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Is there an early ultrasonographic pattern in salivary glands in both primary and secondary Sjögren syndrome?

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ABSTRACT

Background. Sjögren syndrome (SS) is a systemic chronic inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs. Ultrasonography (US) demonstrates specificity and sensibility in major salivary glands (SG) evaluation. Recent data confirm US might be used as primary evaluation technique for its ability to show structural alterations of parenchyma (1).
Objective. To assess the gray scale (GS) parenchymal inhomogeneity of major SG in patients with established primary and secondary SS and correlate with clinical and biological data.
Methods. Consecutive patients with SS were recruited and SG US was performed. Inhomogeneity of glandular parenchyma was quantified binary on each gland. ESSDAI and ESSPRI scores were calculated. Statistics was performed with SPSS.
Results. Twenty one (42.85% primary SS, 90.47% female) consecutive patients were included. Mean age was 53.66+/-12.99 years and disease duration 5.33+/-3.74 years. Antibody SSA/SSB presence was found in 85.7% (18/21). ESSDAI mean was 8.67+/-8.9 (0-29), ESSPRI 10.13+/-5.59(0-20). There were no differences regarding ESSDAI and ESSPRI in the two groups (primary and secondary SS). Right parotid gland showed alterations in 71.4% patients (77% with primary SS, 66% with secondary SS). Frequently inhomogeneity was found in all major SG (33%, 22% left and right submandibular, 77%, 44.4% left and right parotid glands) in primary SS. Both submandibular glands were symmetrically involved ($p<0.02$). Duration of disease was negatively correlated to inhomogeneity of right parotid gland ($p<0.02$).
Conclusion. Inhomogeneity in major SG in GS US was found in the majority of patients with primary and secondary SS. The symmetrical involvement of submandibular glands was significant. The inhomogeneity appears in the early period of diagnosis. No major differences were found between two groups.

Keywords: ultrasonography, salivary glands, Sjögren syndrome, glandular inhomogeneity, semiquantitative score

INTRODUCTION

Sjögren syndrome (SS) affects mainly exocrine glands with dryness due to inflammatory infiltrates within the glandular parenchyma. SS can present as an entity by itself, without an underlying autoimmune condition – primary SS (pSS) – or may occur in conjunction with an underlying autoimmune condition – secondary SS (sSS). Diagnosis of SS is based on a combination of clinical signs and symptoms, autoantibody presence and salivary gland biopsy. Invasive methods as salivary scintigraphy and highly specific sialography are part of AECG criteria (2), but patients are often reticent due to invasive technics and radiation exposure. The AECG criteria include salivary gland biopsy and anti SSA/SSB antibodies as an important part of classification in primary SS (pSS). However, some patients are reluctant to biopsy and these cases require an alternative measure for diagnosis.

Moreover, a technique that would be sensitive to demonstrate in the early changes of disease with better accuracy to predict changes and evaluates the risk of lymphoma development and also repeatable for the follow-up would be of great value.

Ultrasonography (US) is a noniradiating imaging method. Patients are compliant to repeated in-

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vestigations and can be performed practically in an unlimited number of times. Therefore, may be useful as outcome for follow-up and detect the signs of disease progression.

US demonstrated its specificity and sensibility in major salivary glands (SG) evaluation and allows detection of the involvement of SG in both primary and secondary SS (2,3,4). Recent data confirm US might be used as primary evaluation technique for its ability to show structural alterations of parenchyma (5,6,7). Various scoring systems have been proposed using characteristics as size of glands, parenchymal inhomogeneity, echogenicity, clearness of the borders and vascularization. (8,9,10,11)

OBJECTIVE

To assess the gray scale (GS) parenchymal inhomogeneity of major SG in patients with established primary and secondary SS and correlate with clinical and biological data.

PATIENTS AND METHODS

We performed a single centre cross sectional study at the Rheumatology Unit of "Sf. Maria" Hospital Bucharest. The study enrolled 21 patients presented during October 2015 and February 2016 with diagnosis of pSS (primary SS) or sSS (secondary). Inclusion criteria were: the diagnosis of SS according to AECG criteria (12) along with the presence of clinical symptoms of xerostomia and xerophthalmia. Exclusion criteria include any of the following: Past head-and-neck irradiation, hepatitis C virus infection, acquired immunodeficiency syndrome (AIDS), prior lymphoma, sarcoidosis, graft *versus* host disease.

