Sjögren’s syndrome

Sjögren’s syndrome criteria

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American-European and Japanese Groups’ criteria compared and contrasted

Classification criteria are necessary to identify diseases for which no diagnostic or specific tests yet exist. They are especially of value within the systemic rheumatic diseases. Their main purpose is to organise crude data and information into useful information which will improve clinical care, treatment, and follow up. Classification criteria need to be foolproof so that it is unlikely that changes will be needed in the immediate future.

“Classification criteria should not be interdependent”

Furthermore, they should be carefully defined, with variables independent of each other, totally inclusive, mutually exclusive, and clinically relevant. Epidemiological studies show us that the most common disease within the systemic rheumatic diseases is primary Sjögren’s syndrome (SS), followed by rheumatoid arthritis. For primary SS, no international or American College of Rheumatology (ACR) classification set of criteria exists and as the time from a patient’s first symptom to diagnosis is 7–9 years, it seems obvious that a new set of classification criteria is needed to add to the seven different sets of criteria produced during the past 25 years.

The US-Eur Consensus Group is to be congratulated upon its agreement that the Schirmer-I eye test should be performed with standardised paper strips in unanaesthetised and closed eyes, thus following the European and the Japanese tradition. They also recommend that the equivalent oral test, unstimulated whole sialometry, should be performed during a 15 minute period without subjects having eaten or smoked in the two preceding hours as a minimum. This collecting time has, for many specialists in oral medicine/oral surgery/odontology, been considered unacceptable long, although evaluation and validation of the techniques showed that shorter periods were less valid. Therefore, in many places, evaluation of the basal function of the salivary glands is carried out with a shorter sampling time. Even the stimulated whole sialometry (chewing paraffin or equivalent) collecting period, for which five minutes is recommended, is often reduced. A fairly popular test in America and Japan is the two minute Saxon test, during which time the subject chews a preweighed cotton pellet. The difference between the weight before and after chewing gives the amount of saliva produced. In the evaluation of the function of the exocrine glands we are interested foremost in their function under basal conditions.

Lobal salivary gland biopsies

One of the arguments of the US-Eur Consensus Group against other established sets of criteria for SS is that the tests or combination of tests used have not been validated. Although this statement may be true from a statistical point of view, it is obvious that tests which have had their place in daily clinical use for 70 or 100 years have certainly proved their clinical validity. One must be cautious about making such a statement and wonder why the US-Eur Consensus Group has not validated its own test suggestions—for example, the lower lip biopsy: 4 mm² (as they suggest) sacrilege? Furthermore, it is the author’s experience that reading tissue section samples from small salivary glands—taken for diagnostic purposes—all too often gives rise to significant discrepancies even among pathologists. A second evaluation of labial salivary gland biopsy specimens significantly changed the initial diagnosis in 32/60 (53%) cases studied. It might be time to consider the idea that any oral tissue specimen for diagnostic purposes should be sent to an oral pathologist and when evaluating manuscripts which deal with oral specimens the editor of the journal should have the privilege of requiring sections for a blind secondary opinion among an expert histology panel.

Other classification criteria using lower lip biopsy as an investigational procedure stick to this original description. There is no proof at all that the anti-SSA and/or anti-SSB autoantibodies, whether in the tissue or circulating in the blood have any pathogenic role. And newer interesting proteins such as anti-fodrin, anti-muscarin, anti-Ku, anti-SS56 autoantibodies, and BAFF (B cell activating factor from the tumour necrosis factor family)—are not mentioned but might be more disease specific. By claiming item VI or item IV, or both, to be mandatory only a subgroup of patients with primary SS will be included. This might facilitate inheritance investigations, but for drug trials the European Medical Evaluation Agency (EMEA) in London might reject them, because they only represent a subgroup of patients. Medical companies doing phase II/III clinical trials as well as the EMEA must bear this in mind and devise stratification protocols.

Interdependency of classification criteria

The US-Eur Consensus Group continues the previous European group scheme by
Table 1  An overview of three sets of classification criteria for patients with Sjögren’s syndrome

<table>
<thead>
<tr>
<th>Name and year first introduced</th>
<th>American-European consensus group 2002</th>
<th>Japanese expert group 1999</th>
<th>Copenhagen criteria 1974-75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Require subjective ocular symptoms</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Require objective oral symptoms</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Minimum number of abnormal objective tests required for the diagnosis of KCS</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>How many abnormal objective tests required for the diagnosis of stomatitis sicca?</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Requirement for abnormal FS</td>
<td>&gt;1 focus per 4 mm²</td>
<td>&gt;1 focus per 4 mm²</td>
<td>&gt;1 focus per 4 mm²</td>
</tr>
<tr>
<td>Positive anti-SSA/SSB autoantibodies and or abnormal FS</td>
<td>Absolute requirement</td>
<td>Not mandatory</td>
<td>Not mandatory</td>
</tr>
<tr>
<td>Will usually miss past and/or present cigarette smokers?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

KCS, keratoconjunctivitis sicca; FS, focus score in lower lip biopsy.

*For the diagnosis of primary SS, positive anti-SSA/SSB autoantibodies and/or abnormal FS is mandatory plus at least four of six items; †For the diagnosis of primary SS, two of four different items should be positive; ‡For the diagnosis of primary SS, two abnormal functional tests from the eyes and mouth are required.

considering six different items for each patient. If four or more items (excluding a special combination, see below) are fulfilled the patient is said to fulfil the classification criteria for SS, but this only holds true if the items are independent of each other. An abnormal focus score (item IV) and the presence of anti-SSA and/or anti-SSB autoantibodies (item VI) in serum are, however, not independent variables. When tests are dependent on each other they should be either combined into one item or one of them discarded. Thus in most cases positivity of one is followed by positivity of the other, meaning that a subject either fulfils none or two of the four items. In the latter case if the patient in addition says “yes” to having ocular (item I) and oral (item II) symptoms, four items are fulfilled, but neither of these items proves the main clinical point of interest — the exocrine dysfunction.

