Comparison of Lacrimal and Salivary Gland Involvement in Sjögren’s Syndrome

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Objectives: To determine the performance of different tear and salivary tests applied in Sjögren’s syndrome (SS) and to disclose how these tests relate to common serologic tests in SS.

Design: In addition to the routine ocular and oral tests for diagnosing SS (Schirmer test, rose bengal score, unstimulated whole saliva flow, and parotid sialography), tear breakup time and flow rate of glandular saliva (parotid and submandibular-sublingual [SM/SL]) were evaluated in patients referred for diagnosis of SS. Patients were categorized into primary SS, secondary SS, and non-SS groups according to the revised European classification criteria for SS.

Setting: Referral center.

Patients: Referred sample of 80 consecutive patients.

Main Outcome Measure: Correlation between ocular and salivary measures.

Results: Breakup time performed insufficiently in diagnosing SS, as opposed to the rose bengal score. In patients with primary and secondary SS, a clear correlation was noted between tear and saliva quality and secretion rate, and between the rose bengal score and parotid sialography. Increased rose bengal scores also correlated significantly with hyperglobulinemia and presence of SS-B antibodies in serum, with duration of subjective eye dryness, and with decreased tear-gland function. With regard to the oral tests, whole, parotid, and SM/SL salivary flow decreased significantly with increasing duration of oral complaints, with the stimulated SM/SL flow rate showing the strongest decrease and being more specific in diagnosing SS. Also, parotid sialography was more specific in excluding patients without SS than the commonly applied diagnostic criterion of secretion of unstimulated whole saliva.

Conclusions: The rose bengal score remains the eye test of choice, as it has the highest specificity for SS. Hyperglobulinemia and especially positive serologic findings for SS-B may warrant close monitoring of the eyes, since these serum findings appear to relate to the severity of ocular surface damage. Parotid sialography and stimulated secretion of SM/SL saliva are more specific in diagnosing SS than unstimulated secretion of whole saliva.


JOGREN’S SYNDROME (SS) is considered a systemic autoimmune disease with the exocrine glands as main target organs. Since the tear and salivary glands are almost invariably affected, the oral and ocular sicca components form a significant part of this syndrome. The diagnosis of SS is based largely on subjective and objective findings confirming damage or dysfunction of tear and salivary glands, in accordance with one of the international sets of diagnostic criteria.1

Recent studies by Kalk et al1-3 showed that, in addition to unstimulated whole saliva, parotid and submandibular-sublingual (SM/SL) gland salometry and sialochemistry not only are proper tools for diagnosis of SS, but have a potential in assessing the disease progression and activity. Such data are unknown for the lacrimal glands. Therefore, the main objective of this study was to determine the performance of different eye tests and to disclose how these tests relate to serologic and salivary tests used for diagnosing SS.4,7

METHODS

PATIENTS

Eighty consecutive patients who attended the outpatient clinic at the Department of Oral and Maxillofacial Surgery of the University Hospital Groningen, Groningen, the Netherlands, between August 1, 1997, and April 30, 2000, were
included in this study. The patients were referred under suspicion of SS by rheumatologists, internists, neurologists, otolaryngologists, general practitioners, and dentists. Reasons for referral were not limited to ocular or oral manifestations such as eye dryness, mouth dryness, and swelling of the salivary glands, but also included arthralgia and fatigue. According to the revised European classification criteria, the diagnostic workup for SS, carried out in all patients, included the following aspects: subjective complaints of oral and ocular dryness, collection of unstimulated whole saliva, parotid sialography, histopathologic examination of salivary gland tissue, serologic testing (SS-A and SS-B antibodies, immunoglobulin levels), and eye tests (rose bengal score, Schirmer tear test). In addition, tear break-up time (BUT), collection of stimulated whole saliva, and sialometry and sialochemistry of parotid and SM/SL glands were performed. Patients were categorized as having primary SS (pSS), secondary SS (sSS), or no SS (non-SS) (Table 1). The use of xeroergic drugs (ie, antihypertensives, β-blockers, antihistamines, and psychotropics) was relatively frequent in all patients (pSS, 16 [50%]; sSS, 14 [56%]; non-SS, 16 [69%]).

