PAROTID GLAND ULTRASONOGRAPHY AS A DIAGNOSTIC TOOL IN PRIMARY SJÖGREN'S SYNDROME

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SUMMARY
The diagnostic value of parotid gland ultrasonography (Acuson 128, 7 MHz transducer) was studied in 62 patients with primary Sjögren's syndrome (SS) and in 69 controls of similar age and sex distribution. Different degrees (mild, evident or gross) of parenchymal inhomogeneity (PIH) were the most important sonographic changes in SS; they occurred in 83.9% of the patients. The sonographic results (the presence or absence of PIH) were in accordance with the parotid sialographic and scintigraphic findings and the histology of the minor salivary glands in 87.3, 84.7 and 84.3% of the cases, respectively. Of the degrees of PIH, only evident and gross PIH are thought to be of true diagnostic value for SS. On the basis of the good agreement between the sonographic and sialographic results, consideration of the introduction of parotid sonography as an alternative to sialography is suggested in SS if the latter method cannot be performed.

KEY WORDS: Primary Sjögren's syndrome, Parotid gland ultrasonography, Parenchymal inhomogeneity.

SUBJECTIVE xerostomia is one of the main symptoms of primary Sjögren's syndrome (SS) [1, 2]. It is often the first complaint to present, but the disease can also begin with systemic (articular, vascular, lung, etc.) symptoms [3, 4]. The xerostomia in SS is a consequence of the reduced saliva production caused by the chronic autoimmune inflammation of the salivary glands [5, 6]. However, a subjective feeling of dry mouth is known to occur in other diseases (diabetes mellitus, hypovolaemia, sarcoidosis, infective diseases, respiratory and renal insufficiency) and conditions (smoking, drugs, old age and snoring). For this reason, objective tests are needed to verify that the xerostomia is a result of SS. Of the different methods available for the detection of salivary involvement, besides histological examination of the minor salivary glands, parotid sialography, salivary gland scintigraphy and unstimulated saliva production examination have been accepted by the criterion system of the European Community [7]. Sialography is considered to be the most specific imaging method [8, 9], but it also has several disadvantages [10-13], as has scintigraphy [12, 14]. In recent years, publications have appeared on the diagnostic value of parotid sonography in the detection of gland involvement in SS, but opinions in this respect are contradictory [10, 11, 15-19].

We present our findings on the clinical value of parotid sonography in the detection of salivary gland involvement in primary SS patients.

PATIENTS AND METHODS
Since 1993, ultrasound examination of the parotids has been performed in 62 SS patients with systemic symptoms (60 females and two males) and 69 controls (58 females and 11 males). According to the 'Preliminary criteria for the classification of Sjögren's syndrome' [7], 53 patients met the criteria for definite and nine for probable SS. The mean age of the SS patients was 53.2 yr (range 29-80), which was similar to that of the controls (mean age 49.1 yr, range 22-74). The mean duration of subjective xerostomia in the SS patients was 9.8 yr (range 3 months–31 yr).

Two groups served as controls for the ultrasound examination. The first group (C1), without complaints of xerostomia, consisted of 19 healthy subjects and six patients with diseases generally not involving the parotid glands (e.g. atopic dermatitis, venous thrombosis of the leg, irritable bowel syndrome, osteoporosis, etc.). The second control group (C2) comprised patients with diseases which can affect the salivary glands (22 with diabetes mellitus, 11 with chronic liver diseases of different origin and 11 with hyperlipidaemia). Subjective xerostomia occurred occasionally in all diabetic patients, in five patients with liver disease and in six hyperlipidaemic patients.

