

Why do we have so many classification criteria for Sjögren's Syndrome? What will show up in the next millennium?

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Even though there has been a tremendous increase in our medical knowledge during the 20th century there are still diseases in which we do not yet understand the etiology and the involved pathophysiological mechanisms. Furthermore, the medical profession sometimes has difficulties in differentiating disorders as various patient categories might have similar although not identical symptoms. It is only possible to offer rational pharmacotherapy if the diagnostic procedures can discriminate between the closely related diseases because even closely related disorders often require different therapy. This is especially true within the systemic chronic rheumatic diseases in which there is a great need for internationally accepted classification criteria but such criteria does not exist today. In daily clinical practice most rheumatologists rely on the ACR (American College of Rheumatology) criteria e.g. within rheumatoid arthritis (1), systemic lupus erythematosus (2). Pitfalls are, however, evident. For example, erosions of the bones of the hands are a separate criterion for rheumatoid arthritis (1) although erosions in 70% of patients are known to start in the forefeet. Also, within systemic lupus erythematosus (N = 177) specificity and sensitivity for the classification criteria were tested against 2 (two) patients only with primary Sjögren's syndrome (SS) (2), although these two diseases have many symptoms in common. Moreover, it seems that neither of these two patients had discoid lupus erythematosus nor leukopenia (2).

One of the main problems within SS is the notion that at least three different specialties (ophthalmology, oral medicine & rheumatology) must be involved for the evaluation of the clinical history and for performing the diagnostic tests of the exocrine glands. Sjögren centres with this combined expertise only exist in a few places. Other problems within SS is the tendency to accept the diagnosis of primary SS if only one type of exocrine glands is involved (3) - although it has been clear since Sjögren's thesis (4), that the involvement and hypofunction of both the tear glands and the salivary glands is what the medical world requires to diagnose primary SS.

The past year's discussion concerning SS (5) has, however, brought attention to the distinction between primary and secondary SS - the latter being present if the patient has another well defined connective tissue disorder and in addition to that develops dysfunction of the lachrymal and/or salivary glands.

When planning and accepting classification criteria (Table1) it should be clear that the various criteria ought to be independent of each other, which is not always the case. E.g. in vitro experiments with biopsy specimens of swollen parotid and lachrymal glands have shown production of IgM-RF, gammaglobulin and anti-SS-A/-B antibodies. Parotid swelling and "positive serology" are thus not completely independent variables.

Much argumentation and concerns have dealt with the discrepancy between the subjective symptoms and the objective data. The Copenhagen (5) and Japanese II (3) criteria are the only set of criteria which rely solely on objective findings (Table 1). So, these criteria will have no difficulties in including patients without subjective ocular and oral complaints. This lack of subjective complaints in spite of severely impaired laboratory tests is rather common in young adults and even more evident in children.

If subjective symptoms are to be used as part of the classification criteria it must be remembered that there can be many symptoms. The oral and the ocular ones used by the preliminary European criteria (6, 7) have been shown to have the highest combined sensitivity and specificity when vali-

dated in a population of known SS patients. However, it can be questioned whether one of the ocular symptom questions – relief of symptoms if using tear drops – is merely a result of treatment rather than a genuine disease activity sign. At a time when the evaluation of diseases within internal medicine is judged and validated mostly by the results of objective tests or investigations, it seems strange to include treatment results among classification criteria - especially as other independent objective tests exist.

The three most commonly used objective tests to diagnose KCS are the Schirmer-1 test, the break-up time and the van Bijsterveld score which respectively measure the tear volume production, the stability of the tear film and the damage done to the ocular surface. However, objective tests for stomatitis sicca are fewer and not quite similar to the ocular tests. The unstimulated whole sialometry, which corresponds to the Schirmer-1 test, is the only oral test that is similar to an eye test. Therefore, other types of objective oral tests have been included. The salivary gland scintigraphy shows both a dynamic and functional picture, whereas the sialography and lower lip biopsy both are static and give little information about the actual production of saliva from the salivary glands (5). Furthermore, the evaluation of histological focus score, which has been considered by many researchers and clinicians to be "the golden proof" has recently got a severe set back, as the smoking habits of patients have been shown to have an impact on the development of focus score 1 (8). Thus present and even past smoking might result in "false negative" focus score (8). The "protective" effect of smoking was shown to be dose dependent already significant with only 21 cigarettes/week (8). This information combined with the finding of a "positive focus score" in 1-2% of the general population (9) imply that the result of lower lip biopsy focus score cannot be trusted in past and present smokers. As smoking habits change over time and between communities, it might be difficult to compare focus score percentages between Sjögren centres if the smoking history of the patients is not recorded.

Some sero-immunological markers and cellular counts are certainly over-represented in primary SS (IgM-RF; hyper-IgG-emia; ANA; anti-SS-A/SS-B antibodies; cryoglobulinemia; leukopenia; eosinopenia; low CD4-T-lymphocytes counts) but it has never been proven that these abnormalities play any pathophysiological role in the development of this disease. They, however, might give a clue to the prognosis in the individual case. The question whether any of these abnormalities must be required for the diagnosis of primary SS is still not answered. Where scientific investigations in which the primary outcome aim is strictly given, any combination of these abnormalities may give rise to more homogenous groups of patients which might be an advantage in, for example, genetic studies. In daily clinical diagnostically and practically follow-up there is no proof that the "sero-negative" patients suffer less/more than the "sero-positive" patients. Consequently cellular and immunological abnormalities need not be a *sine qua none* for the diagnosis of primary SS.