CLINICAL AND LABORATORY FINDINGS

At inclusion in the study, sicca symptoms were collected consecutively by means of ESSPRI; additional data about duration of disease, comorbidities and ongoing treatments were also recorded. Among laboratory abnormalities, we included: the presence of cytopenia [i.e. neutropenia (neutrophils < 1,500/mm^3); lymphopenia (lymphocytes < 1,000/mm^3); anemia (haemoglobin < 12 g/dl); thrombocytopenia (<150,000/mm^3)], low levels of C3 (<90 mg/dl) and C4 (<20 mg/dl), and hypergammaglobulinaemia (IgG > 16 g/l), hepatitis C and B positivity and thyroid disfunction. In addition to routine blood tests, we also assessed the presence of anti-Ro/SSA and anti-La/SSB (commercial ELISA kit) and RF (nephelometry). Schirmer's test was performed by the same ophthalmologist. ESSDAI (13) and ESSPRI (14) score was calculated.

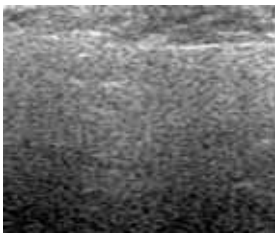
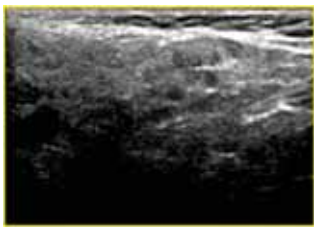
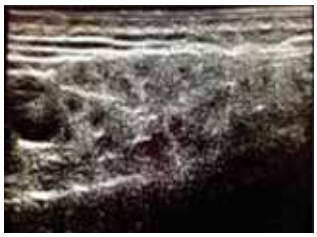
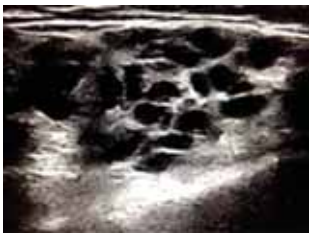
US EXAMINATION

SG US was performed by a rheumatologist trained in musculoskeletal ultrasound, blinded to clinical data, using a Esaote MyLab25Gold machine equipped with a 7.5- to 12.5- MHz linear probe. Patients were lying in the supine position with the neck extended and head slightly turned on the opposite side (Table 2). The parotid glands were scanned in both the longitudinal and transverse planes, while the submandibular glands were scanned longitudinally only. All US examinations were performed using a multiplanar scanning technique according to EULAR guidelines for musculoskeletal US in rheumatology. We considered parenchymal inhomogeneity and echogenicity as US parameters. The echogenicity was defined as normal or decreased in

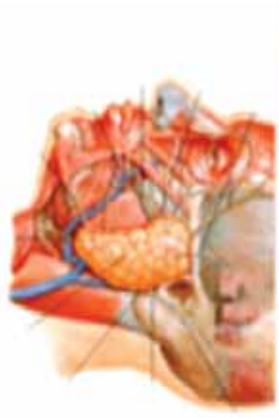
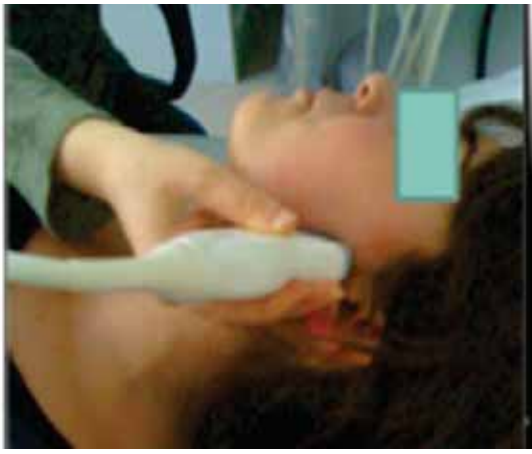
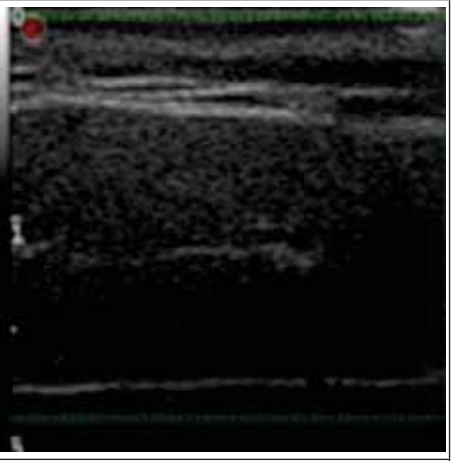
TABLE 1. *Demographic characteristics*

