Incomplete Sjögren's syndrome

There are many autoimmune diseases and each of them has at least one feature that is characteristic for the disease. This feature may be a single symptom or sign but is more commonly a combination of several symptoms and signs. Diseases can be recognized by their characteristic combination of features, the so-called "face" of the disease. This "face" plays a crucial role in the diagnostic process for the disease.

In addition to the characteristic (specific) features, there are many nonspecific features such as fatigue, (nonerosive) arthritis, myositis, Raynaud phenomenon and several abnormal laboratory findings (see the orange circle in figure 19.1) that occur in many auto immune diseases. The clinical relevance of these nonspecific features is highly variable. Nonspecific features can be attributed to a particular disease if there is also a characteristic feature of the disease in question. This is illustrated by the red area in figure 19.2. In this example, typical features of Sjögren's syndrome are present in which case the accompanying nonspecific features such as fatigue or antinuclear antibodies (ANA) are attributed to Sjögren's syndrome as well. For nonspecific features that are treated differently depending on the disease to which they belong, additional investigations may be required to exclude a background other than Sjögren's syndrome.

Examples of this are arthritis and polyneuropathy where rheumatoid arthritis and diabetes mellitus have to be excluded respectively.

The next step may be to investigate whether the patient fulfils the diagnostic criteria for the most likely diagnosis, e.g. Sjögren's syndrome. This is especially

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**Figure 19.1** Schematic representation of nonspecific (orange circle) and more or less disease specific features (yellow circles). None of the symptoms and signs are present in all patients with a particular disease. Abbreviations. CCP: cyclic citrullinated peptide; ANA: antinuclear antibodies; RF: rheumatoid factor; BM: basal membrane; IF: immunofluorescence.

**Figure 19.2** Schematic representation of a particular combination (red area) of nonspecific and more specific features suggesting Sjögren's syndrome. Abbreviations: see legend of figure 19.1.
In the majority of cases within the first five years of onset, to a defined systemic autoimmune disease occurs. The evolution of patients with an undifferentiated onset will not develop of all pathologic features. However, about 70% of patients with an undifferentiated onset may evolve to definite conditions, or remain indefinitely undifferentiated, or experience a remission. The disease in patients with an undifferentiated systemic autoimmune disease is characterized by the absence of major organ involvement.

The laboratory profile of stable undifferentiated connective tissue disease is mild and characterized by the presence of single autoantibody specificities. This is well illustrated by the study of Brun et al. They found that only 40.9% of patients with an expert clinical diagnosis of Sjögren's syndrome fulfilled the criteria for Sjögren's syndrome (see chapter 4 for further details of this study). There are at least two possible explanations for this discrepancy.

The first may be that this is due to the fact that symptoms or signs do not always begin at the same time and that the patient will fulfill the diagnostic criteria at some point in the future. Clinical experience indicates that this will only happen in a minority of patients and that the majority will not fulfill diagnostic criteria even 10 or 20 years later.

A second explanation could be that any method of dividing patients into two groups (those with and those without Sjögren's syndrome using whatever decision rule), is very artificial implying that different rules will never give the same result.
Vaz et al analysed 184 patients with UCTD. The patients of this group with antibodies to SSA/Ro and/or SSB/La (27% of the cohort) presented a higher prevalence of leukopenia and sicca syndrome but not of other clinical features suggestive of Sjögren’s syndrome. These data prove that there is an intermediate group between healthy people and people with "full" (fulfilling the criteria) Sjögren’s syndrome that has features that are characteristic of Sjögren’s syndrome (sicca syndrome and antibodies to SSA/Ro and/or SSB/La). Based on data on the course of the disease in patients with UCTD, the majority of them will probably not evolve to full Sjögren’s syndrome. Such intermediate groups were found previously in patients with interstitial cystitis/bladder pain syndrome (see figure 19.4).

None of the intermediate patients has evolved to a differentiated connective tissue disease such as Sjögren’s syndrome or SLE to date (unpublished data, J.P. van de Merwe).

Ramos-Casals et al analyzed the clinical features of patients with a well-established diagnosis of primary Sjögren’s syndrome according to the 1993 criteria and tested whether they fulfilled the 2002 classification criteria. The main difference between the 1993 and 2002 criteria is that the latter require 1. a positive salivary gland biopsy, or 2. the presence of antibodies to SSA/Ro and/or to SS-B/La. The serological item was also fulfilled in the 1993 criteria if a test for ANA or rheumatoid factor was positive. Only 286 (45%) of 507 Sjögren’s patients according to the 1993 criteria fulfilled the 2002 criteria. A similar low sensitivity of the 2002 criteria as compared to the 1993 criteria was found previously in prevalence studies.

It is shocking that there is no formal diagnosis for a large group of patients who fulfil the 1993 criteria but not the 2002 criteria for Sjögren’s syndrome.

From these results it can be concluded that in addition to patients who fulfil the 2002 classification criteria for Sjögren’s syndrome, another group exists of about the same size. These patients have similar local and systemic disease manifestations, and fulfil the 1993 criteria for Sjögren’s syndrome but not those of 2002. It is shocking that there is no formal diagnosis for this large group of patients while it is crystal clear that they have the same disease as those who fulfil the 2002 criteria for Sjögren’s syndrome.