### ASSESSMENT OF THE OCULAR COMPONENT

As part of the diagnostic workup, the duration of ocular symptoms was recorded, defined as the time between referral and first complaints induced by ocular dryness.

The Schirmer test was carried out with a filter-paper strip (Color Bar, Schirmer tear test standardized sterile strips; Eagle Vision, Memphis, Tenn) of 0.5 × 30 mm. The strip was placed in the lower fornix between the medial and lateral third of the eyelid of the unanaesthetized eye. After 5 minutes, the amount of wetting was measured from the extrafornical position of the strip. A value of 5 mm or less per 5 minutes was considered diagnostic of SS, according to the European classification criteria for SS.3,9

The rose bengal test, was used to quantify the degree of staining. The test was performed by placing a 1% rose bengal solution in the lower fornix of both eyes and asking the patient to make 1 or 2 full blinks. Afterward, the intensity of staining of both medial and lateral bulbar conjunctiva and of the cornea was scored, each section up to 3 points (1, sparsely scattered; 2, densely scattered; and 3, confluent), so that a maximum score of 9 could be obtained. A score of 4 or more was considered diagnostic of SS, according to the European classification criteria for SS.

The tear BUT was defined as the interval between a complete blink and the appearance of the first randomly distributed dry spots. A 1% fluorescein solution was put in the inferior fornix of both eyes. The patient was asked to blink a few times, and then the interval in seconds between the last blink and the first break in the tear film was measured.3,10

### ASSESSMENT OF THE ORAL COMPONENT

As part of the diagnostic workup, the duration of oral symptoms was recorded, defined as the time between referral and first complaints induced by or related to oral dryness.

Parotid sialography was performed according to the method described by Kalk et al. In brief, after cannulation of the parotid main duct, the gland was filled through low-pressure retrograde injection of an oil-based contrast liquid (Lipiodol UF; Guerbet, Paris). On average, 0.7 mL of contrast liquid was infused. Subsequently, posteroanterior (6° mediolateral) and lateral radiographs were made. The sialograms were scored according to the criteria of Blatt.31

For collection of both whole and glandular saliva, the patients were instructed not to eat, drink, or smoke during 90 minutes preceding the sialometric assessment. All assessments were performed at a fixed time of the day, in this study between 1 and 3 PM, to minimize fluctuations related to a circadian rhythm of salivary secretion and composition.

Unstimulated and citric acid–stimulated whole saliva were collected according to the method described by Navahesz.4 For collection of unstimulated whole saliva, the patient was seated comfortably with eyes open, head tilted slightly forward, and instructed to rest for 15 minutes and to minimize movements. During the collection period, the saliva was allowed to drip off the lower lip into a preweighed test tube. For collection of stimulated whole saliva, the patient was positioned in a similar way and a 2% (wt/vol) citric acid solution was applied to the lateral borders of the tongue at 30-second intervals. The patients were allowed to spit the saliva accumulating in the floor of the mouth into preweighed test tubes. A collection period of 10 minutes was used.

Glandular salivas were collected according to the method described by Kalk et al.2 The samples were collected in preweighed plastic tubes from both individual parotid glands by using modified Lashley cups (Carlson-Crittenden cups), and simultaneously from the SM/SL glands by syringe aspiration. Saliva from the SM/SL glands was collectively aspirated, as separate aspiration is difficult in clinical practice because of the close anatomic relationship between the orifices of both glands and the frequent presence of communicating ducts between the submandibular and sublingual main ducts.