The scientific tools will certainly continue to develop in the next millennium and we are hopeful that some of the investigations are going to throw more light on the multifactorial pathophysiological mechanisms. Epidemiological studies tell us, that primary SS is found worldwide (11) and consequently it is not likely that local environmental factors play any greater role, and search for viral infections has so far been unsuccessful (12).

Treatment studies have shown that some medications are better than placebo (review 13). Although we do not know why some related drugs might be effective (14) while others are not (15) we feel that the effectiveness of dihomogammalinoleic acid (Efamol) could be due to an altered composition of the cellular membrane (16, 17). Muscarine receptors (M_1 - M_3) seem involved in the pathogenesis of SS and might thus explain the effectiveness of treatment with muscarine agonists, such as pilocarpine (18) and civelamine.

Promising animal experiments in the NOD mice, which spontaneously develop lymphocytic infiltrations in the lachrymal, salivary and pancreatic glands, have shown that treatment with the

truncated form of high affinity receptor for tumor necrosis factor alpha (sTNF-R1) prevents lymphocytic infiltrates into the lachrymal and pancreatic glands (19). Conclusions from similar animal studies and human treatment investigations in the beginning of the next millennium might give further clues to the ethiopatogenetic processes involved.

We feel confident that research within the neurological and other closely related spheres can be of great help even in primary SS. Unstimulated and stimulated whole sialometry in vivo result in abnormal low values, while experiments with stimulation of the nerves innervating the salivary glands in vitro from the same patients result in normal saliva production (20). This indicates that the transduction of the neurosignal could be abnormal (20). If dysfunction of the neural stimulation of the exocrine glands is shown to be of the greatest concern, it might give hope for tailored designed drugs in the next millennium. Only few medical companies are, however, at present involved in exocrine glandular research. If this theory is correct it supports the advice given to patients that partial or total excision of any exocrine gland should only be done under very special conditions.

In conclusion we describe the most common pitfalls when using the various classification criteria set within primary SS. Especially we point to the recent observation that present or past smoking may result in false negative focus score. Abnormal functional objective test results of the exocrine glands are to be preferred and should be the base for international classification criteria. As the ethiopathological processes are unknown some potential ones are discussed above. They should explain among others why some medications are better than placebo. We feel confident that the continuous development and research activity within basic science (e.g. the human genome project) and advanced medicine within the next millennium may explain the various factors involved in the ethiopathogenesis of primary SS.

Table 1. Similarities and dissimilarities for establishing keratoconjunctivitis sicca and stomatitis sicca according to the seven criteria sets required for the diagnosis of primary Sjögren's syndrome.

Name	Copen- hagen criteria	Japanese criteria	Greek criteria	California criteria	Preliminary European criteria	European classification criteria	Preliminary revision of Japanese criter.
Invented	1975/76	1977	1979	1986	1993	1996	1997
Ref. with discussion	5	5	5	5	6	7	3
Dry eye and/or mouth symptoms	-	+	+	+ 1)	+ 4)	+ 4)	-
Exclusively objective abnormalities	+	-	-	+ 1)	- 4)	- 4)	+
Symptoms and abnormal objective test results	-	+	+	+ 1)	+ 4)	+ 4)	-
Uses routinely the: Schirmer-1 test	+	+	+	+	+	+	+
Break-up time	+	-	-	-	-	-	-
van Bijsterveld score	+	+	+	+	+	+	+ 5)
Fluorescein test	-	+	-	+	-	-	+
Accept one abnormal tear gland test as evidence of KCS	-	-	+	-	+	+	-
At least two abnormal tear gland tests as evidence of KCS	+	+	-	+	-	-	+
Use routinely: History of parotid gland enlargement	-	- 2)	+	-	-	-	-
Unstimulated whole saliva	+	-	-	-	+	+	-
Stimulated whole saliva	-	-	-	-	-	-	+
Stimulated parotid flow rate	-	-	+	+	-	-	+
Sialography	+	+	-	-	+	+	+
Salivary gland scintigraphy	+	-	-	-	+	+	+
Histology of glands from lower lip biopsy	+	+ 3)	+	+	+	+	+
Histology as a separate criterion	-	+	+	+	+ 4)	+ 4)	+
More than one abnormal oral test – incl. lower lip biopsy	+	+ 3)	+	+	- 4)	- 4)	+
Can Sjögren's syndrome be diagnosed if lower lip biopsy is refused or normal?	+	-	-	-	+ 4)	+ 4)	+
Use abnormal values in serum: anti-SS-A/Ro or -SS-B/La ab or ANA or IgM-RF	-	-	-	+	+ 4)	+ 4)	+
	-	-	-	+	+	-	-
Operates with terminology probable/definite SS	-	+	+	+	-	-	+

1. Prefer to rely on objective tests only.
2. Recurrent salivary gland swelling is a separate criterion for probable Sjögren's syndrome.
3. Biopsy from tear gland may replace lower lip biopsy.
4. Require at least 4 (of least which two might be subjective) of 6 items fulfilled.
5. Accept van Bijsterveld score at 1 as abnormal, where others only accept at least 4 as abnormal (at a 0-9 scale).

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