	N or min-max	Mean+/- s.d. or %
Disease duration, years	1-12	5.33+/-3.746
Age	28-84	53.66+/-12.998
Sex (f/total)	19/21	90.47
pSS/sSS	9/12	42.85
ESSPRI	0-20	10.13+/-5.59
ESSDAI	0-29	8.67+/-8.904
Anti SSA/SSB positivity (pSS)	18/21 (8/18)	85.71
Biopsy focus score > 1 (pSS)	7/8 (4/7)	87.5
RF positivity	15/21	71.42
C3	49-137	120.55+/-22.08
Lymphocyte (*10^3)	0.54-2.80	1.35+/-0.61
CRP	0.39-95.94	10.17
Schirmer (mm)	2-19	8.52+/-4.03
f- female; pSS- primary SS; sSS- secondary SS; RF- rheumatoid factor		

TABLE 2. *Score grading and examples*

Score 0	Score 1	Score 2	Score 3

Patient position.

comparison to thyroid gland parenchyma and the surrounding tissue (muscles, subcutaneous fat). Parenchymal homogeneity was graded from 0 to 3 for each gland according to US scoring system described by Theander et al. (15) grade 0 indicating complete homogeneity and grade 3 severe inhomogeneity with cysts and confluent hypoechoic areas. Grade 1 was considered mild inhomogeneity with isolated hypoechoic areas, while grade 2 represented evident inhomogeneity due to multiple hypoechoic areas of variable size, not uniformly distributed. We have not considered in the study the volume of SG. Associations between SG US and clinical and laboratory characteristics were analyzed.

STATISTICAL ANALYSIS

Results were reported as means+/- s.d. according to data distribution. Nominal variables were reported as absolute value number and percentage. Data were compared using $\chi 2$ tests, unpaired t-tests as appropriate. Spearman's rank correlation was performed for correlations between SG US score, ESSDAI, ESSPRI, duration of disease.

RESULTS

Twenty-one (42.85% primary SS, 90.47% female) consecutive patients were included. Mean age was 53.66+/-12.99 years and disease duration 5.33+/-3.74 years (Fig. 1, Fig. 2). Antibody SSA/SSB presence was found in 85.7% (18/21). ESSDAI mean was 8.67+/-8.9 (0-29), ESSPRI 10.13+/-5.59 (0-20). Demographic and clinical characteristics of the patients are shown in Table 1. There were no differences regarding ESSDAI and ESSPRI in the two groups (primary and secondary SS), although articular manifestations were frequently found in sSS (secondary to rheumatoid arthritis) 11/12 (in pSS 6/9), while glandular component of ESSDAI was confirmed in 4/9 cases with pSS (in comparison to 1/12 with sSS).

Rheumatoid factor (RF) was positive in 4/9 patients with pSS and 11/12 with sSS.

Frequently inhomogeneity was found in all major SG (33%, 22% left and right submandibular, 77%, 44.4% left and right parotid glands) in primary SS (Table 3). Right parotid gland showed alterations in 71.4% patients (77% with primary SS, 66% with secondary SS). Both submandibular glands were symmetrically involved ($p<0.02$).

A score >=1 was achieved in 19/21 patients (duration disease mean 4.74+/- 3.39), while score 3 was possible in patients with disease duration under a year. During first 3 years of disease, 7/13 patients had alterations compatible to grade 1, while grade 2 was found between 3rd to 8th years from diagnosis in 5/5 patients.