Analysis of results

The US-Eur Consensus Group carried out a receiver operating curve analysis to define the accuracy of different combinations of positive items in correctly identifying patients, but although calculation of sensitivity and specificity is of importance, the predictive value (not stated) of a given test is more desirable.

Objectivity and subjectivity

It is somewhat surprising that the US-Eur Consensus Group still sticks to symptoms from the eyes (item I) and the oral cavity (item II). By saying yes to at least one of three predefined questions for each exocrine gland, two items are fulfilled. In a world otherwise requiring proof by objective methods 50% (two of four items) of the requirement for primary SS may be fulfilled by a subjective opinion — which is not easy to convert into hard data. On the other hand, experience tells us that children, many teenage patients, and young mothers of children born with complete congenital heart block quite often deny having symptoms, although all the objective tests for dysfunction of the exocrine glands give abnormal results. This probably arises because these young patients have had irritation and discomfort for most of their lives and accept any discomfort as a normal condition. The Japanese researchers who had the largest number of patients came to the conclusion that symptomatology should not be included as items in the classification criteria for SS but that the clinicians should be aware of them. Thus they only rely on objective test results. In so doing they support the Copenhagen criteria — the first classification criteria set up. The classification criteria set up by the Japanese expert group make a diagnosis easier.

Lachrymal and salivary glands

The US-Eur Consensus Group has not changed the requirements for objective proof of dysfunction of the lachrymal and salivary glands. The tests which can be performed are similar to those presented earlier by the Europeans. It is still emphasised, however, that of the various tests which can be performed, only one single abnormal test result is sufficient for objective evidence of lachrymal gland involvement (keratoconjunctivitis sicca) and of salivary gland involvement (stomatitis sicca). Simple objective signs are looked for in nearly every disease and it is difficult to understand why the expert group did not follow the rules of other criteria and require at least two abnormal test results in order to claim that the lachrymal and/or salivary glands are affected and not that one single test is specific. In contrast, following the tradition of the Copenhagen criteria, the Japanese expert group agreed that for the diagnosis of keratoconjunctivitis sicca and for the diagnosis of stomatitis sicca at least two objective tests for the lachrymal gland and at least two objective tests for the salivary gland should give abnormal results (table 1).

Investigational procedure

The US-Eur Consensus Group present a classification tree, showing that the investigational procedure for a given patient should start with answering ocular/oral symptoms followed by ocular examination and a lower lip biopsy. The latter procedure is being questioned more and more by patients and from a pragmatic point of view it seems more logical to start with a serum autoantibody profile if the consensus group’s proposals are otherwise followed.

The US-Eur Consensus Group also suggested that the presence of any three of the four items III, IV, V, VI is sufficient for the diagnosis of primary SS. In doing so the group broke the traditional and
original definition of primary SS as
being a systemic disorder with involve-
ment of lachrymal plus salivary glands.
With no dysfunction of the lachrymal
glands but sole involvement of the
salivary glands (item IV), as also observed
by histopathology (item IV), will more or
less automatically (as these are not inde-
pendent variables - see above) give rise
to fulfilling item VI. The Japanese expert
group did not reach this conclusion.

Exclusion criteria
Finally, the US-Eur consensus re-
introduced the exclusion criteria which
previously have been discarded with the
argument that some of them might be
irrelevant in the clinical situation. Before
making their final diagnoses, clinicians
should always go through possible exclu-
sion diagnoses, as when diagnosing
rheumatoid arthritis, etc. The Japanese
expert group followed the previous
agreement by not adding an exclusion
list because exclusion items should
follow relevant and good clinical prac-
tice.

Terminology
As stated in the introduction it is a great
step forward that the performance of
various tests is identical on either side of
the Atlantic Ocean. If different, it would
make little sense to perform validation.
Likewise the terminology should be
identical. For example, “extraglandular
manifestations” within SS is supposed to
mean organs different from the main
exocrine glands—even the thyroid, an
endocrine gland. Consequently, the
coined terminology “non-exocrine
manifestations” is to be recommended.\(^\text{11}\)

CONCLUSION
The US-Eur Consensus Group for Classi-
fication Criteria of Sjögren’s Syndrome is
to be congratulated on the proposal that
the basal test for the evaluation of the
lachrymal gland, the Schirmer-I test,
should be performed as most Europeans
have been doing (see above) and that the
basal test for the evaluation of the
salivary glands, the unstimulated whole
sialometry for 15 minutes, similarly
should be performed as most Europeans
are doing (see above). However, the most
important criterion of the group—
namely, that positivity of circulating
anti-SSA and/or anti-SSB antibodies,
and/or \(\geq 1\) lymphocyte focus per 4 mm\(^2\)
salivary gland tissue is an absolute
requirement, is not supported by scien-
tific evidence. Together with other crite-
rina and discussed in light of the simulta-
neous Japanese criteria, the US-Eur
proposed criteria might be valid for a
subgroup of patients with primary SS. In
daily clinical life, and as inclusion
criteria for patients taking part in drug
trials, they will probably have a limited
timeframe (fig 1).

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I thank Tom Manthorpe for his helpful
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Figure 1 An overview of the various sets of criteria and their year of introduction.
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