Sjögren’s syndrome criteria.

Manthorpe, Rolf

Published in:
Annals of the Rheumatic Diseases

DOI:
10.1136/ard.61.6.482.

2002

Citation for published version (APA):
Sjögren’s syndrome criteria

R Manthorpe

doi:10.1136/ard.61.6.482

Updated information and services can be found at:
http://ard.bmjournals.com/cgi/content/full/61/6/482

These include:

References
This article cites 10 articles, 4 of which can be accessed free at:
http://ard.bmjournals.com/cgi/content/full/61/6/482#BIBL

2 online articles that cite this article can be accessed at:
http://ard.bmjournals.com/cgi/content/full/61/6/482#otherarticles

Rapid responses
You can respond to this article at:
http://ard.bmjournals.com/cgi/eletter-submit/61/6/482

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections
Articles on similar topics can be found in the following collections
• Connective tissue disease (157 articles)

Notes

To order reprints of this article go to:
http://www.bmjournals.com/cgi/reprintform

To subscribe to Annals of the Rheumatic Diseases go to:
http://www.bmjournals.com/subscriptions/
Sjögren’s syndrome

Sjögren’s syndrome criteria

R Manthorpe

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.1 A look at articles published in English within this field shows that the European criteria from 1993 or 19962–3 are the ones most commonly cited, while the Copenhagen criteria4 are used in China and, seemingly, the ones most used worldwide.

COMMENTS AND COMPARISON

To establish intercontinental criteria an American-European (US-Eur) Consensus Group5 and a Japanese expert group6 have, without knowing of each other’s existence, simultaneously come up with two new—rather different—sets of classification criteria. We shall examine these with the main focus being upon the work of the consensus group, remembering that primary SS is defined as a chronic autoimmune exocrinopathy involving dysfunction of the lachrymal glands giving rise to keratoconjunctivitis sicca, plus dysfunction of the salivary glands giving rise to stomatitis sicca.

Tests for dysfunction of lachrymal and salivary glands

First of all, 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 unacceptably 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 original report it was stated1 that >1 focus per 4 mm² which—believe it or not—makes a huge difference.

“Don’t include symptoms in classification criteria—some patients deny them”

Other classification criteria using lower lip biopsy as an investigational procedure stick to this original description.7 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-muscarini, 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 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.8 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.

Obligatory criterion of the US-Eur Consensus Group

Probably the most revolutionary statement put forward by the US-Eur Consensus Group is their absolute claim, or obligatory criterion, that any given patient with SS must have either anti-SSA/anti-SSB autoantibodies (item VI) or a positive lower lip biopsy (item IV), or both. They define, as do the Japanese expert group, a positive lip biopsy as one focus of lymphocytes or more—adjacent to normal appearing mucous acini—per 4 mm² glandular tissue. In the original report it was stated1 to be >1 focus per 4 mm² which—believe it or not—makes a huge difference.

[www.annrheumdis.com](http://www.annrheumdis.com)
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 positivety of one is followed by positivity of the other, meaning that a subject either fulfills 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.3 In so doing they support the Copenhagen criteria—the first classification criteria set up.4

Smoking and Sjögren’s syndrome
A huge retrospective study has been presented at international rheumatological congresses in various parts of the world proving that the smoking of cigarettes had a great influence upon the focus score in the lower lip biopsy.8 Smokers as well as past smokers with primary SS diagnosed according to the Copenhagen criteria (at least two abnormal test results for the lachrymal glands plus at least two abnormal test results for the salivary glands) usually had a lower lip focus score of ≤1 and simultaneously no circulating anti-SSA and/or anti-SSB autoantibodies.16 There was a highly dose dependent curve, the threshold being 21 cigarettes a week.17 It is worth mentioning, that even for patients who had stopped smoking years before, the negative smoking effect upon the lower lip 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.

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

### Table 1 An overview of three sets of classification criteria for patients 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>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Require objective oral symptoms</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Minimum number of abnormal oral objective tests required for the diagnosis of KC5</td>
<td>1 focus per 4 mm²</td>
<td>≥1 focus per 4 mm²</td>
<td>≥1 focus per 4 mm²</td>
</tr>
<tr>
<td>How many abnormal objective tests required for the diagnosis of stomatitis sicca</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Requirement for abnormal F5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Positive anti-SSA/SSB autoantibodies and or abnormal F5</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.
original definition of primary SS as being a systemic disorder with involvement of lachrymal plus salivary glands. With no dysfunction of the lachrymal glands but sole involvement of the salivary glands (item V), as also observed by histopathology (item IV), will more or less automatically (as these are not independent 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 exclusion 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 practice.

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.11 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.11

CONCLUSION

The US-Eur Consensus Group for Classification 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 ≥1 lymphocyte focus per 4 mm² salivary gland tissue is an absolute requirement, is not supported by scientific evidence. Together with other criteria and discussed in light of the simultaneous 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 lifetime (fig 1).

ACKNOWLEDGEMENT

I thank Tom Manthorpe for his helpful scrutiny of my English.

Ann Rheum Dis 2002;61:482–484

REFERENCES


