British Sjögren's Syndrome Association

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Sjögren's Criteria: an old debate re-opened

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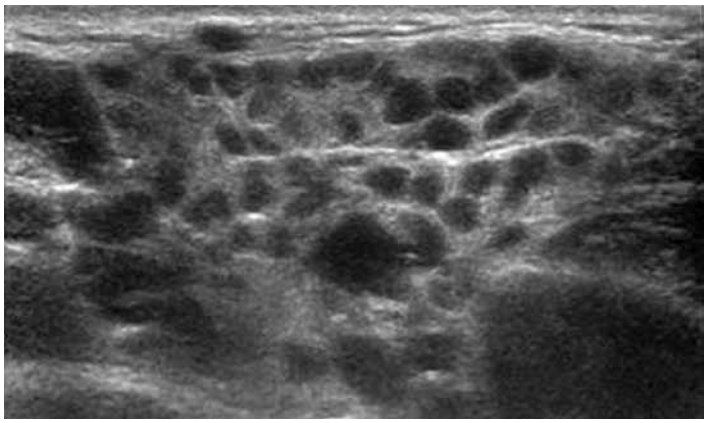
How do you diagnose Sjögrens Syndrome (SS)? A simple question but not a simple answer. In clinical practice we would generally expect most people with SS to describe some symptoms of dryness– usually of the eyes or mouth, have some physical evidence of reduced tear and/or saliva production, and also have evidence of some autoimmune process underlying their dryness. Currently, this means being antibody positive by having either of the autoantibodies called anti-Ro or anti-La, which are found in about 70-80% of SS sufferers, or evidence of inflammation on a labial (lip) gland biopsy.

In the last few years or so, ultrasound examination of the Salivary glands showing a characteristic 'Swiss cheese' appearance is also being used to give a general idea of whether SS might be present although this is not a conclusive test in antibody-negative patients – a labial gland biopsy is still a requirement to investigate matters fully in many patients. Furthermore, the labial gland biopsy also gives an idea over the long-term risk of lymphoma through the presence of characteristic structures called germinal centres being present the biopsy.



Ultrasound of the parotid salivary gland of a patient with advanced Sjögren's Syndrome showing the characteristic 'Swiss cheese' appearance of black areas and white lines instead of the normal plain grey appearance throughout (with thanks to Dr John Rout for kindly providing this picture).

Ultimately, however, not everyone falls neatly into the above categories. Furthermore there is no single test that can be used on its own – for example the biopsy sample is not always positive – presumably because the bit of it with the inflammation was missed, or the anti-Ro/La antibodies are negative but other antibodies such as the antinuclear antibody (ANA) or rheumatoid factor (RF) are seen. Another example is that the anti-Ro/La antibodies can be undetected in the blood and are picked up for some other reason. For example they can rarely transfer from a mother with them into their baby's blood stream and cause heart rhythm problems in the baby, which then leads to their identification in the mother. However, if the mother has no symptoms does she have SS? These are the sort of issues that arise and the diagnosis is then determined by the doctor in consultation with the patient.

Clinical practice is one thing but research is another. In research there has to be absolute clarity about who does and does not have Sjögrens Syndrome so that the information from research can be properly evaluated i.e. everyone knows what group of people are being discussed in the research paper. As a result of this, the medical community has developed what are called 'classification criteria' to 'classify' who has a particular condition. In many ways these 'classification criteria' are also used as a rule of thumb for diagnosis, and as such they are not called 'diagnostic criteria' because there needs to be more 'wiggle room' in clinical practice, which is only right and proper.

In the 1980's/1990's the issue of classification criteria was hotly debated among the community of researchers in SS and there were at one time 11 different sets of classification criteria for SS all with their proposers and critics. In 2002 Professor Claudio Vitali and colleagues developed the American-European Consensus Group (AECG) classification criteria for SS. These required evidence of three out of four of the following:

- Reduced tear production
- Reduced whole saliva production
- Positive anti-Ro/La antibodies
- Positive lip gland biopsy.

In patients with only two of these four (but either the antibodies or the biopsy had to be one of these two) they also had to have both dry eyes and dry mouth to fulfil the criteria.

These AECG criteria have been very widely used as the gold standard ever since then. Very occasionally there has been a paper from Japan using the 'Japanese criteria' but other than that the AECG criteria have been used virtually without exception. They are easy to use in a routine clinic and those individuals with positive anti-Ro/La antibodies and features of

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both dry eyes and dry mouth can have the diagnosis confirmed without special tests such as the biopsy (although we still recommend the biopsy to assess lymphoma risk even in these individuals). What didn't happen, however, was for these criteria to be endorsed by any of the large international organisations such as the American College of Rheumatology (ACR) or the European League against Rheumatism (EULAR).

In 2012, however, the Sjögrens International Collaborative Clinical Alliance (SICCA) published an alternative provisional criteria endorsed by the American College of Rheumatology (ACR). To fulfil these criteria patient have to have two of three components:

- Positive anti-Ro or anti-La antibodies or a combination of both antinuclear antibodies at high level (ANA>1:320) and a positive rheumatoid factor (RF)
- A positive lip biopsy;
- Objective eye dryness measured using a specific assessment the Ocular Staining Score (OSS).

The SICCA group was formed by Dr Troy Daniels and colleagues in the USA and elsewhere following the award of a large research grant of over $5 million by the National Institutes for Health (NIH) in the USA. It is currently led by Professors Caroline Shiboski and Lindsey Criswell.

In many ways these alternative criteria are very similar to the AECG criteria. Both have the same biopsy criteria. Both were established in people with dryness symptoms. The ACR criteria allow ANA+RF not just anti-Ro/La which is a matter of debate but only affects perhaps 1% of potential sufferers so this difference will likely be resolved by discussion one way or the other. They don't allow for other measures of assessing dry eyes such as the Schirmer (blotting paper) strip and nor do they allow for saliva measurements, as an alternative to biopsy or dry eye assessment, an option in some patients. These changes from the AECG means that a doctor in a clinic knowing the antibody results can't make the 'diagnosis' without a formal eye assessment by an ophthalmologist or a lip biopsy result (which in some circumstances they can with the AECG criteria) and this perhaps makes them less flexible in clinical practice. In theory it allows for the diagnosis to be made in someone with a positive biopsy and positive antibodies even if they don't have any dryness symptoms or measurements, which is an interesting topic for debate. The proponents of these criteria would argue that everyone should have a lip biopsy and an ophthalmology expert assessment anyway (which is generally true) so what does this matter anyway. Furthermore these criteria can be simpler in some situations i.e. someone with dry eyes in an ophthalmology clinic using the OSS and positive anti-Ro antibodies would fulfil these criteria without further assessment, so in this situation it is simpler than the AECG criteria.

Perhaps the summary, however, is that both criteria seem to identify the same patients in most circumstances i.e. if the patient has dry eyes or dry mouth as a starting point it doesn't seem to matter too much which approach you use – the AECG or the ACR-SICCA provisional criteria – the outcome in terms of who gets classified with SS is pretty much the same.

At the moment there is discussion taking place about trying to blend the two criteria together into a single new international consensus criteria and then seeking endorsement for this from ACR and EULAR. This would avoid the situation of having more than one set of criteria for research which is likely to cause confusion and unhappiness in the field. Hopefully these discussions will be successful.