Original article

Assessment of major salivary gland size in primary Sjögren's syndrome: Comparison between clinical examination and ultrasonography

Pauline Marteau [a,*], Divi Cornec [a,b], Maelenn Gouillou [c], Sandrine Jousse-Joulin [a,b], Dewi Guellec [a], Sebastian Costa [b,d], Thierry Marhadour [a], Guillermo Carvajal Alegria [a,b], Sophie Varache [a], Yves Gauvin [e], Sylvie Boisramé [f], Laetitia Le Pottier [b,g], Yves Renaudineau [b,g], Jacques-Olivier Pers [b,f], Alain Saraux [a,b], Valérie Devauchelle-Pensec [a,b]

[a] *Service de rhumatologie, centre national de référence des maladies auto-immunes rares de l'adulte CERAINO, CHU de Brest, 29200 Brest, France*
[b] *UMR1227, lymphocytes B et autoimmunité, université de Brest, Inserm, LabEx IGO, 29200 Brest, France*
[c] *Centre d'investigation clinique, CHRU Brest, 29200 Brest, France*
[d] *Anatomie et pathologie, CHRU Brest, 29200 Brest, France*
[e] *ORL, CHRU Brest, 29200 Brest, France*
[f] *Odontologie, CHRU Brest, 29200 Brest, France*
[g] *Laboratoire d'immunologie, CHRU Brest, 29200 Brest, France*

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ABSTRACT

Objective: Parotidomegaly is a criterion of the EULAR Primary Sjögren Syndrome Disease Activity Index (ESSDAI). The cut-off value was set at 3 cm in length for the parotid gland, 2 cm for the submandibular glands. However, clinical appreciation of salivary glands size remains hazardous. The objective is to evaluate inter-observer reproducibility of parotid gland measurement by palpation, and to secondary evaluate its reliability compared to US assessment.
Methods: Outpatients with primary Sjögren Syndrome (pSS) or with a diagnostic suspicion, in a single reference centre, were included. They underwent clinical examination by two independent investigators (VDP and DC), evaluating: parotid gland swelling, parotid gland size (direct measurement with a decameter under the mandibular angle), and pain. Cohen's kappa coefficient was calculated to determine inter-observer concordance for parotid gland swelling, and intraclass correlation coefficient to determine inter-observer agreement of gland size measurement.
Results: Thirty-four patients (33 women, 1 man) were included. Clinical data were complete for 33 patients. Inter-observer concordance Kappa coefficient was 0.90 [0.76–1.00] for detection of parotidomegaly over 66 parotid glands. It was of 0.60 [0.42–0.73] for gland length measurement. For one observer, the median cut-off for defining parotidomegaly was 4.15 cm; for the second observer, it was of 4.92 cm. For submandibular glands palpation, no correlation was found between investigators. A significant association between clinical parotidomegaly and a larger echographic surface was found.
Conclusion: Clinical measurement of parotidomegaly was concordant between two observers on a binary mode (presence/absence). However, concordance on direct measurement was weak. US could be a complementary examination.

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1. Introduction

Primary Sjögren's Syndrome (pSS) is a systemic auto-immune condition, affecting primarily the exocrine glands [1]. Among them, salivary gland involvement, due to immune-leaded focal lymphocytic infiltration [2,3], is a hallmark of the disease [4]. It results in loss of function, and morphological changes of the glands. There

* Corresponding author at: Service de rhumatologie, hôpital de la Cavale Blanche, BP 824, 29609 Brest cedex, France.
E-mail address: pauline.marteau@chu-brest.fr (P. Marteau).

are different subtypes of salivary glands but only parotid and submandibular glands are accessible to physical examination. They are frequently enlarged in pSS, affecting approximatively 10% of the patients during the course of the disease [5]. It is considered as a marker of disease activity, and as a predictive factor of lymphoma development [6].