Ultrasound examinations
All patients and controls were examined with a real-time high-resolution ultrasound system (Acuson 128) equipped with a 7 MHz linear transducer. During the examination of the parotids, the patients were in a supine position with the head turned a little to the opposite side. Both parotids were examined in transversal (in the cranial to caudal direction) and in longitudinal (in the anterior to posterior direction) planes. During the examination, the parenchymal homogeneity, echogenicity and size of the gland were evaluated. In cases of parenchymal inhomogeneity (PIH), similarly as in the evaluation procedure of De Vita and colleagues [18], three grades of PIH were distinguished. In mild PIH, a diffuse microareolar structure could be seen, the borders of the hypoecho-
genic areolae were blurred, and the areolae were generally <2 mm in diameter. In evident PIH, larger (2–6 mm in diameter) hypoechoic areas with a sharp border predominated. Gross PIH was characterized by the presence of large (>6 mm in diameter) circumscribed hypoechoic areas. In the different categories, the areolae (areas) of the given sizes predominated, but a few smaller or larger ones also occurred. These areas were generally round or oval.

The parenchymal echogenicity was determined in comparison with that of the masseter. The size of the parotid was considered to be normal if its width was 27 ± 7 mm. The sonographic pictures were judged by the initial examiner (EM), and then by an independent observer (IK) who was unaware of the results of the previous evaluation. The observers were not informed about the clinical diagnoses.

**Sialography**

During sialography, water-soluble contrast medium (Iodamide, 300 mg I/ml; Schering) was used. After cannulation of the main parotid duct, the ductal system was filled with the contrast material without over-pressure. To prevent a possible secondary infection, tobramycin (Brulamycin) was added to the contrast medium. After the ductal system had been filled, an X-ray picture of the parotid was taken from a lateral view. In the evaluation of the radiograms, the changes were considered to be characteristic of SS if one of the four known patterns (punctate, globular, cavitary or destructive) could be seen [11, 20]. The sialograms were evaluated independently by a radiologist (EM) and a rheumatologist (GP), and then re-evaluated by an independent radiologist (IK). The radiologists were unaware of the clinical diagnoses.

**Parotid gland scintigraphy**

Parotid gland scintigraphy was performed with a scintillation gamma camera (MB 9200, Gamma). During the examination, the patients were in a supine position. Following the i.v. injection of 140 MBq 99mTc-pertechnetate, anterior, right and left images of the parotids and the thyroid were taken. Half-way through the examination (at 30 min), oral lemon juice stimulation was applied. Grading of the scintigrams was based on the isotope uptake of the parotid relative to that of the thyroid and on the rate of isotope excretion. In accordance with the classification of Schall et al. [21], four categories were distinguished, ranging from normal conditions to a practically absent gland function. The scintigram was considered abnormal if both parotids exhibited a diminished isotope uptake or excretion. The scintigrams were evaluated by one experienced examiner (MR), who was unaware of the clinical diagnosis.

**Histology**

Lower lip biopsy for histological examination of the minor salivary glands was evaluated in 51 (44 definite and seven probable SS) of the 62 patients. The histology was considered positive if at least one focus of ≥50 mononuclear inflammatory cells per 4 mm² was found [7, 8].

**Laboratory investigations**

Routine laboratory and immunoserological examinations (antinuclear antibodies (indirect immunofluorescence on rat liver substrate), IgM rheumatoid factor (latex test, positive if titre ≥1:40), anti-native DNA (radioimmunoassay), anti-SSA, anti-SSB, anti-RNP and anti-Sm antibodies (enzyme-linked immunosorbent assay; ImmunoDOT), LE cell phenomenon (rotatory method utilizing heparin and glass beads), and concentrations of complement C3 (rocket immunoelectrophoresis), circulating immunocomplexes (complement consumption test) and serum immunoglobulins (Mancini technique) were performed in all patients.

**Statistical analysis**

After one-way analysis of variance (parametric/Kruskal–Wallis), the Bonferroni test was applied for pairwise comparison of the age of the patients and the duration of subjective xerostomia, while the Mann–Whitney U-test was used for pairwise comparison of the clinical variables (presence of organ manifestations, histological and immunological changes) in the groups of SS patients exhibiting different sonographic patterns of the parotids.

**RESULTS**

In the evaluation of the sonographic patterns of the parotids, the findings were concordant bilaterally in practically all cases. In the few patients where the degrees of PIH were different in the left and right parotids, the higher degree was taken. Results are listed in Table I.