Unstimulated salivary secretions were collected during 5 minutes, followed by collection of stimulated secretions during 10 minutes. The saline glands were stimulated with citric acid solution (2% wt/vol) applied with a cotton swab to the lateral borders of the tongue at 30-second intervals. Mixing of the acid solution applied to the tongue and SM/SL saliva pooling anteriorly in the floor of the mouth (orifices of the SM/SL glands) was carefully avoided. Lag phase, defined as the time from first acid application on the tongue until first visible sa-
sSS, secondary Sjogren's syndrome.

to calculate receiver operating characteristic (ROC) curves17
Calc, version 5.0, software; MedCalc, Mariakerke, Belgium) nm after addition of molybdate and reduction with bisulfite in
ver ions. Inorganic phosphate was measured at 340 and 383
(3000 ppm). Chloride ions were measured by titration with sil-

dium, chloride, calcium, and phosphate. Sodium ions were mea-

ly. The following salivary components were quantified: so-

A 3- to 4-year diagnostic delay was observed in the pa-

tients with SS studied, estimated by the duration of their

complaint, whereas one third reported simultaneous on-

and another one fourth reported eye dryness as the first

In addition, increased serum levels of immunoglobulins were observed in patients with pSS and sSS (Table 3).

The BUT performed poorly as a diagnostic test for SS, with a specificity of only 4%, when the original thresh-

do of 10 seconds was used. The ROC plot analysis showed

an optimum threshold at 3 seconds (≤3 seconds), with a

sensitivity of 76% and a specificity of 74% for SS (like-

lihood ratio, 2.9). The ROC plot analysis further showed

that the diagnostic performance of the BUT was super-

rior to the performance of the Schirmer test. However,

none of the tear tests could compare with the diagnostic

value of the rose bengal score. The rose bengal score was

the only ocular manifestation that worsened signifi-

antly with increasing duration of subjective eye dry-

ness (Table 4).

ORAL TESTS

When compared with rates in the non-SS group, stimu-

lated secretory flow rates of the SM/SL glands were sig-

nificantly decreased in both the pSS and sSS groups (Table 3). In addition, increased sodium and chloride

concentrations and decreased phosphate concentration

were measured in stimulated parotid saliva in patients

with pSS and sSS when compared with the non-SS
group (Table 3).

According to the European classification criteria, 23
(72%) of the pSS and 19 (83%) of the sSS group tested
positive for the ocular component, as did 13 (57%) of the non-SS

group (Table 1). When the radiographic criterion only

was applied (presence of sialectasia on a sialogram, per-

centages are based on the number of patients with avail-

able information), 28 (100%) of the patients with pSS and

16 (76%) of those with sSS tested positive, whereas only

3 (8%) of the non-SS group did. All salivary flow rates

decreased significantly with increasing duration of oral

complaints, with the stimulated SM/SL flow rate show-

ing the strongest decrease (Table 5). In another study,

it also has been shown that stimulated SM/SL flow rate in

combination with parotid sodium and chloride concen-

tration is the most accurate diagnostic test, reaching

a sensitivity of 0.85 and a specificity of 0.96.3

SEROLOGIC TESTS

Serum SS-A and/or SS-B antibodies were present in 24
(75%) of the patients with pSS and 11 (46%) of the pa-

tients with sSS, compared with 3 (13%) of the non-SS

group (Table 1). In addition, increased serum levels of

immunoglobulins were observed in patients with pSS and

sSS (Table 3).
Table 3. Ocular Tests, Oral Tests, and Serum Immunoglobulin Levels of Patients With and Without SS*

