CLINICAL AND GENETIC DIFFERENCES BETWEEN AUTOANTIBODY POSTIVE AND NEGATIVE RHEUMATOID ARTHRITIS.

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Objectives: Antibodies against citrullinated antigens (anti-CCP) are highly specific for RA and associated with RA-progression and development. It has been suggested that anti-CCP-positive and negative disease are distinct disease entities. To obtain a better appreciation of the nature of anti-CCP-positive and negative disease, we investigated whether the association of genetic and environmental risk factors, the outcome of disease and response to therapy differs between anti-CCP-positive and negative disease.
Methods: A population based inception cohort was established in 1993 and since then each year about 150 patients with recent-onset arthritis were included. Of these patients yearly X-rays of hands and feet were made and detailed clinical phenotypical characteristics were recorded. DNA variants and serological features were determined by standard techniques. A Randomised Controlled Trial using Methotrexate in Undifferentiated Arthritis (UA) patients was analysed to determine whether response to treatment differs between anti-CCP-positive and negative patients.
Results: In the inception cohort, the presence of shared epitope HLA-class II antigens (SE) was only a risk factor for anti-CCP positive RA {OR 3.38 (2.61-4.38)} and not for anti-CCP negative RA {OR 1.22 (0.93-1.60)}. The environmental risk factor smoking was only a risk factor for development of anti-CCP antibodies and intriguingly only in SE-positive patients. The SE-negative allele HLA-DR3 was associated with anti-CCP negative disease.
When the patients progressed from the pre-arthritic stage and presented with arthritis at the clinic, 37% presented with undifferentiated arthritis (UA). Of anti-CCP positive patients with UA, 80% developed RA within one year, whereas only 25% of the anti-CCP negative patients with UA progressed to RA. Nonetheless, when all RA patients were analyzed for clinical presentation, no difference was observed between anti-CCP positive and anti-CCP negative patients with respect to joint distribution patterns, morning stiffness or age of onset, suggesting that the arthritogenic insult is similar in both anti-CCP positive and anti-CCP negative patients. However, the anti-CCP positive patients had a fourfold higher yearly rate of joint destruction, indicating differences in outcome and the anti-CCP positive had much lower rates of remission, indicating differences in persistency.
Remarkably, the progression to RA and the destruction of joints in UA-patients that were (placebo-controlled)- treated with Methotrexate, was only inhibited in patients that were anti-CCP-positive.
Conclusion: Differences in genetic risk factors, gene-environmental interactions, outcome of undifferentiated arthritis, and rate of joint destruction all indicate that anti-CCP positive arthritis is a distinct disease entity compared to anti-CCP negative RA that can react differently to treatment.