The ESSDAI (EULAR Sjögren's Syndrom Disease Activity Index) [7] is a validated score assessing pSS systemic activity. It is based on a domain-by-domain evaluation, for which 3 to 4 levels of activity are described and weighed by a domain-specific coefficient. Salivary gland involvement is defined as follows: no hypertrophy, small glandular swelling (parotidomegaly $\leq$ 3 cm, submandibular gland < 2 cm, lacrymal gland < 1 cm), major glandular swelling (parotidomegaly > 3 cm, submandibular gland > 2 cm, lacrymal gland > 1 cm), respectively scoring 0, 1, 2, and multiplied by 2 [8]. Appreciation of glandular swelling, in ESSDAI, is only based on physical examination, and the abovementioned thresholds are derived from experts' consensus. Association between glandular swelling and lymphoma, especially non-Hodgkin lymphoma, has often been pointed out [9–11]; the increased risk for lymphoma is probably related to B-cell hyperactivity. Glands and lymph nodes palpation is part of the routine examination in pSS patients.

To our knowledge, the reliability of gland palpation to detect pathological swelling was never questioned. Yet, if major parotidomegaly, with its recognizable "hamster cheeks" aspect, can hardly be missed, slight changes in the size of parotid or submandibular glands may be not so easily detected in routine examination. Normal parotid gland nests in the parotid lodge, between the angle of the mandible and the sternocleidomastoid muscle; submandibular gland lies under the mouth floor, behind the body of the mandible, over the digastric muscle. Depending on adiposity, they might not always be conveniently palpated. Only the most superficial part of the parotid gland is accessible to palpation.

Imaging of salivary glands in SS is a developing field. In the 2002 American European Consensus Group classification (AECG) criteria [12], functional or morphologic imaging of the salivary glands by sialography or scintigraphy were validated for objective assessment of their involvement. These invasive procedures are not part of the 2016 ACR/EULAR [13] criteria, and only salivary flow rate measurement has been selected to assess salivary gland function. Ultrasound (US), on the other hand, is a non-irradiating, non-invasive technique, which attracted a lot of interest since the 90's [14]. It was favourably compared to sialography and salivary scintigraphy [15–19].

US assessment of the abnormal heterogeneity of the glandular parenchyma in patients with pSS [20] (hypoechoic, hyperechoic

streak, sometimes calcifications, intraglandular adenopathy) has a good multi-observer reliability [21]. Its integration in the classification criteria could enhance their diagnostic performances [22]. Data suggest that US findings are constant over time among untreated patients [23]. Gland size can be appreciated by surface-area measuring; normal parotid surface is around 3–4 cm^2, normal submandibular gland area around 1–2 cm^2 [24]. Several semi quantitative scores have been developed to grade salivary-gland US abnormalities in patients with pSS [14,25–28]; gland size is seldom considered. So far only one study considered volume measurement [22] Therefore, an international group of experts was gathered in 2012, aiming at providing a standardized scoring system [28,29].

The main objective of this study was to determine inter-observer reproducibility of parotid and submandibular gland palpation; the secondary objective was to compare this clinical assessment with US findings.

2. Methods

2.1. Study population

Thirty-four consecutive patients from the Brittany DiaPss Cohort [22] were included. Twenty were also taking part in the ETREINTE study, preliminary work to the consensual US-SG core items definitions [30]. Fourteen were consulting for diagnostic evaluation, or for their follow-up visit. Clinical features, immunological status (antinuclear antibodies, anti-SSA – both anti Ro 60 and 52 kDa, anti-SSB, anti-native DNA, ANCA, ACPA, rheumatoid factors), and histological analysis of minor salivary glands biopsy (focus score) were collected at inclusion. The evaluating physician defined a diagnosis of pSS or non-pSS for each patient, according to AECG criteria. The study was approved by Brest University Hospital ethical committee.

2.2. Physical examination

All patients underwent clinical examination of the major salivary glands by two rheumatologists with an expertise in SS (VDP, DC). For each patient, pain and swelling of each parotid and submandibular gland were reported. The length of each gland, when palpable, was reported; for parotid glands in the longitudinal axis behind the mandibular ramus (Fig. 1); for submandibular glands, in the transversal axis behind the inferior border of the jawbone. Each physician was blinded to their fellow's conclusions concerning these clinical measurements.