<table>
<thead>
<tr>
<th></th>
<th>pSS (n = 32)</th>
<th>sSS (n = 25)</th>
<th>Non-SS (n = 23)</th>
<th>Control Subjects (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schirmer value, mm/5 min</td>
<td>4.5 ± 4.7†</td>
<td>8.2 ± 8.2†</td>
<td>10.2 ± 8.8</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Rose bengal score</td>
<td>5.7 ± 2.1†</td>
<td>5.0 ± 2.4†</td>
<td>2.7 ± 2.0</td>
<td>0</td>
</tr>
<tr>
<td>Breakup time</td>
<td>2.7 ± 3.3†</td>
<td>3.4 ± 3.9†</td>
<td>5.7 ± 3.6</td>
<td>&gt;10</td>
</tr>
<tr>
<td><strong>Oral tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstimulated flow rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid, mL/min per gland</td>
<td>0.01 ± 0.03</td>
<td>0.02 ± 0.03</td>
<td>0.03 ± 0.07</td>
<td>0.05 ± 0.06</td>
</tr>
<tr>
<td>SM/SL, mL/min per SM/SL gland</td>
<td>0.02 ± 0.03†</td>
<td>0.07 ± 0.12</td>
<td>0.10 ± 0.11</td>
<td>0.12 ± 0.12</td>
</tr>
<tr>
<td>Whole saliva</td>
<td>0.05 ± 0.08†</td>
<td>0.11 ± 0.18</td>
<td>0.16 ± 0.22</td>
<td>0.23 ± 0.15</td>
</tr>
<tr>
<td>Lag phase, s</td>
<td>144 ± 178</td>
<td>218 ± 237†</td>
<td>62 ± 137</td>
<td>9 ± 54</td>
</tr>
<tr>
<td><strong>Stimulated flow rates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid, mL/min per gland</td>
<td>0.15 ± 0.19</td>
<td>0.13 ± 0.15</td>
<td>0.19 ± 0.12</td>
<td>0.52 ± 0.42</td>
</tr>
<tr>
<td>SM/SL, mL/min per SM/SL gland</td>
<td>0.24 ± 0.35†</td>
<td>0.25 ± 0.30†</td>
<td>0.42 ± 0.25</td>
<td>0.46 ± 0.24</td>
</tr>
<tr>
<td>Whole saliva</td>
<td>0.55 ± 0.68</td>
<td>0.58 ± 0.30†</td>
<td>0.79 ± 0.44</td>
<td>1.58 ± 0.46</td>
</tr>
<tr>
<td>Composition stimulated saliva, mEq/L</td>
<td>18 ± 22†</td>
<td>19 ± 18†</td>
<td>3 ± 3</td>
<td>14 ± 12</td>
</tr>
<tr>
<td>Parotid chloride</td>
<td>33 ± 27†</td>
<td>26 ± 15</td>
<td>19 ± 8</td>
<td>16 ± 12</td>
</tr>
<tr>
<td>Parotid phosphate</td>
<td>4.1 ± 1.9†</td>
<td>4.9 ± 1.8†</td>
<td>6.5 ± 2.4</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Immunoglobulins, g/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26.5 ± 9.5†</td>
<td>22.4 ± 6.5</td>
<td>19.0 ± 6.5</td>
<td>&lt;18</td>
</tr>
<tr>
<td>IgG</td>
<td>20.1 ± 7.5†</td>
<td>17.1 ± 5.5</td>
<td>14.1 ± 4.9</td>
<td>8.5±10.0</td>
</tr>
<tr>
<td>IgA</td>
<td>3.3 ± 1.8</td>
<td>3.6 ± 1.7</td>
<td>2.9 ± 1.3</td>
<td>0.9±4.5</td>
</tr>
<tr>
<td>IgM</td>
<td>3.1 ± 3.8</td>
<td>1.7 ± 0.8</td>
<td>2.0 ± 1.2</td>
<td>0.6±2.6</td>
</tr>
</tbody>
</table>

Abbreviations: ND, not determined; pSS, primary Sjögren’s syndrome; SM/SL, submandibular-sublingual; SS, Sjögren’s syndrome; sSS, secondary Sjögren’s syndrome.

*Values are mean ± SD. As a reference, salivary normal values are given for a group of nonmedicated healthy control subjects.18
†Significant difference between SS and non-SS groups (pSS vs non-SS and sSS vs non-SS).
‡Significant difference between pSS and sSS groups.

Table 4. Correlation Between Tear Function Tests and Their Relationship to Duration of Subjective Eye Dryness in Patients With SS

<table>
<thead>
<tr>
<th></th>
<th>Spearman r (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duration</td>
</tr>
<tr>
<td>Schirmer test</td>
<td>-0.03 (.82)</td>
</tr>
<tr>
<td>Rose bengal score</td>
<td>0.24 (.03)</td>
</tr>
<tr>
<td>BUT</td>
<td>-0.05 (.67)</td>
</tr>
</tbody>
</table>

Abbreviations: BUT, breakup time; SS, Sjögren’s syndrome.