Recently proposed diagnostic criteria for interstitial cystitis/bladder pain syndrome show that the exclusion of patients with typical clinical features of the disease in question can be avoided by the introduction of various types of disease within the classification. This allows that a single set of criteria with subtyping is useful in clinical practice as well as for scientific studies.
Keratoconjunctivitis sicca, focal lymphocytic sialoadenitis and sicca syndrome

The diagnosis of Sjögren’s syndrome is made on the basis of exclusion of diseases that may mimic Sjögren’s syndrome (confusable diseases), such as sarcoidosis and lymphomas. In addition, positive findings are necessary, such as:

- eye symptoms
- mouth symptoms
- swelling, duct abnormalities and lymphocytic infiltration of salivary glands
- diminished tear secretion
- diminished saliva secretion
- autoantibodies to SSA/Ro and/or SSB/La

Usually, for a diagnosis of Sjögren’s syndrome, 4 items have to be documented. When patients do not fulfill the diagnostic criteria for Sjögren’s syndrome and other diseases are excluded, it is likely in many cases that the disease is essentially the same as Sjögren’s syndrome but with less manifestations (figure 19.5).

The Swedish ophthalmologist Henrik Sjögren became famous because he recognized that some patients with keratoconjunctivitis sicca may have particular systemic features, a syndrome later described as Sjögren’s syndrome. Other patients have typical eye and mouth symptoms without objective abnormalities, usually called sicca syndrome. Other patients have parotid swelling, an abnormal lip biopsy and antibodies to SSA/Ro and SSB/La, with no eye symptoms or abnormal eye tests for 20 or more years. This may be called focal lymphocytic sialoadenitis.

There is no scientific basis nor is it reasonable to consider these separate combinations of features of Sjögren’s syndrome as diseases that have nothing to do with Sjögren’s syndrome. The opposite seems more logical and more likely.

Conclusion

The presented data are compatible with the hypothesis that there is a continuous spectrum from no disease to full-blown Sjögren’s syndrome. Any cut-off point for the diagnosis of Sjögren’s syndrome is artificial in this situation and suggests that there are only two possible outcomes: you have Sjögren’s syndrome or you do not. Application of a cut-off point in clinical practice is a self-fulfilling fallacy that causes a lot of harm for Sjögren’s patients who do not fulfill the criteria.

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**Figure 19.5 Flow chart for the diagnosis of Sjögren’s syndrome (see chapter on diagnosis for further details. The yellow squares show the number of criteria items present.**

*Abbreviations: ES: eye symptoms; MS: mouth symptoms; ET: abnormal eye tests; LB: abnormal lip biopsy; KCS: keratoconjunctivitis sicca; FLS: focal lymphocytic sialoadenitis.*

The following list represents a simplified example of the possible continuum:

- no disease
- sicca symptoms of the eyes
- sicca symptoms of the mouth
- keratoconjunctivitis sicca
- focal lymphocytic sialo-adenitis
- Sjögren’s like syndrome (3 items of the 1993 or 2002 criteria present)
- patients who fulfil the 1993 criteria but not the 2002 criteria for Sjögren’s syndrome
- patients who fulfil the 2002 criteria for Sjögren’s syndrome
**Sjögren or SLE, or Sjögren and SLE?**

Patients with primary Sjögren’s syndrome may fulfil the diagnostic criteria of SLE without having SLE. See text below

**Fulfilling diagnostic criteria without having the disease**

The fact that not all patients who are considered to have a particular autoimmune disease by experts fulfil the diagnostic criteria for that disease is an inevitable consequence of making diagnostic criteria as specific as possible to avoid the enrolment of patients that do not have the disease under investigation. It is less well-known that the opposite may also occur: patients may fulfil diagnostic criteria without having the disease. This is illustrated in the next example.

Patient X with Sjögren’s syndrome has the following manifestations of the disease:

1. fatigue
2. symmetric nonerosive polyarthritis
3. a daily feeling of dry mouth ≥3 months
4. a recurrent sensation of sand in the eyes
5. Schirmer test OD/OS: 3 and 4 mm
6. photosensitivity
7. leukocyte count: 3.2 x 10⁹/l
8. antinuclear antibodies (ANA)
9. antibodies to SSA/Ro and SSB/La
10. rheumatoid factor 400 IU/ml; the anti-CCP test is negative

The patient fulfils the American-European criteria 1 for the diagnosis of primary Sjögren’s syndrome on the basis of the manifestations 3, 4, 5, and 9. The other disease manifestations can also easily be attributed to Sjögren’s syndrome: photosensitivity correlates with the presence of antibodies to SSA/Ro, 60-70% of Sjögren’s patients have a positive ANA test, 10-15% has arthritis and 25% a low leukocyte count.

The patient also fulfils the ARA criteria for the diagnosis of systemic lupus erythematosus 3 on the basis of manifestations 2, 6, 7 and 8.

On the basis of the symmetric polyarthritis and the rheumatoid factor, a diagnosis of early rheumatoid arthritis could also be considered. However, the negative test for antibodies to CCP strongly argues against rheumatoid arthritis. 4

**References**

CHAPTER 19 INCOMPLETE SJÖGREN'S SYNDROME

JOOP P. VAN DE MERWE - SJÖGREN'S SYNDROME: INFORMATION FOR PATIENTS AND PROFESSIONALS

Latest additions or modifications (date: dd.mm.yyyy)

<table>
<thead>
<tr>
<th>Date</th>
<th>Addition/Modification</th>
<th>Pages</th>
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</thead>
<tbody>
<tr>
<td>01.08.2009</td>
<td>first version</td>
<td>147-150</td>
</tr>
<tr>
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<td>conversion to another DTP program</td>
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<tr>
<td>09.09.2009</td>
<td>more about negative effects of using cut-off point in diagnostic criteria in clinical practice</td>
<td>141-142</td>
</tr>
<tr>
<td>09.02.2010</td>
<td>paragraph added on keratoconjunctivitis sicca, focal lymphocytic sialoadenits and sicca syndrome; idem figure 19.5</td>
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