2.3. Salivary glands ultrasonography

All patients underwent US assessment of the major salivary glands on the same day by an experienced examiner (SJJ or SV). Patients lay in supine position, with slight extension of the neck, head turned on the contralateral side of the examiner. Measures were performed with an iU22 scanner (Philips Medical Systems, Andover, MA, USA) or a Mylab 60 scanner (Esaote, Firenze, Italy), with a linear 5–15 MHz probe. Echogenicity, heterogeneity of the parenchyma, visualisation of cysts and calcifications, surface of the gland (in cm^2), quality of vascularization were reported. Surface was reported by automatic calculation from manual begirding of the gland. Surface of more than 5 cm^2 for the parotid gland, and more than 3 cm^2 for the submandibular gland, were arbitrarily proposed for defining glandular hypertrophy.

2.4. Statistical analysis

Characteristics of pSS patients and non-pSS patients were compared using Fisher exact test for categorical data and Wilcoxon

Fig. 1. Measuring the parotid length.

Table 1
Patients characteristics.

|	Sjögren	Non-Sjögren	*P*-value
Number of patients	24	9	
Gender (Women)	24 (100%)	9 (100%)	1.000[a]
Mean age (y) Mean ± SD	52.5 ± 12.2	46.0 ± 10.7	0.67
Symptoms duration at diagnosis (y) Mean ± SD	6.8 ± 7.0	6.0 ± 9.6	0.64
Salivary flow < 0.1 mL/mn	18 (75%)	3 (33.3%)	0.04
Schirmer < 5 mm in at least 1 eye	9 (37.5%)	0 (0.0%)	0.04
SSA antibody	21 (87.5%)	1 (11.1%)	< 0.001[a]
Accessory salivary gland biopsy: Focus-Score ≥ 1	21 (87.5%)	0	< 0.001[a]
ESSDAI (mean)	5 ± 3.0	NA	

[a] Fisher exact test.
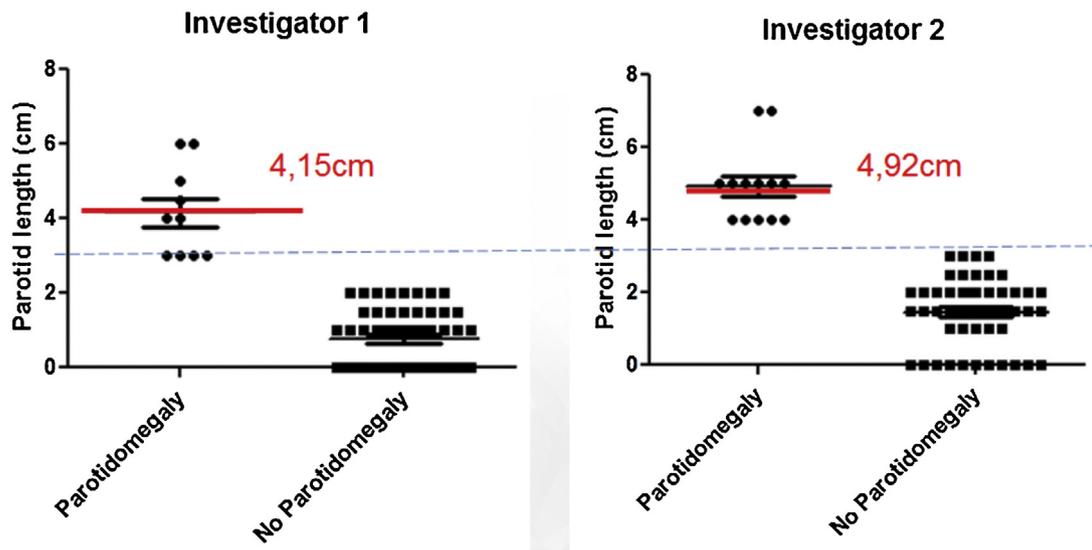
Fig. 2. Distribution of parotid gland sizes for each investigator.

test for continuous variables. Concordance between examiners was evaluated by Cohen's kappa coefficient for binary variables and by intraclass coefficient for continuous variables. Statistical analysis was performed by a biostatistician (MG) using the SAS 9.4 software.