Correlation Between Ocular, Oral, and Serologic Manifestations in SS

The Schirmer test correlated significantly with the stimulated secretion of the SM/SL glands in patients with SS (r = 0.29, P < .01). The rose bengal score correlated highly significantly with the severity of radiographic changes observed with parotid sialography (r = 0.39, P < .01) when radiographic changes were graded by their size and shape as punctate, globular, cavitary, or destructive sialectasia.11 The total level of immunoglobulins in serum of patients with SS as well as the presence of SS-B antibodies correlated positively with the rose bengal score (immunoglobulin concentration: r = 0.22, P < .01; SS-B: t test, P < .05).

Comment

Tear and salivary gland measures were extensively investigated in patients with SS to compare exocrine disease manifestations regarding onset, severity, and progression. Obviously, patients with SS manifested decreased values for tear and saliva secretion, altered quality and composition of tear and saliva fluid, and marked pathologic changes with imaging techniques (ocular staining and parotid sialography). This is in contrast to findings in the patients in the non-SS group, who were referred because of similar subjective Sjögren-like complaints (eg, eye dryness, mouth dryness, and swelling of the salivary glands), but who, during the subsequent diagnostic procedures, showed partly dissimilar objective ocular and oral features. In addition, the majority of patients with SS had positive serologic findings for SS-A/B autoantibodies and high immunoglobulin levels in serum.

Among all studied tear tests, the rose bengal score remained the test of choice regarding diagnostic accuracy. Despite the use of improved thresholds by ROC plot analysis, BUT reached only moderate specificity and sensitivity as a test for SS. The low potential of the BUT for discriminating between patients with and without SS is in accordance with results from the study by Vitali and coworkers.5 With regard to the oral tests, whole, parotid, and SM/SL salivary flow showed significant negative correlations with the duration of oral complaints, and which stimulated SM/SL flow rate showed the strongest relationship with duration of oral complaints. This is in agreement with the work by Kalk et al,3 in which...
the stimulated SM/SL flow was found to be the strongest predictor of SS of all saliometric variables.

Concerning the diagnostic performance of the tear and salivary tests as currently included in the European classification criteria for SS, no unequivocal conclusions can be drawn from this study, because the same criteria were used in this study to support the diagnoses by which patients were categorized. Therefore, the calculated sensitivity and specificity from these tests are enhanced by an incorporation bias. Nevertheless, it can be concluded from this study that both the Schirmer criterion (wetting ≤5 mm/5 min) and the sialometric criterion (unstimulated flow rate of whole saliva ≤1.5 mL/15 min) as proposed in the European classification criteria seem to produce many false-positive test results (about half of the patients without SS in our study tested positive for these criteria). When further evidence from future studies supports that these secretory tests are indeed rather nonspecific for SS, the thresholds of these tests should be critically reconsidered, or the tests should be replaced by tests with better diagnostic performance in the international criteria for SS. We consider measurement of stimulated SM/SL flow an excellent alternative for the currently applied salivary flow test (measurement of unstimulated whole saliva), since it proved a very specific diagnostic test for the oral component of SS.3

Rose bengal scores correlated significantly with decreased tear gland function (Schirmer test), altered tearfilm quality (BUT), and the duration of subjective complaints of eye dryness. In line with these ocular data, oral studies have reported sialographic alterations (punctate, globular, and cavitary sialectasia) to be related to a decrease in salivary gland function 18.20 and to the duration of complaints of oral dryness. 12 Since sialography and rose bengal staining appear to relate to duration of subjective complaints and to glandular function, both diagnostic techniques may have valuable use for monitoring disease progression of SS. Disease progression can also be monitored by measuring salivary gland function, as different salivary profiles can be observed, depending on the duration of disease. 2 3 With regard to the salivary profiles, one of the most striking observations was reduction in SM/SL secretion accompanied by a normal to subnormal parotid flow. The decrease in SM/SL flow highly correlated with the decrease in lacrimal flow. This correspondence in secretory dysfunction may be somehow related to the fact that the lacrimal and SM/SL glands share the same seromucous exocrine nature. In contrast, the parotid gland is a serous exocrine gland.