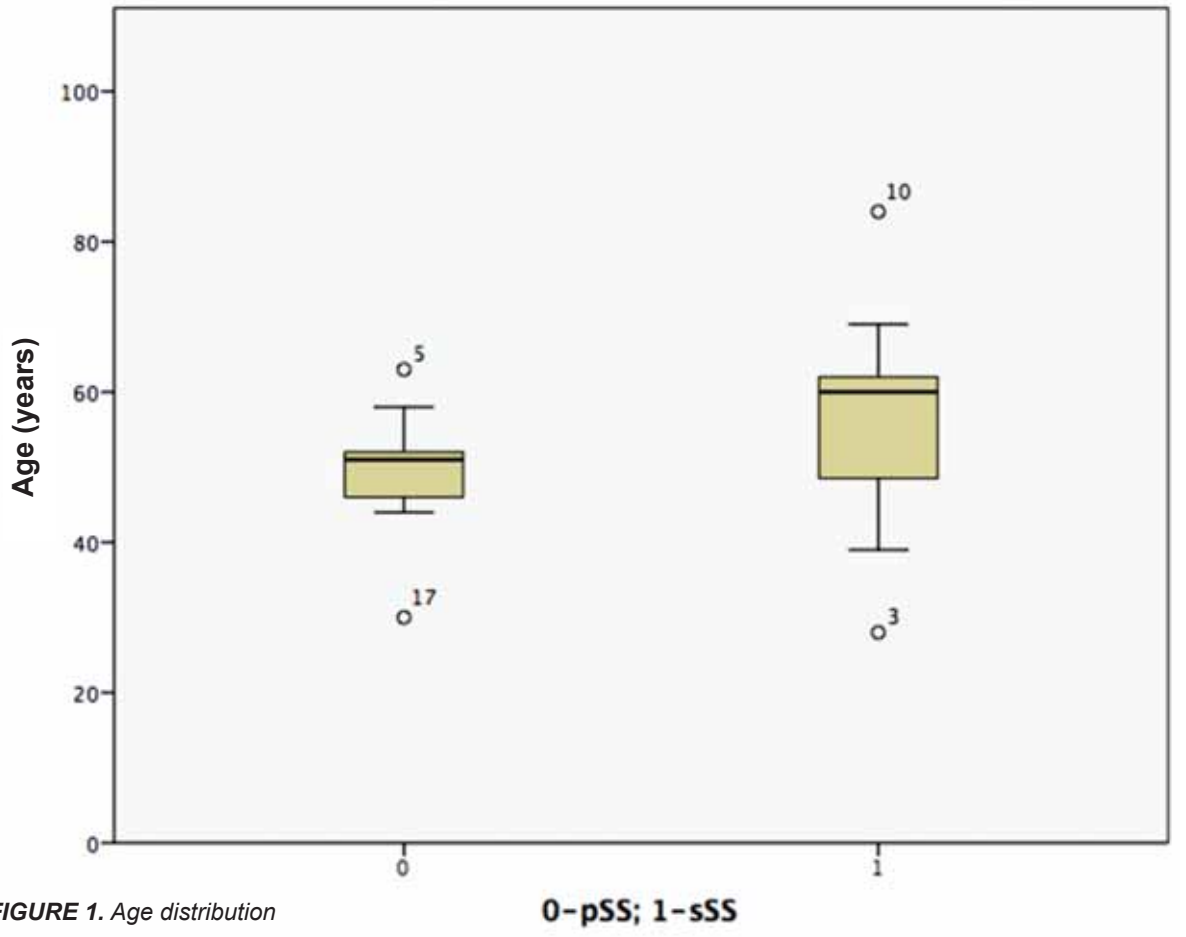


FIGURE 1. *Age distribution*

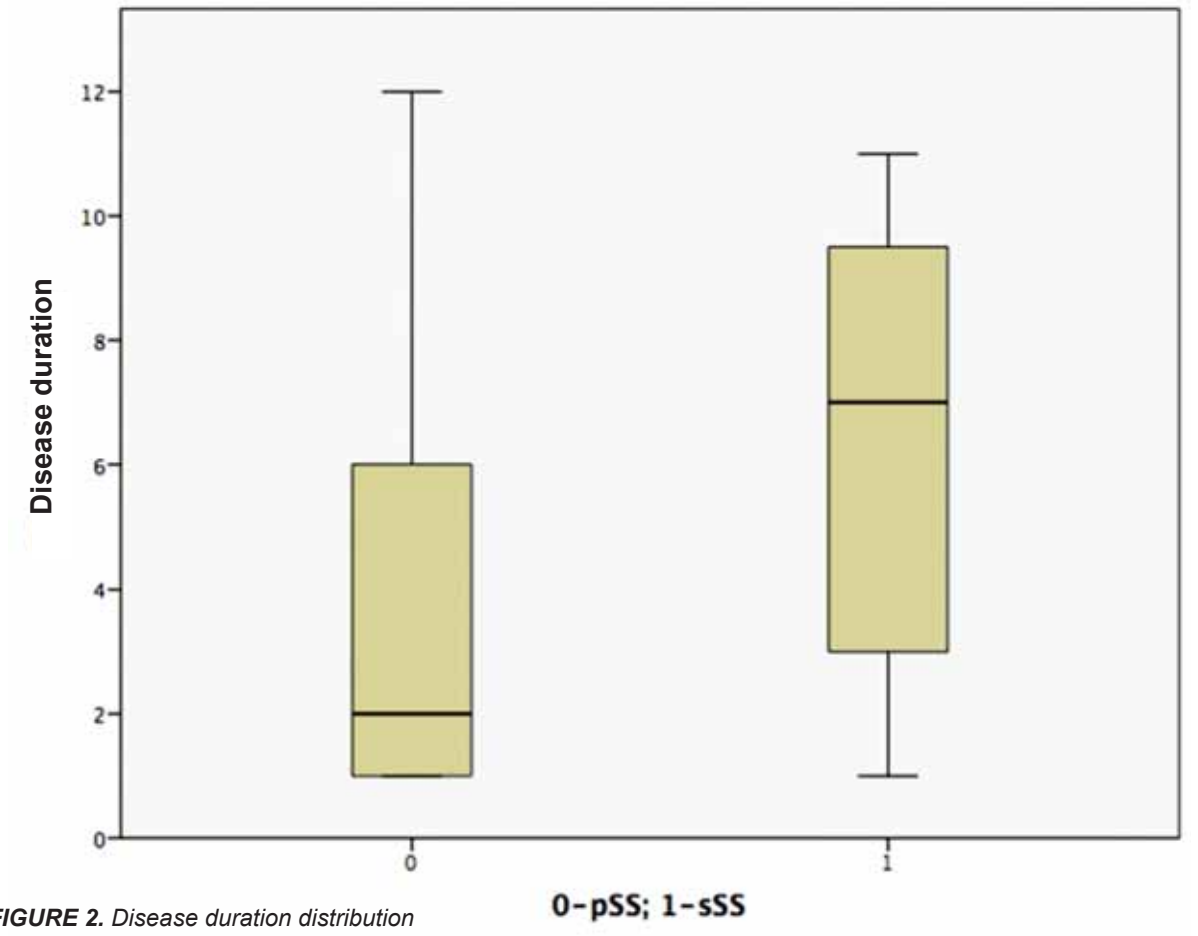


FIGURE 2. *Disease duration distribution*

TABLE 3. *Scoring distribution in patients with pSS and sSS*

Score	pSS N (%)	sSS N(%)
0	1 (11.11)	1 (0.83)
1	5 (55.5)	8 (66.6)
2	3 (33.3)	2 (16.6)
3	0 (0)	1 (0.83)

By setting a cut-off value of 1, 88.8% patients with pSS and 84.03% with sSS showed alterations (Table 2). Anti-Ro/SSA antibodies were positive in 8/9 cases (88.8% pSS) and 11/12 cases (91.66% sSS). Patients with SS presented SG US score values distributed across all categories (i.e. 0.95% for score 0; 61.9% for score 1; 23.8% for score 2; 0.47% for score 3). Given the mean disease duration 5.33 years, mild inhomogeneity (score 1) was the most frequent found alteration in both pSS and sSS. Duration of disease was negatively correlated to inhomogeneity of right parotid gland (r -0.412; $p<0.02$).