2.5. Funding

No funding for this study.

3. Results

3.1. Patients characteristics

Thirty-four patients were included; all but one were women. One patient underwent physical examination by one examiner only and was excluded from the final analysis. Twenty-five had primary SS; nine were diagnosed with isolated sicca syndrome. There were no differences between the two groups for age, duration of symptoms, objective mouth dryness evaluated by salivary flow. Understandably, pathological Schirmer test, presence of anti-SSA (Anti Ro 60 kDa) antibodies, and histological analysis of minor salivary glands with a focus score of one and more were significantly more frequent among SS patients. Patients characteristics are presented in Table 1.

3.2. Concordance between observers for glandular physical examination

Concordance between investigators was very good (0.90, CI 95 [0.76–1.00]) for assessment of parotid gland swelling using binary item. Investigator 1(VDP) found 11 swollen parotids, versus 13 for Investigator 2 (DC). For evaluating the gland size however, intraclass correlation coefficient was only moderate (0.60, CI 95 [0.42–0.73]). While Investigator 1 diagnosed parotidomegaly for a size equal or superior to 3 cm, Investigator 2 established parotidomegaly only for measures strictly superior to 3 cm (Fig. 2). For submandibular glands, however, concordance between investigators was not assessable. Investigator 1 did not find any palpable glands, while investigator 2 reckoned 6 glandular hypertrophies over 10 palpated glands (Table 2).

3.3. Agreement between physical examination and ultrasonographic evaluation for glandular hypertrophy

Agreement between clinically defined parotid enlargement and US hypertrophy was low for both investigators: Spearman's rank correlation coefficient was respectively of 0.24 ($P = 0.06$) for Investigator 1, and of 0.30 ($P = 0.02$) for Investigator 2 (Fig. 3). The number of clinically undetected parotid gland hypertrophy measured over 5 cm2 by ultrasound was sixteen for Investigator 1 and fourteen for Investigator 2. Concordance between an echographic surface superior to 5 cm^2, and parotid gland length superior to 3 cm, was low (Cohen kappa's coefficient being respectively 0.363 ([0.256–0.470]) for Investigator 1, and 0.313 ([0.193–0.433]) for Investigator 2). The number of clinically undetected parotid gland hypertrophy measured over 5 cm2 by ultrasound was sixteen for Investigator 1 and fourteen for Investigator 2. The thresholds for glandular hypertrophy used in US assessment (respectively 5 cm^2 for parotid gland and 3 cm^2 for submandibular gland) were based on expert opinion and were not validated in previous studies. A significant association

Table 2
Concordance between investigators for clinical assessment.

	Investigator 1	Investigator 2	Concordance
Pain	6/33 (18%)	5/33 (15%)	0.67 [0.33–1.00][a]
Parotid gland hypertrophy (right-hand side)	6/33 (18%)	7/33 (21%)	0.90 [0.72–1.00][a]
Parotid gland hypertrophy (left hand side)	5/33 (15%)	6/33 (18%)	0.89 [0.68–1.00][a]
Parotid gland hypertrophy (all glands)	11/66 (17%)	13/66 (20%)	0.90 [0.76–1.00][a]
Parotid gland length (mean ± 1SD)	1.97 (± 1.57) cm	2.07 (± 1.72) cm	0.60 [0.42–0.73][b]
Palpated submandibular glands (number)	0	10/66 (15%)	NA
Submandibular glands hypertrophy	0	6/66 (9%)	NA

