Original Article
The correlation between ultrasound changes of the parotid gland and the clinical findings in Sjögren’s syndrome

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Abstract: The aim of this study is to investigate the association of salivary gland ultrasonography (SGUS) findings with the clinical, histological, and serological features of Sjögren’s syndrome (SS). A total of 195 patients with suspected SS underwent SGUS for the evaluation of salivary gland involvement. The clinical and serologic features were compared between groups classified by their SGUS scores. The association between SGUS and these features of SS was explored using a multivariable linear regression analysis. The proportion of SGUS changes in patients with primary SS was significantly higher than it was in their counterparts with secondary SS. The degree of ultrasound changes in the parotid gland was highly correlated with the clinical dry mouth score, SSA positive intensity, high IgG-emia, and the lip gland pathological index (P < 0.05). Parotid ultrasound has value in the diagnosis and evaluation of Sjögren’s syndrome, and its different types of performance may have a predictive value for the syndrome’s clinical features.

Keywords: Sjögren’s syndrome, salivary gland ultrasonography, clinical features

Introduction
Sjögren’s syndrome (SS) is a chronic autoimmune disease in which multiple exocrine glands are damaged, characterized by dry mouth and possible multiple systems involvement including the lungs, kidneys, blood, nerves, and joint muscles, etc. [1, 2]. It is prevalent among middle-aged women, with an incidence rate between 0.29~0.77%. Previously, diagnosis relied on an invasive examination of a labial gland biopsy [3], which can cause much pain. In recent years, ultrasound has been commonly used in clinical tests due to its convenience, non-invasiveness, and low cost [4, 5]. A large number of studies have confirmed that parotid ultrasound has a high sensitivity and specificity for the diagnosis of SS [6, 7]. A few researchers found that the similarities and differences of ultrasound performance are related to its clinical features. Our medical team routinely performed parotid ultrasound examinations in inpatients and outpatients who were admitted to our department starting in January 2015, and we recorded their clinical data, including the clinical manifestations, signs, course of the disease, whether or not it was combined with other rheumatism, as well as the serological indicators, such as inflammation and antibodies, and the pathological index of the labial gland. Through the end of January 2018, data from a total of 195 patients with Sjögren’s syndrome were collected. The patients’ ultrasound findings and clinical features were statistically analyzed, and the results are presented below.

Objectives and methods

Subjects
195 patients with Sjögren’s syndrome diagnosed in our Department of Rheumatology from January 2015 to January 2018 (according to the EULAR 2010 revised SS classification criteria [8]), including 123 cases with primary Sjögren’s syndrome (pSS) all underwent a labial examination of the labial gland and were diagnosed with focal lymphocytic infiltrating salivary...
Ultrasound changes and the parotid gland

There were 11 males and 112 females. The average age was 54.6±12.1 years old. There were 72 cases of secondary Sjögren’s syndrome (sSS), consisting of 9 males and 63 females with an average age of 53.2±11.7 years old. Among the sSS group, there were 19 cases of lip gland pathological examination consistent with FLS performance, 20 cases of systemic lupus erythematosus, 16 cases of systemic sclerosis, and 8 cases of myositis. Exclusion criteria: history of neck, head, and face radiotherapy, hepatitis C virus infection, AIDS, sarcoidosis, amyloidosis, graft versus host disease, and immunoglobulin IgG4-related diseases. The study was approved by the hospital ethics committee, and an informed consent from each of the patients was obtained.

Clinical symptoms and signs

In those cases in which there was dry mouth and dental caries, the degree was assessed according to the dry mouth scale (11-55 points), the overall medical condition, and the VAS score of the doctor, etc. The length of the disease (less than 1 year: 1 point; 1 to 3 years: 2 points; 3-6 years: 3 points; 6-9 years: 4 points; 10 years or more: 5 points), accompanying symptoms, including eye dryness (filter paper test: below 5 mm/5 mins: 1 point; 5 mm/5 mins or more: 0 points), the corneal fluorescence staining score (0-4 points), joint muscle pain (1 point), pulmonary interstitial lesion (1 point), interstitial nephritis (1 point), blood system involvement (1 point), and nervous system involvement (1 point) were all counted.

Laboratory examination

The following parameters were measured: the erythrocyte sedimentation rate (ESR), C hypersensitivity reaction protein (CRP), serum amyloid protein (SAA), and other inflammatory indicators, including the serum rheumatoid factor (RF), complement-3/4 (complement-3/4, C3/C4), immunoglobulin-G (Immunoglobulin, IgG) levels, and antinuclear antibodies (ANA) titers, anti-SSA, SSB (European method) positive (+~++; + +), lip gland tissue index (no lymphocytic infiltration: 0 point; slight: 1 point; moderate, but < 1 spot: 2 points; ≥ 1 stove: 3 points; ≥ 2 stoves: 4 points).