Dryness and fatigue were evenly distributed with tendency to score mostly 2 and 3 (scale 0-10) in both pSS and sSS. Mild inhomogeneity was found in patients reporting mild fatigue and dryness (Fig. 3 and 4). Clinical swelling of parotid gland was observed in 4/21 patients, 50% scoring mild inhomogeneity, while 11 cases with score 1 showed no clinical tumefaction. Schirmer test was found positive in 13/21 patients with mild inhomogeneity (score 1), 3/21 patients showed mild alterations but SSA/SSB negative; the diagnosis has been confirmed with biopsy.

Treatment with anticholinergic drugs and artificial tears was necessary in patients with severe inhomogeneity (score 3), while methotrexate, prednisone and hydroxicloroquine was initiated in early stages of parenchymal alterations (Fig. 5).

DISCUSSION

The evaluation of salivary gland involvement contributes significantly to the diagnosis of SS. Therefore, development of noninvasive and accurate diagnostic strategies for salivary glands would significantly benefit SS patients. So far, a number of studies have confirmed SG US to be a reliable tool in diagnosing SS in patients with sicca symptoms (1,2) and frequently showed high specificity and sensitivity over 60%, independently of the grading system adopted. A number of unresolved questions remain in SS. How can earlier diagnosis be achieved? Is there a need to include SG US in the classification criteria? (16) Since the accuracy of SG US has been recognized as comparable to that of scintigraphy, sialography and biopsy, invasive methods (17,18),