PIH occurred in 52 of the 62 SS patients (83.9%), more frequently in definite SS (48/53, 90.6%) than in probable SS (4/9, 44.4%). Whereas the PIH was always mild in probable SS, in definite SS evident and gross PIH were the dominant patterns (38/53). A special change within the PIH was the secondary calcification observed in 12 patients with evident or gross PIH and in one patient with mild PIH. The characteristic sonographic pictures in SS are depicted in Fig. 1.

A decreased parenchymal echogenicity was the other sonographic change which correlated well with the PIH, although it was not so sensitive to the gland involvement as the PIH. A decreased echogenicity was detected in 33 of the 62 SS patients (53.2%). It occurred almost exclusively together with PIH (Table IA). An enlarged parotid was present in nearly half of the SS patients (29/62, 46.7%, Table IB). The distributions of enlarged and normal-sized parotids were similar among the definite and the probable SS patients, and were nearly the same among patients with or without PIH. In the control groups, evident or gross PIH was not observed, and the occurrences of mild PIH and decreased parenchymal echogenicity were also significantly lower (<10%) than in patients with SS (Table I). Although an enlarged parotid was rare (in
TABLE I
Relationship between parenchymal homogeneity and echogenicity of parotids (A) and that between parenchymal homogeneity and size of parotids (B) in primary Sjögren's syndrome (SS) patients (n = 53 definite, n = 9 probable) and controls (n = 69).

(A)

<table>
<thead>
<tr>
<th>Parenchymal homogeneity</th>
<th>Normal</th>
<th>Decreased</th>
<th>Total</th>
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<tr>
<td>D-SS Homogeneous</td>
<td>4</td>
<td>1</td>
<td>5</td>
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<tr>
<td>(n = 53)</td>
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<td>D-SS Inhomogeneity</td>
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<tr>
<td>Mild</td>
<td>8</td>
<td>2</td>
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<tr>
<td>Evident</td>
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<td>4</td>
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<td>Gross</td>
<td>3</td>
<td>25</td>
<td>28</td>
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<tr>
<td>P-SS Homogeneous</td>
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<td>(n = 9)</td>
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<tr>
<td>P-SS Inhomogeneity: mild</td>
<td>4</td>
<td>0</td>
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<tr>
<td>C1* Homogeneous</td>
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<td>2</td>
<td>24</td>
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<td>(n = 25)</td>
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<tr>
<td>C1* Inhomogeneity: mild</td>
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<td>0</td>
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<tr>
<td>C2* Homogeneous</td>
<td>40</td>
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<td>41</td>
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<td>(n = 44)</td>
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<td>C2* Inhomogeneity: mild</td>
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(B)

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<thead>
<tr>
<th>Parenchymal homogeneity</th>
<th>Normal</th>
<th>Enlarged</th>
<th>Total</th>
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<tbody>
<tr>
<td>D-SS Homogeneous</td>
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<td>(n = 53)</td>
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<tr>
<td>D-SS Inhomogeneity</td>
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<td>Mild</td>
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<td>Evident</td>
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<td>Gross</td>
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<td>27†</td>
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<td>P-SS Homogeneous</td>
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<td>C1* Homogeneous</td>
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<td>(n = 44)</td>
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<td>C2* Inhomogeneity: mild</td>
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D-SS, definite SS; P-SS, probable SS; PIH, parenchymal inhomogeneity; n, number of subjects; C1, 19 healthy controls + six control patients with diseases generally not involving the parotids; C2, 44 control patients with diseases which can affect the parotids (22 with diabetes mellitus, 11 with chronic liver diseases and 11 with hyperlipidaemia).

In P-SS patients and controls, evident and gross PIH did not occur.

In one additional patient with gross parenchymal inhomogeneity, the parotid was smaller than normal.

two of the 25 cases) in group C1, it was observed in about one-third of group C2, but was generally not accompanied by any change in the parenchymal homogeneity or echogenicity.