Parotid gland ultrasonography

A Japan ALOKA (model: α10) color ultrasound scanner was used for the examination of the bilateral parotid gland with a probe frequency of 8–13 MHz. The results of the evaluation of the parotid ultrasound were assessed using a scoring system [9], 0 points: normal gland, echo uniform; 1 point: substantial echo is weakened, mildly uneven, a little high echo line can be seen; 2 points: obvious echo of uneven echo, diffuse distribution of hypoechoic nodules, diameter < 2 mm, high echo line increased; 3 points: nodular hypoechoic area increased fusion, diameter 2~6 mm, high echo line distribution disorder; 4 points: hypoechoic nodules > 6 mm, or gland atrophy (gland up and down diameter < 5.0 cm, left and right the diameter was < 3.0 cm and the thickness was < 1.0 cm), and there were many high echo lines (Figure 1).

Statistical analysis

The data were entered and analyzed using SPSS 25.0 software. The measurement data were expressed as X ± s and a t-test was used for comparisons between groups. A Spearman rank correlation analysis was used to analyze the relationship between dry mouth and dental caries in the SS patients, and the length of the disease, the accompanying symptoms, the inflammation index, the antibody index, and the parotid ultrasound score. P < 0.05 was considered a significant difference.
Ultrasound changes and the parotid gland

Results

Comparison of the clinical data between the two groups

The pSS group had no significant differences in terms of disease duration, the dry mouth scale score, accompanying symptoms, the filter paper test, the inflammation index, ANA titer, SSA, SSB, C3, and C4 compared with the sSS group. However, there were statistical differences between the IgG and labial gland pathology scores, and especially between the RF and SGUS scores, which were statistically significant (P < 0.01), suggesting that SGUS has a high diagnostic value for primary Sjögren's syndrome (Table 1).

Correlation between the clinical manifestations and SGUS scores in patients with primary Sjögren's syndrome

The SGUS scores of the 123 patients in the pSS group and the clinical data were analyzed using Spearman's rank correlation coefficient, and the factors with an r value greater than 0.5 were obtained as scatter plots as follows, respectively, for the dry mouth scores (Figure 2A, r = 0.768, P < 0.05), hyper IgG-emia (Figure 2B, r = 0.773, P < 0.05), the labial index of the labial gland (Figure 2C, r = 0.697, P < 0.05), and the SSA positive intensity (Figure 2D, r = 0.685, P < 0.05).

Discussion

SS is a common, chronic autoimmune disease. In 2015, ACR proposed the significance of parotid ultrasonography (SGUS) in its clinical diagnosis. SGUS scores are higher in patients with anti-SSA and/or SSB, pathological Schirmer stimulation/non-stimulation, and high VAS scores [10]. In order to further explore the relationship between the clinical features of parotid ultrasound and Sjögren's syndrome, our department recruited 195 patients with SS in our hospital from the beginning of 2015 to the beginning of 2018, and the relationships between parotid ultrasound and the clinical features, including clinical symptoms, laboratory tests, and pathology, were analyzed. The results showed that the proportion of patients with SS with ultrasound changes (Elke's simplification score ≥ 1) was as high as 95.8%, especially in primary Sjögren's syndrome, but in patients with other rheumatisms, the positive rate of SGUS was low, which suggests that the specificity of parotid ultrasound in the diagnosis of primary Sjögren's syndrome is better (P < 0.05). A previous study reported that parotid ultrasound has a higher value in pSS, but there are few studies on the difference between pSS and sSS. A study by Cornec et al. showed that the positive rate of parotid ultrasound was 62.8% and 12.5% in pSS and sSS patients, respectively. In this study, with reference to the currently accepted ultrasound standard, the boundary value of SS was 2. The results showed that the positive rate of SGUS in pSS was 65.0%, and the positive rate in sSS was 41.6%. Although our data is different from the counterpart report of Cornec [11], the conclusion that SGUS is more sensitive than sSS in pSS is consistent. Hence, we believe that the sputum

Table 1. Comparison of the clinical manifestations, signs, laboratory tests, pathology, and ultrasound between the two groups