[a] Cohen's kappa coefficient.
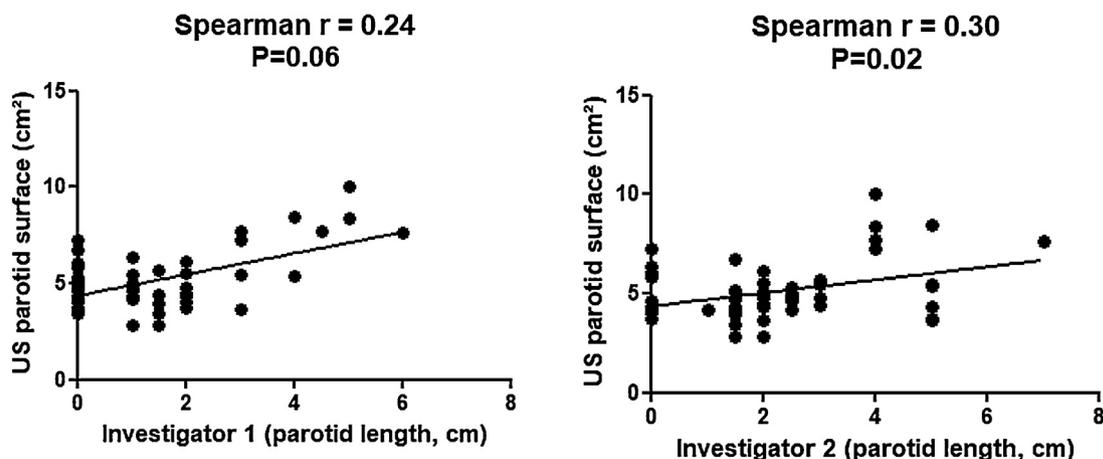[b] Intraclass correlation coefficient.

Fig. 3. agreement between physical examination and US parotid surface measurement, bold line: mean size for parotidomegaly. Dotted line: 3-cm threshold.
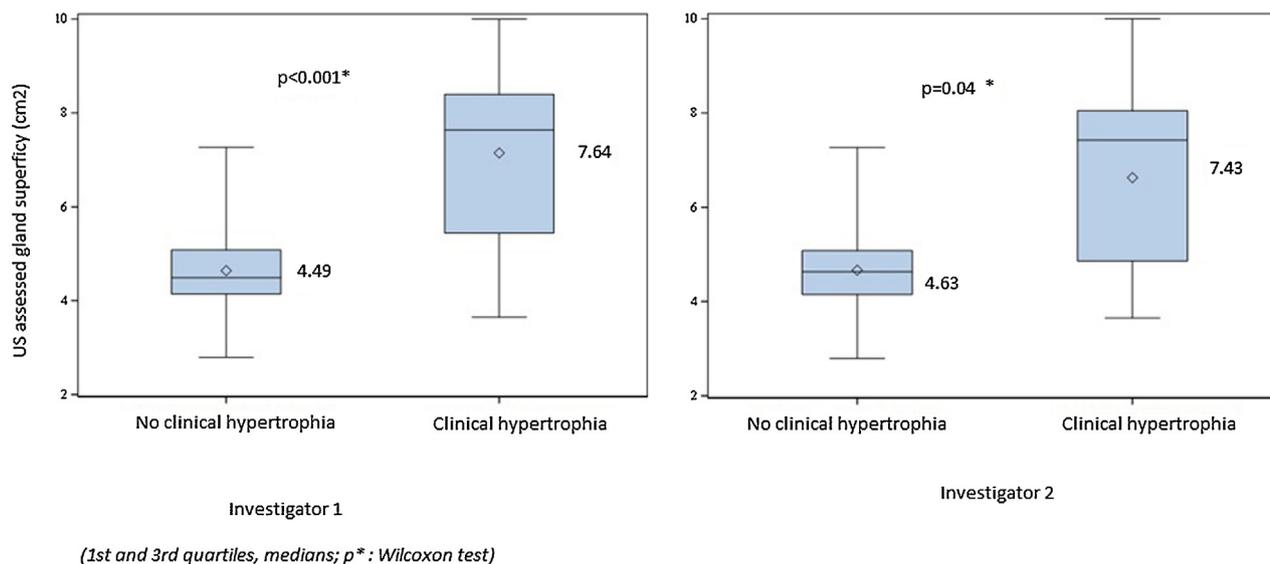

(1st and 3rd quartiles, medians; p* : Wilcoxon test)

Fig. 4. Distribution of US assessed gland superficy for each investigator.

between clinical parotidomegaly and a larger echographic surface was found (Fig. 4).