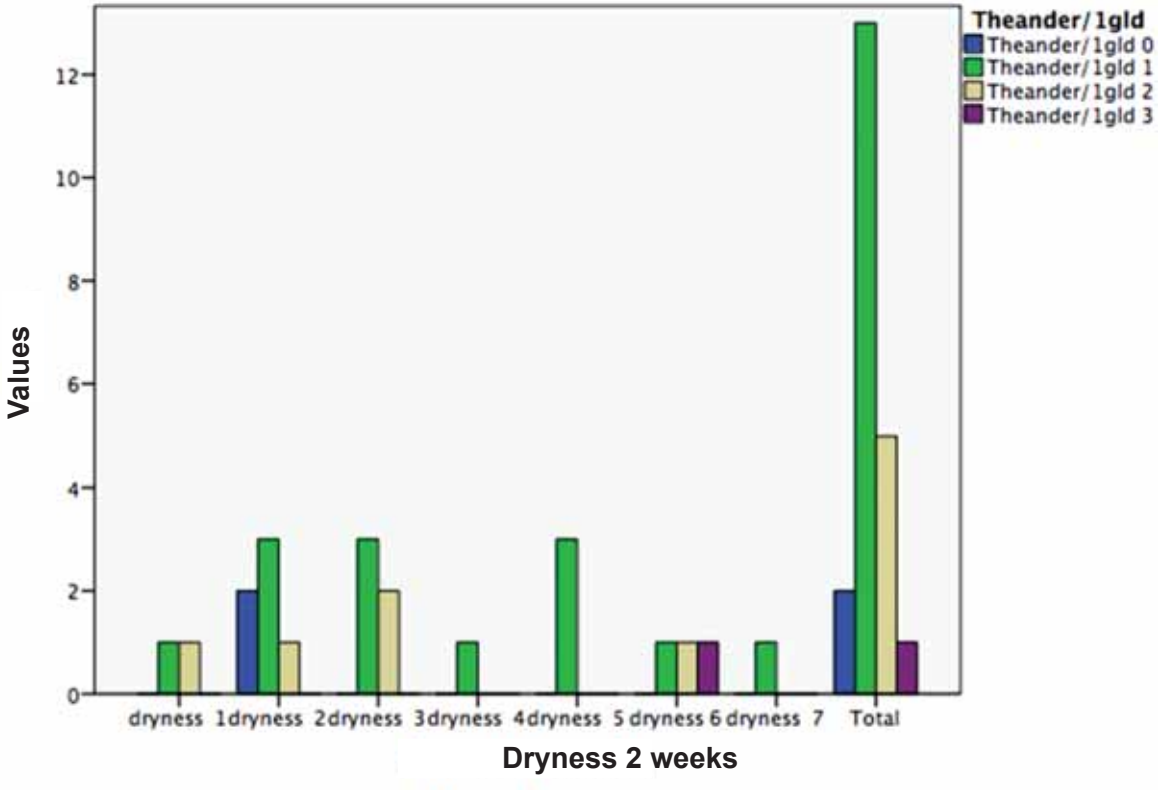


FIGURE 3. *Dryness distribution and SG US score*

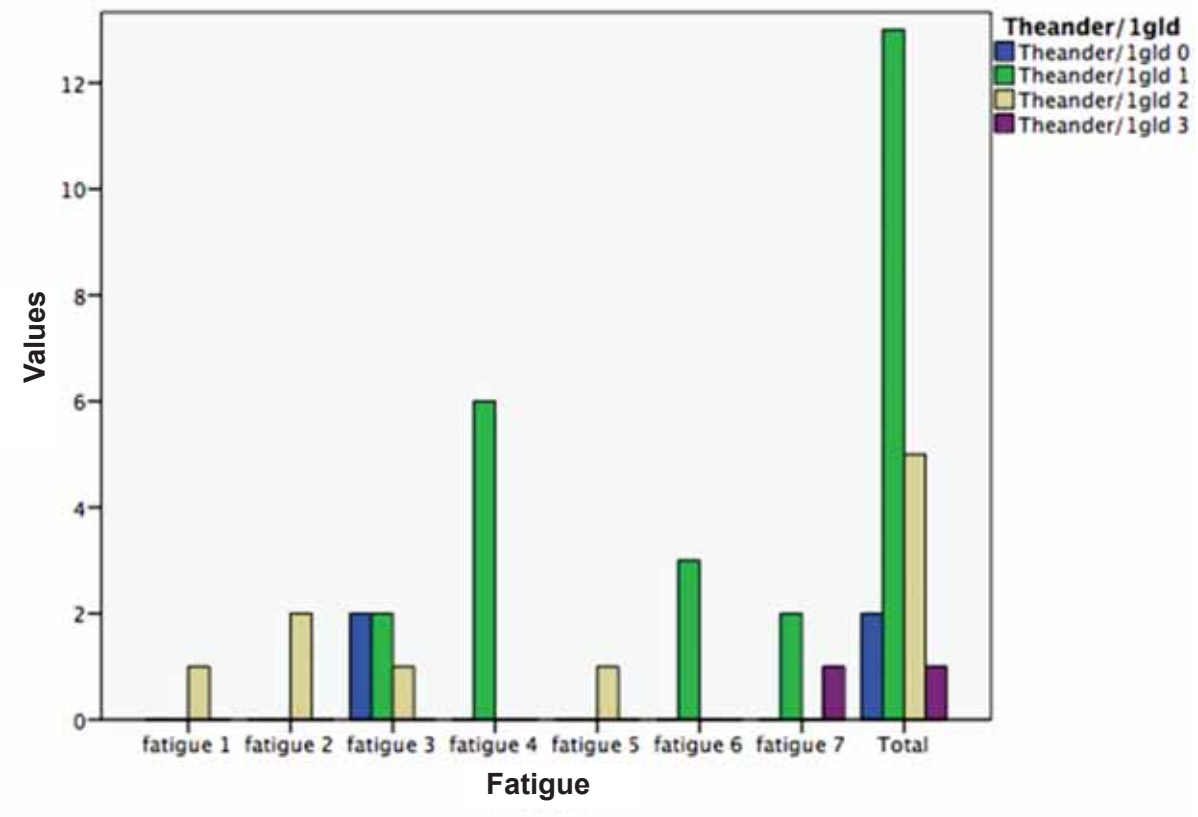


FIGURE 4. *Distribution of fatigue and SG US score*

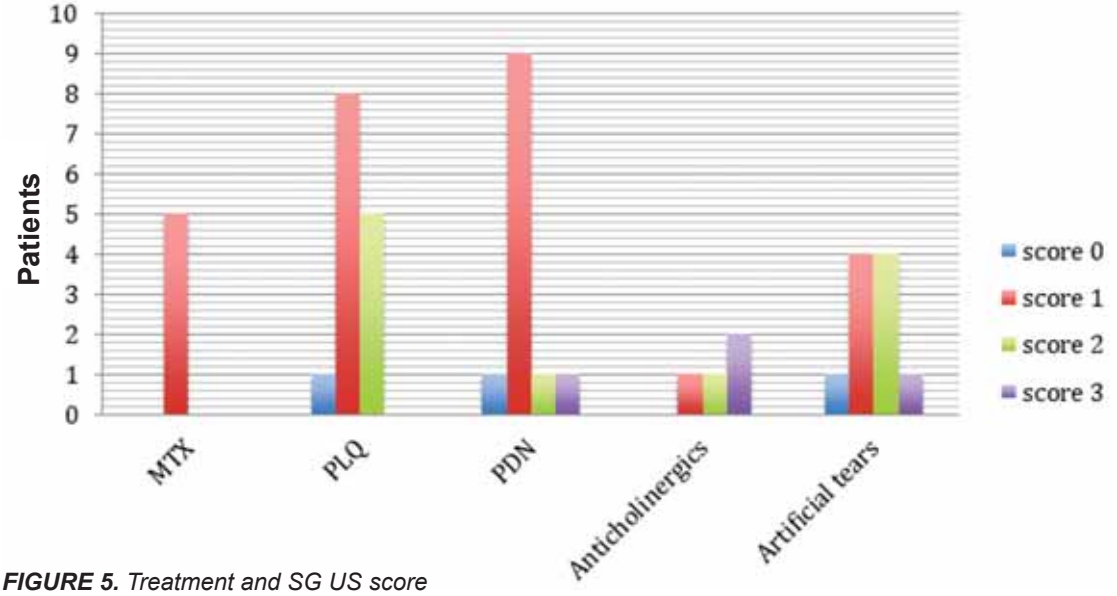


FIGURE 5. *Treatment and SG US score*

repeteadly SG US has been proposed as a new imaging method useful for diagnosis. However, different research groups have presented various scoring systems, including different characteristics such as size and volume, echogenicity and homogeneity, clearness of the borders and vascularization.

The present US study provides useful information using a very simple scoring system for major salivary glands, easy to learn and to assess. This technique could allow the rheumatologists and patients to include the examination into a regular outpatient visit and would be suitable for repeated longitudinal analyses. The score evaluates only the inhomogeneity, demonstrated before as a useful diagnostic tool (1). Again, the applicability of assessment, similar to Schirmer‘s test and sialometry, would give an important advantage in this scenario.

The SG US score for inhomogeneity was also the parameter in which interobserver agreement was the highest, the most important feature in SS was the

presence of hypoechoic areas. Though, there are differences in the reported diagnostic accuracy of US abnormalities in salivary glands, therefore the lack of standardization. Possible explanations might be the limited number of patients and the US equipment (type of machine, different frequencies and type of transducers). Inadequate objectivity in evaluating pathological changes should be considered when acquiring US images. Moreover, the operator experience is needed.

In fact, the presence of hypoechoic rounded multiple parenchymal lesions seems to be a pathognomonic feature of primary SS (1).

