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.[1] A look at articles published in English within this field shows that the European criteria from 1993 or 1996[2 3] are the ones most commonly cited, while the Copenhagen criteria[4] are used in China and, seemingly, the ones most used world wide.

COMMENTS AND COMPARISON

To establish intercontinental criteria an American-European (US-Eur) Consensus Group[5] and a Japanese expert group[6] 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 unanæsthetised 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 evaluation of the function of the exocrine glands we are interested foremost in their function under basal conditions.

Labial 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: is 4 mm^2 (as they suggest) sacrosanct? 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.[7] 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 mm^2 glandular tissue. In the original report it was stated[8] to be >1 focus per 4 mm^2 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.[8] 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)[9]—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 Sjögren's syndrome

Name and year first introduced	American-European consensus group 2002*[5]	Japanese expert group 1999†[6]	Copenhagen criteria 1974–75‡[4]
Require subjective ocular symptoms	Yes	No	No
Require objective oral symptoms	Yes	No	No
Minimum number of abnormal oral objective tests required for the diagnosis of KCS	1	2	2
How many abnormal objective tests required for the diagnosis of stomatitis sicca?	1	2	2
Requirement for abnormal FS?	⩾1 focus per 4 mm^2	⩾1 focus per 4 mm^2	>1 focus per 4 mm^2
Positive anti-SSA/SSB autoantibodies and or abnormal FS?	Absolute requirement	Not mandatory	Not mandatory
Will usually miss past and/or present cigarette smokers?	Yes	No	No

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.[6] 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.[10] 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.[10] There was a highly dose dependent curve, the threshold being 21 cigarettes a week.[10] It is worth mentioning, that even for patients who had stopped smoking years before, the negative smoking effect upon the lower lip focus score and the anti-SSA and/or anti-SSB autoantibodies was still evident decades later.[10] Although the consumption of cigarettes in America has been falling dramatically during recent years and is declining in Europe, more than half the adult world population is still smoking cigarettes! Consequently, it is to be expected that the proposal for diagnosing SS as put forward by the US-Eur Consensus Group cannot be used from its very beginning in most potential subjects.

The proposals of the US-Eur Consensus Group make it difficult for a diagnosis of SS to be obtained for past or present cigarette smokers. In contrast, 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

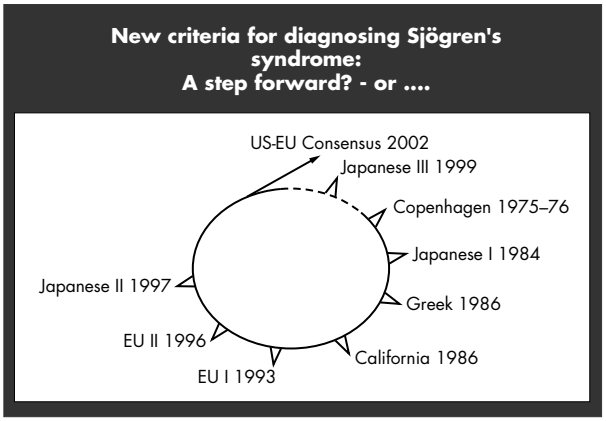

Figure 1 An overview of the various sets of criteria and their year of introduction. Reproduced with permission of the author[1] and the editor from Scand J Rheumatol 2001(suppl 115).

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 reintroduced 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 mm^2 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).

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