4. Discussion

To our knowledge, this is the first study questioning the performance of physical examination of salivary glands in pSS. Our two investigators were rheumatologists, with an expertise in pSS, in a reference specialized centre. Their agreement in identifying swelling of parotid gland was high even though no training session was performed before. The evaluation of the gland size however was only moderately concordant. For submandibular glands, physical examination was not informative. Given the lesser prognosis significance of submandibular swelling, this last result probably does not impact clinical practice. It could however influence disease activity score in studies and highlights the fact that in such evaluation, another procedure is recommended, as for example US evaluation.

ESSDAI score thresholds for moderate or important glandular swelling were defined through experts' consensus [7]. Our study suggests that the physician ability to detect a mild glandular swelling may have been overestimated. We found that

investigators were able to detect parotid gland enlargement equal or more than 3 cm with a good reliability.

US is a non-invasive, feasible technique for morphologic classification in pSS. It has already been shown that its integration in the classification criteria enhanced their diagnostic performances [22] and has proven itself sensitive to change after therapeutic intervention [31]. In a previous study, we described US gland surface in a cohort of 158 patients with suspected pSS [22]. Seventy-eight of them were diagnosed with pSS, while the others were classified as isolated sicca syndrome. In this cohort, parotid gland surface was calculated in the axial and longitudinal planes, by the following formula: (length x width)/2. Mean surface in the longitudinal plane were $3.51 \pm 1.12\,cm^2$ (right hand side parotid) and $3.35 \pm 1.06cm^2$ (left hand side parotid) for SS patients; $3.84 \pm 1.12\,cm^2$ (right hand side parotid) and $3.66 \pm 0.98\,cm^2$ (left hand side parotid) for non-SS patients. There was no significant difference between the two groups. Non-SS patients in this study were not healthy controls, since they were addressed for sicca symptoms.

Wernicke et al. [32] compared US-findings of primary and secondary SS patients with those of two control groups: patients with connective tissue disease (undifferentiated connective tissue disease (UCTD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), other inflammatory or non-inflammatory rheumatic diseases and no glandular complaint, and patients with sicca symptoms (either with or without underlying inflammatory condition) who did not fulfil the criteria for SS. For each patient, volume of parotid and submandibular glands was obtained by multiplication of the diameters in every plane divided by two. Volume was statistically smaller for women amongst asymptomatic controls; it was not linked to any anthropometric data otherwise. In this study, submandibular glands volume was reduced for SS patients (by 33% for female patients with pSS) compared to asymptomatic controls, whilst parotid volume was not. The authors suggest it may be related to histological differences, the mucous component of submandibular glands being more developed and more affected by SS. Clinical description of salivary glands was not detailed in the article.

Volumetric approach of parotid glands by US is limited by its morphologic features; it is composed of two parts, the deepest one being inaccessible to palpation or US assessment [33]. Three dimensional imaging can be obtained by MRI, but its spatial resolution is inferior to US [34].

Our results suggest that parotidomegaly can be detected by palpation, when the longitudinal axis is superior to 3 centimetres. However, physical examination below this threshold appears hardly reliable, while it seems even more hazardous for submandibular glands, and could be responsible for a bias in ESSDAI scoring. In this situation, complementary imaging might be helpful. US is cheap and easily accessible, and is performant for detection of parenchymatous abnormalities, while MRI allows total volume appreciation.

5. Additional informations

The scientific guarantor of this publication is Prof Valérie Devauchelle-Pensec, Rheumatology and Paediatric Units, Morvan and Cavale Blanche Hospital, BP 824, 29609 Brest cedex, France

Tel.: +33 298 347 264; Fax: +33 298 493 627

No complex statistical methods, were necessary for this paper.5) Institutional Review Board approval was provided by a local ethics committee for the creation of the DiAPSS cohort, which has already been presented in previous publications.

The protocol of this study belongs to routine care.

No animals were involved.

Methodology: cross-sectionnal, based on routine care, monocentric.

Disclosure of interest

The authors declare that they have no competing interest.

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