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Published in: British journal of ophthalmology

DOI: 10.1136/bjo.81.6.435

Citation for published version (APA):

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Abstract

Aims—To assess the course of tear gland function of patients with keratoconjunctivitis sicca (KCS) associated with primary (KCS-PSS) or secondary Sjögren’s syndrome (KCS-SSS), and of patients with KCS not related to Sjögren’s syndrome (KCS-NS).

Methods—In 106 patients with dry eye an ophthalmic diagnosis of KCS was made. Subsequent evaluations revealed a diagnosis of KCS-PSS in 31, KCS-SSS in 19, and KCS-NS in 56 patients. Follow up assessments have been performed 10–12 years after initial diagnosis.

Results—At baseline and at follow up tear gland function tests were worse in patients with KCS-PSS compared with the other forms of KCS. At follow up in the KCS-SSS patient group the tear gland function variables returned to marginal normal limits. In contrast with expectation, a marked improvement of the tear gland function variables in the KCS-NS patient group was noted.

Conclusions—In KCS-PSS patients tear gland function is characterised by a steady state situation. In KCS-SSS patients the normalisation of tear gland function variables most probably reflects a remission of the underlying disease. In view of the overall improvement in KCS-NS patients the term age related KCS should be avoided.


Keratoconjunctivitis sicca (KCS) is an eye disease caused by a secretion disorder of the main and accessory lacrimal glands that takes its name from the most conspicuous signs, a decrease in tear volume. KCS not related to Sjögren’s syndrome (KCS-NS) is considered to be a consequence of an age related involution of the glands, a hazardous diagnosis without histopathological confirmation. Less frequently, autoimmune induced lymphoid infiltration of the tear gland may lead to loss of function.

It is assumed that KCS-NS deteriorates more slowly and less profoundly than the dry eye states associated with primary (KCS-PSS) and secondary Sjögren’s syndrome (KCS-SSS), but hard data on the evolution of these distinct disease entities are not available. This makes it difficult to assess prognosis and to assist in patient counselling.

Ocular complications occasionally occur in KCS associated with Sjögren’s syndrome. Early differential diagnosis between KCS associated with Sjögren’s syndrome and KCS-NS is therefore important. Because of the possible development of extraglandular manifestations and an increased risk for lymphoproliferative disease, PSS patients need clinical evaluation on a regular base, whereas SSS patients need careful supervision because of their associated connective tissue disorder.

In the present study we assessed the course of tear gland function and the medical status in patients with KCS-PSS, KCS-SSS, and KCS-NS in a 10 year interval.

Methods

In the department of ophthalmology a clinical diagnosis KCS was made in 106 patients, based on the Schirmer test results, lysozyme tear fluid concentration, and the rose bengal criteria for Sjögren’s syndrome as proposed by Daniels and Talal. Seventy one patients qualified for the follow up examination.

To determine the statistical significance of differences between patient groups at study entrance and at follow up, the χ² test and generalised Kruskal–Wallis test, were used for dichotomous and continuous variables, respectively. Statistical significance of differences within patient groups between study entrance and 10 year follow up was determined with the McNemar test and Wilcoxon signed ranks test for dichotomous and continuous variables, respectively.

Results

STUDY ENTRANCE

Of the 106 patients at entry 73% were females. There were statistically significantly more females in the PSS patient group compared with the other two patient groups—93% versus

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Accepted for publication
13 January 1997
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Table 1 Baseline characteristics of KCS-PSS, KCS-SSS, and KCS-NS patient groups

<table>
<thead>
<tr>
<th></th>
<th>KCS-PSS (n=31)</th>
<th>KCS-SSS (n=19)</th>
<th>KCS-NS (n=56)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>29 (93)</td>
<td>11 (58)</td>
<td>37 (66)</td>
<td>**</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>55.8 (13.2)</td>
<td>58.2 (13.2)</td>
<td>50.7 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Duration (SD)</td>
<td>5.4 (5.1)</td>
<td>3.0 (2.6)</td>
<td>3.8 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Dryness of eyes (%)</td>
<td>28 (90)</td>
<td>15 (79)</td>
<td>51 (91)</td>
<td></td>
</tr>
<tr>
<td>Sandy feelings in eyes</td>
<td>25 (81)</td>
<td>10 (53)</td>
<td>47 (84)</td>
<td></td>
</tr>
<tr>
<td>Tear osyozyme concentration (µg/ml) (SD)</td>
<td>12 (39)</td>
<td>2 (10)</td>
<td>16 (29)</td>
<td></td>
</tr>
<tr>
<td>Schirmer-I test (mm/5 min)</td>
<td>4.5 (3.3)</td>
<td>6.6 (5.0)</td>
<td>9.9 (8.7)</td>
<td>**</td>
</tr>
<tr>
<td>Tear lactoferrin concentration (µg/ml)</td>
<td>4.6 (1.7)</td>
<td>3.0 (1.7)</td>
<td>3.4 (2.0)</td>
<td>**</td>
</tr>
</tbody>
</table>

Table 2 Dropout at follow up

<table>
<thead>
<tr>
<th></th>
<th>KCS-PSS</th>
<th>KCS-SSS</th>
<th>KCS-NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at entry</td>
<td>31</td>
<td>19</td>
<td>56</td>
</tr>
<tr>
<td>Death</td>
<td>8</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Unwilling to cooperate</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Patients at follow up</td>
<td>21</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>With rheumatoid arthritis</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>With dermatomyositis</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>With systemic sclerosis</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>With systemic lupus erythematosus</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3 Characteristics of KCS-PSS, KCS-SSS, and KCS-NS patient groups at follow up

