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Moving towards new criteria in SLE, Sjögren's and APS

SP0010 CLASSIFICATION OF SLE – CHALLENGES AND POTENTIAL SOLUTIONS

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Systemic lupus erythematosus is characterized by a wide variety of autoantibodies, which, if pathogenic, can lead to inflammation, damage, thrombosis or functional defects of essentially all organ systems. The 1982 American College of Rheumatology classification criteria and their 1997 revision have greatly influence the disease concept over the last decades. With the at least 4 out of 11 criteria to be present, they essentially depict the concept of multiple autoantibodies and multiple organs systems. Putting all items on equal weight made the system relatively easy to use and to memorize, but this approach was not entirely intuitive. Dermatologists have criticized that patients could meet the criteria based on fulfilling all 4 mucocutaneous criteria only. Importantly, sensitivity was felt to be suboptimal, reaching 83% in the cohort of the SLE International Collaborating Clinics (SLICC) group, and lower values in very early disease.

The 2012 SLICC SLE classification criteria introduced two new concepts. First, patients have to be positive for autoantibodies, namely for anti-nuclear antibodies (ANA) or antibodies to double-stranded DNA. Second, if patients are autoantibody-positive, classification criteria can be fulfilled by nephritis on histology without any other items. The SLICC groups also introduced large lists of skin and neuropsychiatric symptoms and refined some of the definitions. While many of these ideas are intuitively correct, not all were derived in a pre-defined scientific way. These criteria managed to increase sensitivity to 97% in their own validation data and to a range of 92–99% in other cohorts. At the same time, however, the SLICC set lost specificity, falling to 84% as compared to the 96% of the ACR criteria. This trade-off was presumably influenced by the SLICC group's choice to keep the overall structure the same. Early disease sensitivity was still not optimal.

In a large transatlantic project jointly supported by EULAR and the ACR, we have over the last years tried to develop (even) better SLE classification criteria. The main goals are to have a relatively intuitive set that helps in teaching, increase sensitivity as compared to the ACR criteria, but maintain specificity in the same range, improve the performance in early SLE, involve the larger SLE community as far as possible, and do this in a strictly scientific way. Given that ANA often are the door to SLE in the diagnostic approach, and that ANA have very high sensitivity, but modest specificity for SLE, we explored whether ANA could be used as an entry criterion. Meta-regression, after compiling ANA data of 13,080 SLE patients from a systemic literature search, gave a sensitivity of 97.8% (CI 96.8–98.5%) for a titer of at least 1:80 on HEp2-ANA immunofluorescence. It was therefore decided that HEp2-ANA of $\geq$1:80 would be used as an entry criterion.

Three different approaches were used to maximize the overview on potential items, namely an SLE expert Delphi exercise involving 123 SLE experts, an international early disease cohort with 389 SLE patients and 227 patients with conditions mimicking SLE, and a patient survey, which 339 SLE patients filled out and mailed anonymously. The resulting 41 items were then reduced in a nominal group technique exercise with 7 international SLE experts, resulting in a list of 20 items plus ANA as an entry criterion. These items were then submitted to multi-criteria decision analysis in a two day conference with 6 international experts together with the steering committee. This approach under the same moderator (Dr. Ray Naden) had already been successfully used for the rheumatoid arthritis and systemic sclerosis criteria.

The present results are 20 weighted items, which can be additively used within a continous scale, and a cut-off for classification. Weights for class III or IV lupus nephritis are much higher than for leukopenia or unexplained fever. This candidate system will now be tested against both the ACR and the SLICC criteria in a large cohort of SLE patients and patients with mimicking conditions. If successful, ANA of $\geq$1:80 and weighted criteria will lead to better performance, particularly in early disease, and give us a system that is hopefully intuitive enough to convey an idea of the disease.

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SP0011 SJÖGREN'S CRITERIA REVISITED!

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In clinical practice it is up to the clinician to use their judgement in making a diagnosis of pSS. In research it is essential to have agreed classification criteria so that there is confidence that participants in a study have the specified condition. During the 1980's a number of classification criteria were proposed with a major debate as to the advantages and disadvantages of each of these criteria.