Despite the encouraging results, this study has some limitations: it was a single centre study, small number of patients included and the absence of a control group. However, the main objective in assessing the homogeneity alteration as an early sign was reached. Another particularity of the study was the long disease duration in our patients. Thus, even if further external validation studies appear undoubtedly necessary to corroborate any conclusions, our results seem to increase the amount of evidence supporting the routine use of SG US in the diagnostic algorithm of SS.

CONCLUSION

SG US using a simplified scoring system taking into account only inhomogeneity of the parenchyma proved high specificity and positive predictive value for primary SS as an additional item within a future modified classification criteria (7). It is also has high value for identification of structural alterations even in follow-up.

Our study represents an additional contribution to the amount of the data supporting the use of SGUS for non-invasive diagnosis of SS, even in the early stages of the pSS. SG US is an easy assessment and has the possibility of fast scanning by most rheumatologists with access to ultrasound equipment. For early detection of primary SS, however, and probably for follow-up in clinical trials and of lymphoma development more advanced and elaborate scoring systems, including Doppler assessments of vascularity, might be necessary (7).

Inhomogeneity in major SG in GS US was found in the majority of patients with primary and secondary SS. The symmetrical involvement of submandibular glands was significant. The inhomogeneity appears in the early period of diagnosis. No major differences were found between two groups (pSS and sSS). Further studies in larger cohorts are necessary to confirm our data.

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