La/SSB. Forty of the 77 patients (51.9%) with pSS were anti-Ro/SSA and/or anti-La/SSB positive, 31/77 were ANA positive (40.3%), 29/77 were FR positive (37.7%) and none of the patients with sicca symptoms but without pSS were anti-Ro/SSA or anti-La/SSB positive. Focal sialadenitis was observed in 69/77 patients (89.6%) with pSS.

Inter- and intra-observer agreement in imaging assessment

The reliability of imaging techniques was assessed in 12 pSS patients. The inter-observer reliability showed an overall agreement of 89, 82 and 78% for the presence/absence of parenchymal homogeneity, echogenicity, size of the glands and posterior glandular border, with k-values of 0.832, 0.791 and 0.715, respectively. The intra-observer reliability US assessment showed an overall agreement of 91, 88 and 85%, with k-values of 0.852, 0.821 and 0.804%, respectively. The inter-observer agreements in staging of

disease on contrast sialography and salivary gland scintigraphy were excellent, with *k*-values of 0.791 and 0.843, respectively.

US compared with contrast sialography and parotid gland scintigraphy

Among the 77 patients with pSS, 66 (85.7%) had abnormal US findings (score ≥1 in both parotids or both submandibular glands). The findings of parotid and submandibular glands were in concordance with each other and were equally frequent. The US score was calculated by summing the grades obtained by the evaluation of all four glands and based on the assessment of the five observed parameters. The mean US score in pSS patients was 9.0 (range from 3 to 16). Subjects without confirmed pSS had a mean US score of 3.9 (range from 0 to 9; $P < 0.0001$). From the results of the contrast sialography, 59 pSS patients had abnormal findings of Stage 1 (punctate; $n = 4$), Stage 2 (globular; $n = 8$), Stage 3 (cavitary; $n = 33$) or Stage 4 (destructive; $n = 14$). Fifty-eight pSS patients had abnormal scintigraphic findings of Stage 1 (mild; $n = 11$), Stage 2 (moderate; $n = 18$), Stage 3 (severe; $n = 25$) or Stage 4 (very severe; $n = 4$). The scores of parotid glands on contrast sialography and scintigraphy were closely related to each other ($\chi^2 = 65.53$, $P < 0.0001$). A true-positive result on US, contrast sialography and salivary gland scintigraphy was seen in 46 pSS patients. A false-negative result for all three imaging methods was present in three patients. Of the 79 patients in whom the pSS was excluded, 21 false-positive cases were seen on US, 19 cases on contrast sialography and 33 cases on scintigraphy.

Diagnostic accuracy of imaging diagnostic tests

ROC curves were constructed by computing the sensitivity and specificity of different tests and their accuracy was measured by the AUC-ROC. The calculated contrast sialography AUC-ROC (0.804 ± 0.035; 95% CI 0.733, 0.864) was intermediate between the salivary gland US AUC-ROC curve (0.863 ± 0.030; 95% CI 0.799, 0.913) (differences between areas $= 0.059 \pm 0.039$; 95% CI –0.017, 0.134; $P = 0.129$) and the AUC of the salivary gland scintigraphy ROC curve (0.783 ± 0.037; 95% CI 0.710, 0.845) (differences between areas $= 0.021 \pm 0.044$; 95% CI –0.065, 0.108; $P = 0.629$). The difference between the US AUC-ROC and salivary gland scintigraphy ROC curve was significant (differences between areas $= 0.080 \pm 0.038$; 95% CI 0.006, 0.154; $P = 0.034$), reflecting the accuracy of the US diagnostic assessment. Our findings are represented in Fig. 3. From the ROC curves we computed the optimal cut-off points, corresponding with the maximum sum of sensitivity and specificity. These theoretically optimal upper limits of reference values and corresponding values of positive likelihood ratio are shown in Tables 1–3. For the US score (on a scale of 0–16) and optimal cut-off point >6 comes close to maximizing both sensitivity and specificity. With this optimal cut-off point, sensitivity was 75.3% and specificity was 83.5% (LR 4.58). If a threshold >8.0 was applied the test gained specificity, at the cost of a serious loss of sensitivity (sensitivity 54.5%, specificity 97.5%, likelihood ratio 21.5; Table 1). For the contrast sialography and salivary gland scintigraphy at threshold >1, sensitivity were 72.7 and 70.1%, and specificity were 84.9 and 82.3%, respectively (Tables 2 and 3).