In 1988 a working group of 29 experts from 12 European countries initiated a study to develop consensus criteria. They published their initial findings in 1993 and in 2002 Vitali et al published the American European Consensus Group Criteria (AECG). The AECG criteria have been the most widely used "gold-standard" criteria for the classification of pSS in research studies. Criteria are never fixed in perpetuity, however, and as new technology such as ultrasound becomes more widely used or new data becomes available further revision is likely. In 2013, an International Collaboration, the Sjögren's International Clinical Collaborative Alliance (SICCA) funded by the National Institutes for Health in the USA collected data from 1618 participants to devise the American College of Rheumatology (ACR) preliminary criteria for SS and in 2016 following a further international consensus group exercise the American College of Rheumatology – European League against Rheumatism (EULAR) consensus criteria for Sjögren's syndrome have been published.

In this presentation I will go through the development of these criteria, the underlying rationale and by the end of the talk attendees should have a better understanding of how these criteria can be used in research and to support clinical practice.

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SP0012 ADVANCED APS CRITERIA 2016/2017

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The classification of the anti-phospholipid syndrome (APS) is based on the occurrence of arterial/venous thrombotic events and/or pregnancy complications with no identifiable causes in the persistent presence of medium/high titres of anti-phospholipid antibodies (aPL) detectable by solid phase (anti-cardiolipin – aCL or anti-beta2 glycoprotein I – ab2GPI) tests and/or PL-dependent functional coagulation assays (lupus anticoagulant – LA). These classification criteria are currently also used as diagnostic tools.

aPL represent a risk factor, consequently the presence of two/three positive diagnostic laboratory tests is a valuable parameter to stratify the patients at highest risk for developing the syndrome/recurrences.

The syndrome displays a protean clinical picture depending on the involved tissue/organ. The majority of the clinical (criteria) manifestations are clearly related to vascular ischemic events. However some manifestations apparently cannot be supported by a thrombotic mechanism and alternative pathogenic pathways have been suggested. This is the case for thrombocytopenia, central nervous system involvement such as movement disorders and cognitive abnormalities, and APS nephropathy. Heart valve disease, skin ulcers and livedo reticularis are also frequent events in APS patients and their relationship with vascular thrombosis is unclear. Still debated is the suggestion to include these manifestations as additional clinical diagnostic criteria. The possibility to use all these criteria for ranking the patients as having a definite (standard clinical criteria) or probable APS (non classification criteria) is also debated.

The revised criteria for obstetric morbidity comprise otherwise unexplained pregnancy loss. Some of the obstetric criteria might display low sensitivity/specificity for APS. In particular the attribution to aPL of a pregnancy wastage early on gestational course requires the exclusion of a myriad of ethiologies. Conversely, the rate of late foetal losses is very low, making this criterion rather specific. Placenta-mediated obstetric complications provide another critical field: pre-eclampsia and intra-uterine growth restriction are relatively common. To enhance the specificity for APS, the classification criterion included only cases requiring delivery before 34 weeks of gestation. Medium/high aPL titres and double/triple laboratory tests positivities confer a higher risk for pregnancy complications but recent data seem to suggest that also persistent low aPL titres can be predictive for a negative pregnancy outcome. This finding has been recently explained by the availability of large amounts of b2GPI in tissues of the reproductive system. Even though classification criteria have allowed uniformity in APS diagnosis, there still remain some controversies.

The field of the laboratory classification criteria is even more in progress. Epitope profiling for anti-b2GPI antibodies is quite promising since the characterization of reactivity against the domain 1 of the molecule appears to display a higher specificity for APS and stronger predictive value than the antibodies against the whole molecule. However, anti-domain 1 assay is less sensitive and cannot replace the standard test at the moment. Antibodies against prothrombin (PT) have been reported to be associated with both the vascular and the obstetric APS, in particular when the antibodies are detectable against a solid phase complex of PT with phosphatidylserine (PS) (the so called anti-PS/PT assay). However a clear evidence for their usefulness in the clinical diagnosis and risk stratification for APS patients as well as their true pathogenic role is still debated.

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