As the PIH was the most sensitive sonographic index of parotid gland involvement in our cases, its presence or absence was compared with the results of sialography, scintigraphy and histology of the minor salivary glands (Fig. 2).

The parotid glands were examined in parallel by sonography and sialography in 55 (88.7%) of the 62 SS patients. In the remaining seven patients (11.3%), sialography was not performed for anatomical reasons or because the patients did not agree to it. Characteristic sialographic changes were revealed in 44 (80%; 44 definite and 0 probable SS) of the 55 (49 definite and six probable SS) patients (punctate in 15, globular in 24 and cavitary in five). Concordant results of the two examinations were obtained in 48 (87.3%; both positive in 42 (76.4%; all definite SS) and both negative in six (10.9%; three definite and three probable SS)) of the 55 patients. In the remaining seven cases (12.7%), in five (9.1%; two definite and three probable SS) only sonography (mild PIH) and in two (3.6%; both definite SS) only sialography (one punctate and one globular) demonstrated the structural changes. In all types of sialographic changes, evident or gross PIH was the predominant sonographic pattern (11/15 in the punctate, 19/24 in the globular and 5/5 in the cavitary type).

Sonography and scintigraphy were performed in parallel in 59 SS (50 definite and nine probable) patients. Concordant results were obtained in 50 (84.7%; both positive in 47 (79.6%; 44 definite and three probable SS) and both negative in three (5.1%; one definite and two probable SS)) of the 59 patients. In six cases (10.2%; three definite and three probable SS) only scintigraphy, and in three (5.1%; two definite and one probable SS) only sonography indicated the parotid involvement.

Biopsy specimens of the minor salivary glands were suitable for histological evaluation in 51 SS patients (44 with definite SS and seven with probable SS), who were examined by sonography in parallel. Concordant sonographic and histological results were found in 43 patients (84.3%; both positive in 37 (72.5%; all definite SS) and both negative in six (11.8%; three definite and three probable SS)). In five (9.8%; two definite and three probable SS) patients only the sonographic pattern was abnormal (in four mild and one evident PIH), and in three (5.9%; two definite and one probable SS) cases only histology was positive.

As regards the age of the patients, the duration of the subjective xerostomia and the distribution of organ manifestations (articular in 60, airway in 45, vascular in 26 and renal in 18 of the 62 SS patients), we did not find significant differences between patients with definite SS and patients with probable SS, or between patient groups with different parotid sonographic patterns. In contrast, the histology was positive significantly more frequently in SS patients with evident or gross PIH (32/33) than in patients with mild PIH (5/9; P < 0.001), or in patients with a homogeneous parenchyma (3/9; P < 0.001). Similarly, of the immunological variables, the anti-SSA and/or SSB antibody and the rheumatoid factor positivity were significantly more frequent in patients with evident or gross PIH than in patients with mild PIH (6/14 vs 3/10 vs 31/38 vs 7/14 (P < 0.05) and 31/38 vs 3/10 (P < 0.01); rheumatoid factor: 34/38 vs 6/14 (P < 0.001) and 34/38 vs 2/10 (P < 0.001)).

DISCUSSION

At present, there is no single test of oral involvement which is sufficiently sensitive and specific to form the basis for a diagnosis of SS. Although histological examination of the minor salivary glands is generally considered to be the most important method for the diagnosis of SS, the necessity of the simultaneous performance of other tests is emphasized by most
It is accepted that sialography is the most reliable of the imaging methods [8], in spite of the fact that it can give a negative result in SS, particularly in the early stages of the disease [19]. The disadvantage of this method is that local chronic inflammation can flare up during the procedure. Additionally, in some cases the examination cannot be performed for anatomical reasons, or because of iodine allergy, or the patients do not give their consent [10-12]. The other imaging test, salivary gland scintigraphy, is very sensitive and especially useful in early SS [12, 21, 24, 25]. However, abnormal scintigrams can be encountered not only in SS, but also in other diseases [14], and the rate of positivity increases with age even in healthy subjects [8].