Discussion

Salivary gland involvement in SS is usually evaluated by contrast sialography or labial gland biopsy [3]. Although these two procedures are believed to be the most sensitive and specific diagnostic approaches, their usefulness as a screening test is hampered by their invasive nature [21, 22]. The sensitivity of contrast sialography has ranged from 66% to 95% in different studies [23–25], while diagnostic specificity of parotid sialographic changes in SS is affected by two lines of evidence. First, the sialographic patterns associated with SS are also seen in glands with chronic

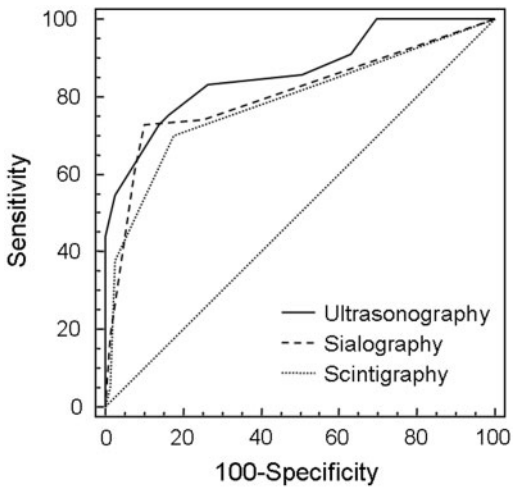

FIG. 3. ROC curves for the performance of the salivary gland US, contrast sialography and scintigraphy in discriminating between pSS and symptomatic controls.

TABLE 1. Sensitivity, specificity (with 95% CI) and positive LR of salivary gland US score

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR
≥0	100.00	95.3, 100.0	0.00	0.0, 4.6	1.00
>0	100.00	95.3, 100.0	21.52	13.1, 32.2	1.27
>1	100.00	95.3, 100.0	22.78	14.1, 33.6	1.30
>2	100.00	95.3, 100.0	30.38	20.5, 41.8	1.44
>3	90.91	82.2, 96.3	36.71	26.1, 48.3	1.44
>4	85.71	75.9, 92.6	49.37	37.9, 60.9	1.69
>5	83.12	72.9, 90.7	73.42	62.3, 82.7	3.13
>6[a]	75.32	64.2, 84.4	83.54	73.5, 90.9	4.58
>7	72.73	61.4, 82.3	86.08	76.4, 92.8	5.22
>8	54.55	42.8, 65.9	97.47	91.1, 99.6	21.55
>9	44.16	32.8, 55.9	100.00	95.4, 100.0	
>10	42.86	31.6, 54.6	100.00	95.4, 100.0	
>11	20.78	12.4, 31.5	100.00	95.4, 100.0	
>12	12.99	6.4, 22.6	100.00	95.4, 100.0	
>13	11.69	5.5, 21.0	100.00	95.4, 100.0	
>14	5.19	1.5, 12.8	100.00	95.4, 100.0	
>15	2.60	0.4, 9.1	100.00	95.4, 100.0	
>16	0.00	0.0, 4.7	100.00	95.4, 100.0	

AUC-ROC = 0.863, S.E. = 0.030, 95% CI 0.799, 0.913. [a]Optimal cut-off point.

TABLE 2. Sensitivity, specificity (with 95% CI) and positive LR of salivary gland sialography

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR
≥0	100.00	95.3, 100.0	0.00	0.0, 4.6	1.00
>0	74.03	62.8, 83.4	74.68	63.6, 83.8	2.92
>1[a]	72.73	61.4, 82.3	84.87	80.0, 91.5	7.18
>2	61.04	49.2, 72.0	92.41	84.2, 97.1	8.04
>3	18.18	10.3, 28.6	98.73	93.1, 99.8	14.36
>4	0.00	0.0, 4.7	100.00	95.4, 100.0	

AUC-ROC = 0.804, S.E. = 0.035, 95% CI 0.733, 0.864. [a]Optimal cut-off point.

TABLE 3. Sensitivity, specificity (with 95% CI), and positive LR of salivary gland scintigraphy

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR
≥0	100.00	95.3, 100.0	0.00	0.0, 4.6	1.00
>0	84.42	74.4, 91.7	41.77	30.8, 53.4	1.45
>1[a]	70.13	58.6, 80.0	82.28	72.1, 90.0	3.96
>2	37.66	26.9, 49.4	97.47	91.1, 99.6	14.88
>3	5.19	1.5, 12.8	98.73	93.1, 99.8	4.10
>4	0.00	0.0, 4.7	100.00	95.4, 100.0	

AUC-ROC = 0.783, S.E. = 0.037, 95% CI 0.710, 0.845. [a]Optimal cut-off point.

