Commentary

Does a positive anti-CCP test identify a distinct arthritis entity?

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Abstract

The introduction of tests recognizing 'anti-citrullinated protein antibodies' (ACPA) has caused a revolution in rheumatology. Immunization against citrullinated proteins is a feature almost unique for rheumatoid arthritis, although ACPA may occur long before the onset of symptoms. Even if the presence of ACPA does not seem to reveal a distinct arthritis phenotype at symptom onset, it predicts an aggressive disease course with unfavourable outcome. Despite the very high diagnostic specificity for rheumatoid arthritis, ACPA-positivity does not always accord with a traditional diagnosis of rheumatoid arthritis at clinical presentation. However, even when these patients are judged to suffer from mild undifferentiated arthritis, they call for follow-up and special attention by rheumatologists.

Introduction

A new era began when analyses identifying 'anti-citrullinated protein antibodies' (ACPA) were introduced for the diagnosis of arthritis. The question of whether ACPA-positive patients constitute a distinct clinical entity presently attracts great interest. In a previous issue of *Arthritis Research and Therapy* Annette van der Helm-van Mil and colleagues give a detailed description of clinical characteristics in very early rheumatoid arthritis (RA) at presentation and during 4 years, comparing patients with and without antibodies to cyclic citrullinated peptide (CCP) [1].

ACPA constitute a growing family of autoantibodies, in which the first member (anti-perinuclear factor) was described over 40 years ago. However, the major breakthrough came with the important series of investigations by Walther van Venrooij and colleagues, who discovered the crucial role of post-translationally citrullinated peptide epitopes and developed the anti-CCP test. These workers also described the test's remarkable diagnostic specificity for RA, with a sensitivity comparable with that for rheumatoid factor (RF) (reviewed in [2]).

Genes, environment and a pathogenetic connection?

Although the aetiology is unknown, several genetic and environmental factors are obviously important in RA. The HLA-DRB1 product 'shared epitope' (SE) is the best known genetic factor associated with RA, and cigarette smoking is the best described environmental susceptibility factor. A gene–environment interaction has been shown for SE and smoking regarding susceptibility to RF-positive RA [3,4], and the presence of anti-CCP antibodies (CCP+) correlates strongly with the presence of the SE [5]. It has been demonstrated that major histocompatibility complex class II molecules expressing the SE can bind and present citrullinated peptides to T cells [6], and that a combination of SE-positive (SE+) and CCP+ is highly predictive of future RF-positive RA [7]. Contrary to nonsmokers, bronchoalveolar lavage cells from cigarette smokers have been reported to express citrullinated antigens [8]. It was also recently reported that smoking is a risk factor to develop CCP+ RA only in SE+ patients [4,8].

Taken together, these observations suggest that immunization against citrullinated antigens in SE+ persons, possibly after triggering by nonspecific adjuvants such as cigarette smoke, may be critical for the initiation of RA. Serum levels of anti-CCP antibodies do not correlate with disease activity, however – although they often drop after institution of disease-modifying anti-rheumatic drugs, at least in RA of short duration [9-11].

Rheumatoid factor versus ACPA in RA

The RF described by Erik Waaler in 1937 is a family of agglutinating antibodies against different epitopes on the Fc part of rabbit IgG exposed on the surface of sheep erythrocytes. The Waaler–Rose haemagglutination assay was

ACPA = anti-citrullinated protein antibodies; CCP = cyclic citrullinated peptide; RA = rheumatoid arthritis; RF = rheumatoid factor; SE = shared epitope.

the prevailing method to analyse RF during the following 50 years, but many additional methods have been developed, including different latex particle agglutination assays and isotype-specific enzyme immunoassays using various sources of IgG as antigen (e.g. human, rabbit, horse).

In the 1987 revised American College of Rheumatology classification criteria for RA, a positive RF test is defined by a cutoff level at the 95th percentile in 'normal control subjects'. In practice this means that up to 5% of middle-aged healthy blood donors, and considerably more patients with non-RA inflammatory disease, can be expected to have a positive RF test. Increasing the cutoff limit increases the diagnostic specificity for RA, but decreases the sensitivity. The 1987 American College of Rheumatology criteria accept 'any method' to analyse RF, thus including antibodies of any isotype (agglutinating or not) and including reactivity to different epitopes on IgG-Fc, such as heterophilic antibodies against nonhuman species.

