British Sjögren's Syndrome Association

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Diagnosing Sjögren's Syndrome

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This may seem pretty obvious – Sjögren's Syndrome, described over 70 years ago, describes a condition in which inflammation of the secretory glands leads to malfunction of the glands thus causing symptoms and signs of dryness. In the outpatient clinic this may be entirely fine and the 'diagnosis' of Sjögren's Syndrome is down to the judgement of the doctor reviewing the patient in front of them.

For research studies it is more complicated however. What are the criteria to distinguish primary (PSS) from secondary Sjögren's Syndrome (SSS) – is it purely the lack of another rheumatic disease? Are there any conditions which look like Sjögren's Syndrome but aren't (exclusion criteria)? Do you have to have dryness symptoms as well as dryness on tests such as the salivary flow rate or Schirmer's filter paper test of eye dryness? Do you have to have dryness of the eyes and mouth or just one or the other? Where do the autoantibody tests, such as for anti-Ro and anti-La antibodies, fit in?

The reason why this is important is that if I publish a paper saying that drug X works fantastically well in 100 patients with Sjögren's Syndrome (according to my criteria to define Sjögren's Syndrome) and you come along and say 'actually half of your patients do not have SS according to my criteria' then we have a problem!

In other rheumatic conditions such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) they have had internationally agreed 'classification' criteria for these diseases for many years – in the case of RA since the 1950s although they were revised again by international agreement in the 1970s and all clinical trials of new medications worldwide use the same criteria.

Until the landmark papers by Dr Claudio Vitali in 1993 and 2002 in which a large number of European specialists in Sjögren's Syndrome carried out a research project to develop internationally agreed criteria, Sjögren's Syndrome was basically in a bit of a mess. There were three main criteria sets in use (as well as a few others) – the San Diego (Californian), the Copenhagen and the Japanese criteria. Each of them was slightly different (and I will discuss this below) and it was very difficult to compare the data from one paper using one of these criteria with another paper using a different criteria set. It also put the pharmaceutical companies off – why invest money in a clinical trial if the experts cannot agree which patients to include.

After the initial paper in 1993 Dr Vitali carried out some further research and this time, an international (European and North American) group of experts, including many of the most respected experts in North America signed up to an internationally agreed criteria set – the American-European Consensus Criteria (AECC).

Let us now review the different criteria sets including this one.

1. The Copenhagen Criteria: Dr R Manthorpe et al 1974-75
These criteria required objective evidence of dryness of both the eyes and the mouth using two tests for each. A positive lip biopsy with at least two collections of lymphocytes (white cells) seen down the microscope in the biopsy sample counted as one of the oral tests. Autoantibodies were not part of this criteria set.

2. The San Diego Criteria: Dr R Fox et al 1986
These criteria also required objective evidence of dryness of both the eyes and the mouth but this time requiring one test only. In addition, however, a positive lip biopsy was also compulsory and evidence of an autoantibody – whether it was anti-Ro, anti-La, rheumatoid factor or antinuclear antibody was also required. One issue here is that the presence of an autoantibody is often dependent on the genetic background of the individual (which may differ quite substantially between China and America for example) and there is no rheumatic disease where the diagnosis is absolutely dependent on the presence of a particular antibody (many patients with RA do not have rheumatoid factor, rare patients with SLE are ANA negative, a minority of patients with scleroderma have anti-centromere or anti-Scl 70 antibodies) so there are going to be antibody negative patients who are 'missed' by these criteria although they might be called 'possible Sjögren's Syndrome'. These criteria also excluded patients with lymphoma, sarcoidosis, acquired immunodeficiency, graft versus host disease – exclusions which also appear in the European criteria.

3. The Japanese Criteria: Dr T Fujibayashi et al 1999
These are broadly similar to the Copenhagen criteria. They only require the presence of a single collection of lymphocytes per high powered field on labial gland biopsy instead of at least two in the Copenhagen criteria.

4. The AECC: Dr C Vitali et al 1993 and 2002
These criteria are quite different to the above three. For a start they include symptoms (dry eyes and/or dry mouth and/or salivary gland swelling) assessed using three eye and three mouth questions, as well as objective criteria, or, in some cases, as an alternative to objective criteria. They do not require the presence of both oral and ocular dryness (and many patients in the routine clinic have only one or the other not both and these will be missed by the other criteria).

The preliminary criteria published in 1993 did not require all the patients to have either a positive biopsy (one or more collection of lymphocytes i.e. the lower threshold like the Japanese criteria) or autoantibodies. The problem, therefore, was that patients could fulfil these criteria without any evidence of an inflammatory cause of their dryness. The revised AECC, however, dealt with this by requiring the presence of either anti-Ro or anti-La (or both), or, a positive lip biopsy. It did mean, however, that in certain patients with anti-Ro and anti-La antibodies (but not all) they allow for the fulfilment of the criteria without having to have a labial gland biopsy – a great relief for many patients. The AECC also allow for the minority of patients who do not have any dryness symptoms – if you have three of; 1) objective dry mouth on testing, 2) objective dry eye on testing, 3) anti-Ro and/or

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anti-La antibodies, 4) a positive lip biopsy then you also fulfil the criteria – i.e. quite similar (but not identical) to the San Diego 'objective only' criteria.

Conclusion

So where does this leave us now? Well in my experience there are very few people who have symptoms but no positive objective tests so I do not think that we are over-diagnosing many people. It requires the presence of antibodies or biopsy, (or both), which means that there has to be some evidence of an immune process, it allows some people not to have a lip biopsy (a great advance), it includes those rare people with objective features but no symptoms (yet), it does not include ANA or rheumatoid factor (which are relatively common and I feel are not specific enough) and all in all is a very flexible and easy to use set of criteria.

More to the point, over the past few years there are very few studies in Sjögren's Syndrome, which do not use these criteria. In those that do not, they generally also include some analysis of data using the AECC as well.

Not everybody is entirely satisfied – there are criticisms that can be levelled at the methodology used to develop the AECC (no study is perfect) and no criteria set is ever fixed in stone – recent developments in salivary gland ultrasound, for example, may allow this technique to be used to diagnose Sjögren's Syndrome with great accuracy.

A study funded by the American National Institutes for Health (The 'SICCA Study'), is, among other projects, going to revisit the criteria issue and we will see, with great interest, what they come up with. Clearly it is very important to welcome new research into Sjögren's Syndrome so I wish this initiative well. I hope, however, that we do not end up back where we were some years ago with more than one criteria set and a split in the international community of 'Sjögrenologists' as I, for one, will feel that this would be a great pity.