Also, a clear correlation was noted between the rose bengal score, disclosing ocular surface damage resulting from tear gland involvement, and parotid sialography, disclosing ductal damage resulting from salivary gland involvement; this is in accordance with the scarce data from the literature. 20 The observed correlation between the 2 diagnostic tests does not necessarily reflect an etiologic connection, but it might be the logical result of the fact that both relate to duration and severity of exocrine malfunction.

The presence of SS-B autoantibodies in serum and/or hyperglobulinemia appeared to be connected with more severe ocular surface damage, as measured by rose bengal staining. This suggests that especially patients with SS with these findings in serum might be at risk for developing profound ocular surface damage and, hence, may require close monitoring by an ophthalmologist.

We conclude that tear tests correlate strikingly with salivary tests. Therefore, theoretically, positive results of evaluation of one component (either ocular or oral) complemented by serologic or histopathologic confirmation, might be sufficient to diagnose SS for clinical purposes, since both components appear to be related. Consequently, further diagnostic testing could be based on clinical indication only, thereby subjecting patients to fewer diagnostic procedures and, hence, achieving a quicker diagnosis with less discomfort. An exception to this theoretical reduction of diagnostic workup is patients who have tested positive for one component and suffer from subjective complaints that indicate involvement of the other component as well. In such cases, additional evaluation is still required to assess whether there is a need for preventive measures or symptomatic treatment. For research purposes, it is evidently preferable to perform full diagnostic testing on both components, yielding maximum external validity. Finally, the presence of SS-B autoantibodies in serum and/or hyperglobulinemia warrants close monitoring of the eyes, since these serologic variables appear to relate to more severe ocular surface damage.

Submitted for publication June 10, 2002; accepted August 6, 2002.

This study was presented at the First International Congress on Salivary Gland Diseases; January 28, 2002, Geneva, Switzerland.

| Table 5. Correlation Between Oral Function Tests and Their Relationship to Duration of Subjective Oral Dryness in Patients With SS |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                            | Duration                   | U-WS                        | U-Parotid                   | U-SM/SL                     | S-WS                        | S-Parotid                   |
|                            | Spearman r (P Value)       | Spearman r (P Value)        | Spearman r (P Value)        | Spearman r (P Value)        | Spearman r (P Value)        | Spearman r (P Value)        |
| U-WS                        | -0.36 (.07)                | 0.88 (<.001)                | 0.88 (<.001)                | 0.66 (<.001)                | 0.69 (<.001)                | 0.90 (<.001)                |
| U-parotid                   | -0.27 (.046)               | 0.76 (<.001)                | 0.77 (<.001)                | 0.69 (<.001)                | 0.67 (<.001)                | 0.68 (<.001)                |
| U-SM/SL                     | -0.37 (.005)               | 0.57 (<.001)                | 0.57 (<.001)                | 0.68 (<.001)                | 0.87 (<.001)                | 0.61 (<.001)                |
| S-WS                        | -0.47 (<.001)               | 0.75 (<.001)                | 0.75 (<.001)                | 0.68 (<.001)                | 0.87 (<.001)                | 0.61 (<.001)                |
| S-parotid                   | -0.30 (.03)                | 0.59 (<.001)                | 0.59 (<.001)                | 0.68 (<.001)                | 0.87 (<.001)                | 0.61 (<.001)                |
| S-SM/SL                     | -0.53 (<.001)               | 0.52 (<.001)                | 0.52 (<.001)                | 0.68 (<.001)                | 0.87 (<.001)                | 0.61 (<.001)                |

Abbreviations: S, stimulated; SM/SL, submandibular-sublingual; SS, Sjögren’s syndrome; U, unstimulated; WS, whole saliva.
REFERENCES