inflammation that is not associated with SS, in recurrent parotitis of childhood [26], and in lympho-epithelial lesions not associated with SS [27]. Second, the results from some studies demonstrate abnormal parotid sialographic findings in control subjects with supposedly normal parotid glands. In two such studies, abnormal sialograms were observed in 15% [5] and 39% [28] of control subjects, which would translate into specificity values of 85 and 61%, respectively. On the other hand, the scintigraphic method with ^{99m}Tc pertechnetate is a non-invasive technique and has been used to evaluate the salivary gland function in patients with SS [17, 29]. Sensitivity of scintigraphy has been 73–80% [17, 29], and specificity quite poor in several studies [30–32]. The low specificity of salivary gland scintigraphy may be derived from the fact that decreased uptake and delayed excretion of ^{99m}Tc pertechnetate is a non-specific phenomenon, not to be considered pathognomonic for SS [17]. Bilaterally decreased uptake and delayed excretion may be seen in patients with other systemic CTDs, chronic recurrent sialodochoadenitis, sialadenosis and physiological ageing as well as in those with SS [17]. Although quantitative scintigraphic studies with computer-assisted analysis of the regions of interest have been attempted, there is still controversy about the optimal method for assessing SS [29, 33]. The original European classification criteria for SS [32] have been criticized, because their use may lead to over-diagnosis. If four of the six classification criteria are met, the specificity and sensitivity of the SS diagnosis should be quite high, ~95%. However, if these four items are subjective feelings of dry eyes and dry mouth associated with diminished lachrymal and salivary flow, then patients with neural dysregulation of the exocrine glands might become false positives [34]. Therefore, in the revised AECG criteria [3], autoantibodies and/or focal sialadenitis are required for a diagnosis of SS. The present study suggests that in combination with a laboratory test for anti-Ro/SSA and anti-La/SSB antibody positivity, US of the major salivary glands also can be useful in the differentiation between patients with pSS and patients with sicca symptoms but without SS. Previously, it has been suggested that US evaluation of the salivary glands is useful in the diagnosis of SS [13]. Kawamura *et al.* [11] and, more recently, Ariji *et al.* [12] showed that descriptive and quantitative assessment of the salivary glands by US efficiently differentiated between diseased and normal glands in patients with SS. They showed that the proposed sonographic gradings correlated well with the sialographic gradings [11, 12]. In the present study, the sensitivity of US imaging at the cut-off point >6 was slightly higher than that of contrast sialography and salivary gland scintigraphy (75.3, 72.7 and 70.1%, respectively), whereas the specificity was quite similar (83.5, 84.9 and 82.3%, respectively). These percentages are within the otherwise wide range of previous studies showing a sensitivity of US between 43% and 90% and a specificity between 83.3% and 100% [11, 12, 35–39]. For this threshold value of >6 in scoring system, the positive LR of an abnormal US was 4.58. For clinicians, the positive LR is the most important measure of a test's performance. The likelihood that a given test result would be expected in a patient with the target disorder compared with the likelihood that the same result would be expected in a patient without the target disorder. If a cut-off point >8.0 was applied, the US scoring system gained specificity, but at the cost of a loss of sensitivity (sensitivity 54.5%, specificity 97.5%, LR 21.5). This high level of LR suggests that the US changes described are sufficiently diagnostic of SS, and therefore, it may be unnecessary to perform contrast sialography or salivary gland scintigraphy on a patient with high anti-Ro and/or anti-La antibody titres. According to our sonographic scoring system [13] the grade 2 corresponds an evident parenchymal inhomogeneity, characterized by multiple scattered hypoechogenic areas usually of variable size (<2 mm) and not uniformly distributed. In fact, it is accepted by the majority of authors [35–39] that the most relevant sonographic sign in SS is parenchymal inhomogeneity, which is considered the most gland important structural change in these patients, and is determined in comparison with that of the thyroid gland [36, 39]. However, only evident inhomogeneity, characterized by multiple scattered hypoechoic areolae to multiple cyst-like changes in the gland parenchyma, can be regarded as being of true diagnostic value for the disease, because mild inhomogeneity may also be present in other disorders with subjective xerostomia. In the differential diagnosis of SS, many conditions can cause an inhomogeneity and hypoechogenicity in the parenchymal of the salivary glands, such as acute bacterial infection, but in this case the structural change is often unilateral. Also abscesses, haematoma and neoplasm are predominantly unilateral. On the contrary, in SS this structural change is, in most cases, bilateral and equally frequent in parotid and submandibular glands [37]. On the other hand, viral infections, chronic parotitis or sarcoidosis, limited only in the parotid glands, can mimic SS parotids, because they can produce similar changes [38]. In our study, which also included patients with sicca syndrome, we observed parenchymal inhomogeneity with hypoechogenic area within the parotid and submandibular glands; however, advance structural changes were more commonly found in SS patients than in patients with sicca symptoms, not fulfilling the criteria for definite SS. We employed the ROC curves to describe how well US examination can distinguish SS patients from those with sicca syndrome. A positive US result was the best performer, followed by salivary gland sialography and scintigraphy. The AUC-ROC in all of these three imaging investigations reached the range of good accuracy.

In conclusion, our experience leads us to believe that salivary gland US is an useful method in visualizing glandular structural changes in patients suspected of having SS and it may represent a good candidate for a first-line imaging tool in the diagnostic setting of the disease as well as a monitoring possibility during the follow-up of SS patients. For this reason, we suggest taking into consideration the introduction of salivary gland US as an alternative structural method to sialography and, in our opinion it would be of interest to complete the classification criteria for SS established by the AECG by this non-invasive imaging procedure, as proposed by other examiners [38–40].

Rheumatology key messages

- Quantitative assessment of salivary glands by US performs better than sialography and scintigraphy in the diagnosis of pSS.
- An US cut-off score of 6 provides an optimum sensitivity (75.3%) and specificity (83.5%) with an LR of 4.58 in detecting pSS.

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