<table>
<thead>
<tr>
<th></th>
<th>KCS-PSS (n=21)</th>
<th>KCS-SSS (n=12)</th>
<th>KCS-NS (n=28)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>19 (90)</td>
<td>8 (67)</td>
<td>29 (76)</td>
<td>**</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>65.8 (15.5)</td>
<td>66.2 (13.2)</td>
<td>58.9 (14.8)</td>
<td></td>
</tr>
<tr>
<td>Duration (SD)</td>
<td>17.7 (6.4)</td>
<td>14.4 (3.8)</td>
<td>15.4 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Dryness of eyes (%)</td>
<td>19 (90)</td>
<td>9 (75)</td>
<td>30 (79)</td>
<td></td>
</tr>
<tr>
<td>Sandy feelings in eyes</td>
<td>15 (71)</td>
<td>4 (33)</td>
<td>26 (68)</td>
<td></td>
</tr>
<tr>
<td>Tear osyozyme concentration (µg/ml) (SD)</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Tear lactoferrin concentration (µg/ml)</td>
<td>815 (570)</td>
<td>1971 (1029)</td>
<td>2163 (1252)</td>
<td>***</td>
</tr>
<tr>
<td>Schirmer-I test (mm/5 min)</td>
<td>5.5 (2.2)</td>
<td>12.5 (4.7)</td>
<td>12.0 (5.5)</td>
<td>***</td>
</tr>
<tr>
<td>BUT</td>
<td>3.8 (4.4)</td>
<td>7.0 (4.5)</td>
<td>7.1 (3.8)</td>
<td>*</td>
</tr>
<tr>
<td>Rose bengal test</td>
<td>4.7 (2.0)</td>
<td>3.3 (1.3)</td>
<td>2.1 (1.6)</td>
<td>***</td>
</tr>
</tbody>
</table>

KCS-PSS = keratoconjunctivitis sicca in association with primary Sjögren’s syndrome; KCS-SSS = keratoconjunctivitis sicca in association with secondary Sjögren’s syndrome; KCS-NS = keratoconjunctivitis sicca not related to Sjögren’s syndrome.

KCS-PSS and KCS-NS patient groups: b = p < 0.05; ** = p < 0.01; *** = p < 0.001.

KCS-PSS and KCS-SSS patient groups: a = p < 0.05; ** = p < 0.01; *** = p < 0.001.

Study follow up

After a 10 year period 71 patients were evaluable for follow up (Table 2). Owing to a variety of reasons 35 patients had dropped out: 24 patients had died, seven patients were unwilling to participate in the study, and four patients were lost for follow up as a result of moving to another location. At baseline no differences in ophthalmic variables were found between patients not evaluable for follow up and patients who were, with exception of suffering from a sandy feeling in the eyes.

Tear function tests

The osyozyme tear fluid concentrations in all three patient groups were well below the limit of 1400 µg/ml (Table 1). Lowest values were found in the KCS-PSS patient group, and no significant differences were noted between the KCS-SSS and the KCS-NS patient groups (Table 1). In the KCS-PSS patient group the Schirmer test values were low when compared with the other groups, whereas in this patient group highest values of the rose bengal test were noted (Table 1).

Signs and symptoms

At follow up no statistically significant differences in signs and symptoms between the three patient groups were noted (Table 3).

Tear function tests

In the 10 year period the KCS-PSS patient group remained essentially the same. The KCS-SSS group showed a tendency to improvement (Table 4). The patients in the KCS-NS group showed a significant and sizeable improvement in both symptoms and signs.

At follow up, again the KCS-PSS patient group showed the poorest tear function, the mean values of all variables, including tear fluid lactoferrin concentration, being within the cause of KCS in the KCS-NS patient group. Of the 19 KCS-SSS patients 11 had rheumatoid arthritis, four had systemic sclerosis, two had dermatomyositis, and two had systemic lupus erythematosus.
Abnormal values: tear lysozyme concentration <1400 µg/ml; Schirmer-I test = 5 mm/5 min; rose bengal test 4.5(1.9) 4.7(2.0) 2.2(1.4) 3.3(1.3) * 3.3(2.0) 2.1(1.6) **

Statistical significances between KCS-PSS and KCS-SSS patient groups: p = p < 0.01. Statistical significances between KCS-PSS and KCS-NS patient groups: b = p < 0.01.

Abnormal values: tear lysozyme concentration <1400 µg/ml; Schirmer-I test ≤ 5 mm/5 min; rose bengal test ≥ 3.

In conclusion, within the population of dry eye patients, referred to a university hospital ophthalmic outpatient’s department specialising in the dry eye syndrome, a considerable number of patients appears to suffer from Sjögren’s syndrome. Tear gland function in PSS patients is characterised by a steady state situation. In KCS-SSS patients a normalisation of tear gland function variables at follow up was noted. In view of an overall improvement of tear gland function in KCS-SSS patients seen over the years we suggest avoiding the term ‘age related KCS’.

Supported by a grant from the Dutch League Against Rheumatism (Het Nationaal Reumafonds).

We wish to thank Professor Dr G J Leppink and Dr J W G Jacobs for their advice on statistical analysis.