Despite access to an international reference serum, there is an obvious lack of standardization regarding RF analyses, which makes it difficult to compare the relevance of different studies on 'seropositive' RA and 'seronegative' RA. Reports on ACPA prevalence rates in RA also vary depending on the choice of analytical method and on the study population. At a diagnostic sensitivity equal to agglutinating RF, the second-generation anti-CCP2 assays detect ACPA of the IgG class with a superior diagnostic specificity for RA. Studies on patients with longstanding RA have shown substantially higher prevalence rates of positive anti-CCP tests [2] than investigations based on patients with very early RA [1]. On the other hand, there is no evidence suggesting that the ACPA prevalence increases with increasing disease duration. Prospective studies on early RA have shown that the anti-CCP status is usually stable from the time of clinical presentation, although the average antibody levels decrease after diagnosis, probably due to medication [9-11]. The lower prevalence rates recorded in incident population-based materials of very early arthritis are probably due to the fact that these study populations comprise patients having milder disease with more favourable outcome compared with selected prevalent cases with longstanding disease.

Anti-CCP antibodies versus clinical presentation, disease course and outcome

The article by van der Helm-van Mil and colleagues gives a detailed description of the synovitis pattern in very early RA and a rating of the synovitis magnitude from baseline to the 4-year follow-up [1]. They found that clinical characteristics were similar in CCP+ patients and in patients without antibodies to CCP (CCP– patients) at baseline, and that the patterns of joint affection were similar during the 4-year follow-up. However, a less favourable disease course was recorded in the CCP+ patient group both regarding the degree of synovitis and joint destruction. One-half of the patient population was initially treated with analgesics followed by antimalarials or sulfasalazine if the initial treatment was insufficient, and the other half of the population was immediately given methotrexate or sulfasalazine. However, detailed information on prescription patterns in CCP+ patients versus CCP– patients is lacking.

In three Swedish prospective studies on early RA, disease progression was compared between CCP+ cases and CCP– cases [5,9,10]. Although they had similar baseline characteristics, two of the studies recorded signs of higher disease activity in the CCP+ patients already at presentation [5,9], and in all three studies a more aggressive disease with unfavourable outcome was seen in these patients. In the study by Kastbom and colleagues, the physicians' higher scoring of global disease activity probably explains the higher preparedness to use potent disease-modifying anti-rheumatic drugs in CCP+ patients from presentation throughout the 3-year follow-up period [9]. However, the discrepant results between the different studies regarding disease activity and severity in CCP+ versus CCP– cases should not be exaggerated. They may be explained by factors such as different disease durations at the study start and different treatment strategies. Numerous studies have shown that ACPA are not only highly specific markers of present (and future) RA, but are also predictors of poor outcome. Different ACPA tests are not interchangeable, however, since they differ regarding diagnostic sensitivity, specificity, and prediction of disease course/outcome [2]. The anti-CCP assays available today offer a good opportunity to introduce well-standardized analysis of a highly disease-specific test for routine diagnosis of RA.

Anti-CCP, rheumatoid factor or both?

It is probable that antibodies against citrullinated proteins will be included among future classification/diagnostic criteria for RA. Nevertheless, RF is still a classification criterion and, despite shortcomings regarding epitope specificity, standardization, and disease specificity, it continues to be a valuable diagnostic tool in rheumatology. However, RF analysis must not be exploited as a screening instrument for patients with aches and pains without signs of synovitis or systemic inflammation. Such abuse results in a high 'noise ratio' of patients with noninflammatory disease without the need for costly referrals to rheumatologists. For nonrheumatologists who are not experienced in joint examination, anti-CCP antibody testing offers a better standardized primary option with a similar sensitivity for RA, but with a superior specificity of established or future disease. However, a few RF-positive cases as well as most RF-negative cases will be missed. Therefore, regardless of serological status, a patient with clinical signs of synovitis in multiple joints should obviously be referred to a rheumatologist despite a negative anti-CCP test.

As with all new diagnostic tests, it will take time to learn how to cope rationally with positive anti-CCP tests in clinical

practice. Certainly, we will identify early cases of anti-CCP+ non-RA, referring to the present American College of Rheumatology classification criteria. Although some anti-CCP+ early arthritis patients may be judged to have mild undifferentiated arthritis, it is imperative that rheumatologists keep an eye on these cases in order to achieve a balanced and solid experience, to monitor disease progression, and to be prepared to institute potent anti-rheumatic treatment before it is too late.

Conclusions

The ACPA era has just begun, but has already proved to be a revolution in rheumatology. Although a positive anti-CCP test does not appear to identify patients with distinct clinical characteristics at presentation, it is superior to RF regarding diagnostic specificity for RA, and the anti-CCP test predicts more severe disease course and outcome.

Competing interests

The author(s) declare that they have no competing interests.

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