<table>
<thead>
<tr>
<th></th>
<th>pSS group (n = 123)</th>
<th>sSS group (n = 72)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>3.1±1.4</td>
<td>3.2±1.3</td>
<td>0.367</td>
</tr>
<tr>
<td>Dry mouth scale score</td>
<td>31.9±14.5</td>
<td>37.5±13.9</td>
<td>0.289</td>
</tr>
<tr>
<td>VAS</td>
<td>6.2±2.1</td>
<td>5.8±2.3</td>
<td>0.312</td>
</tr>
<tr>
<td>Accompanying symptoms</td>
<td>1.8±0.8</td>
<td>1.4±0.6</td>
<td>0.246</td>
</tr>
<tr>
<td>Filter paper test</td>
<td>0.9±0.3</td>
<td>0.8±0.4</td>
<td>0.412</td>
</tr>
<tr>
<td>Corneal fluorescence staining</td>
<td>2.2±1.1</td>
<td>1.9±0.9</td>
<td>0.198</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>8.8±4.9</td>
<td>9.2±5.1</td>
<td>0.221</td>
</tr>
<tr>
<td>ESR (mm/H)</td>
<td>32.8±12.1</td>
<td>35.2±19.4</td>
<td>0.318</td>
</tr>
<tr>
<td>SAA (mg/L)</td>
<td>299.2±187.1</td>
<td>286.2±192.9</td>
<td>0.389</td>
</tr>
<tr>
<td>ANA ≥ 1:320</td>
<td>0.8±0.3</td>
<td>1.0±0.4</td>
<td>0.059</td>
</tr>
<tr>
<td>SSA positive</td>
<td>0.96±0.2</td>
<td>0.98±0.6</td>
<td>0.349</td>
</tr>
<tr>
<td>SSB positive</td>
<td>0.56±0.51</td>
<td>0.12±0.06</td>
<td>0.038</td>
</tr>
<tr>
<td>C3 (mg/ml)</td>
<td>1.0±0.1</td>
<td>1.1±0.2</td>
<td>0.406</td>
</tr>
<tr>
<td>C4 (mg/ml)</td>
<td>1.0±0.2</td>
<td>1.1±0.1</td>
<td>0.437</td>
</tr>
<tr>
<td>IgG (g/L)</td>
<td>28.2±6.5*</td>
<td>24.8±8.4</td>
<td>0.049</td>
</tr>
<tr>
<td>RF (IU/ml)</td>
<td>493±315**</td>
<td>231±104</td>
<td>0.006</td>
</tr>
<tr>
<td>Labial gland pathology scores</td>
<td>2.3±1.1*</td>
<td>1.2±1.2</td>
<td>0.023</td>
</tr>
<tr>
<td>SGUS scores</td>
<td>2.7±1.0**</td>
<td>1.0±0.2</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Compared between the groups, *P < 0.05; **P < 0.01.
Ultrasound changes and the parotid gland

Lesions that SGUS can suggest are more common in patients with pSS.

In addition, the abnormal manifestations of parotid ultrasound, especially low echogenic nodules and diffuse lesions, were highly correlated with the clinical dry mouth scores, SSA positive intensity, high IgG-emia, and the lip gland pathological index (P < 0.05), suggesting that the severity of glandular ultrasound changes are highly consistent with the degree of lymphocytic infiltration and the destruction of the labial gland pathology, further confirming that SGUS may be an effective means for assessing SS activity. There was no significant correlation with the clinical concomitant symptoms and dryness, including the filter paper test, the corneal fluorescence staining score, CRP, SAA, ESR, or other serum indicators, as well as the serum levels of RF, C3/C4, SSB, and the ANA titers.

We want to acknowledge that this study has some limitations. Our study was designed as a retrospective study at a single center. The medical center in which the study participants received treatment was a tertiary hospital, which may lead to bias in terms of the selection of patients (patients tends to have more severe symptoms). Moreover, because our hospital has the advantage of involving traditional Chinese medicine in the diagnosis and treatment of Sjögren's syndrome, there is a large SS patient population in Zhejiang, which means the course of the selected patients and the disease span are large, and there is a certain inevitable statistical deviation, and the degree of individual clinical symptoms, signs, and laboratory results are currently not standardized, especially in clinically accompanying symptoms, more specifically with serious complications, such as the involvement of the nervous system, the involvement of the circulatory system, etc., which affects the results of the study.

Conclusion

Abnormal changes in SGUS are closely related to focal lymphocytic invasive mumps, and clinical manifestations are consistent with dry
Ultrasound changes and the parotid gland

mouth, serum IgG levels, and anti-SSA antibody titers. Relevant indicators of SS disease activity, such as ESR, are irrelevant. This study once again confirmed the value of parotid ultrasound in the clinical diagnosis and evaluation of SS. Clinically, this examination can reduce the rate of missed diagnosis of early SS onset and reduce the inconvenience caused by invasive examinations such as labial biopsy. The future research direction of our research group will involve exploring whether SGUS has the value of evaluating the follow-up treatment effect of SS and assessing the prognosis of lymphoma and other diseases. In addition, the parotid gland, which is the main target organ of Sjögren’s syndrome, is also worthy of further study because of the significant differences in the primary and secondary syndromes.

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Disclosure of conflict of interest

None.

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