Of the newer methods, computed tomography (CT) and magnetic resonance imaging (MRI) can accurately detect the parenchymal inhomogeneity characteristic of SS parotids, but both techniques are expensive [10, 26-28]. Further, CT involves X-ray exposure and MRI a certain discomfort, particularly for patients with claustrophobia, and it cannot be used in patients fitted with a pace-maker. Sonography does not have these disadvantages and is less expensive. Sonographically, the normal parotid is homogeneous and hyperechoic to the masseter, and similarly echogenic to the thyroid. The parotid segment behind the mandibular ramus is not visible or is difficult to visualize sonographically. The sonographic picture of SS parotids has generally been examined by most authors on only small numbers of patients [11, 15, 17, 19]. The exception was the study by De Vita et al. [18], where 27 primary and 26 secondary SS patients were investigated. It is accepted by the majority of authors that the most important sonographic sign in SS is bilateral PIH, ranging from multiple, discrete, scattered hypoechoic areolae to multiple cyst-like changes in the gland parenchyma. The decreased echogenicity was especially emphasized as the other sonographic change by De Clerck et al. [10]. The parotid may be larger or smaller than normal, depending on the predominance of inflammation or atrophy.

Opinions on the clinical usefulness of sonography in SS are not completely unanimous [11, 17-19]. Whereas Kawamura et al. [17] found characteristic sonographic changes in the parotid glands in only one-third of their
Results of US and SI
n=55

Results of US and SC
n=59

Results of US and HI
n=51

FIG. 2.—Comparison of parotid ultrasonographic (US) positivity (parenchymal inhomogeneity) with sialographic (SI) and scintigraphic (SC) results, and histology (HI) of the minor salivary glands in patients with primary Sjögren’s syndrome (SS). n, number of patients examined; +, positive result; −, negative result.

In the differential diagnosis of SS, mainly those illnesses which may be accompanied by diffuse bilateral PIH or multiple cyst-like lesions of the salivary glands have to be considered. Acute bacterial infection can cause an inhomogeneity and hypoechoicinity in the parenchyma, but in most cases only unilaterally. Viral infections which generally involve both parotids can produce similar changes, and it is therefore difficult or impossible to differentiate them from SS parotids on the basis of the sonographic pictures alone [16]. Bilateral cystic changes in the parotid glands may be early signs of HIV infection [26, 29]. Sonographically, these cysts are generally larger than in SS, the matrix is normoechoic, and the cervical adenopathy is more common in this condition than in SS. Diagnostic difficulty may also arise in sarcoidosis limited only to the parotid glands, because this form can mimic the clinical picture of primary SS [30]. In sarcoidosis, the parotid enlargement may be diffuse or nodular, but the changes in the parenchyma generally appear as solid lesions sonographically [11, 15]. Most parotid cysts and duct dilatation caused by calculus usually involve only one of the parotids, appearing as an echo-free, circumscribed lesion sonographically. Congenital dysgenetic disease of the parotids is extremely rare. Abscesses, haematomas and neoplasms with a necrotic or haemorrhagic centre are predominantly unilateral, involving only a certain part of the gland with a blurred contour and hypoechoic centre. These conditions are accompanied by ipsilateral cervical lymphadenopathy, similarly to lymphomas and tumours which are solid lesions sonographically [11, 15, 16, 29]. In spite of the sonographic diagnostic possibilities, it must be emphasized that the diagnosis of salivary gland diseases must in all cases be based on a combined evaluation of the sonographic and clinical findings.

To sum up, our experience on an appreciable number of SS patients leads us to believe, in agreement with other examiners [18], that parotid sonography is a very useful, additional method for diagnosis of the salivary component of SS. It can be used as a first diagnostic step in new suspected cases and as a monitoring possibility during the follow-up of SS patients. For this reason, we suggest consideration of the introduction of parotid sonography as an alternative structural method to sialography. It seems to be particularly justified in cases when sialography cannot be performed.
REFERENCES


