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Psoriatic arthritis: a complex disease

– analyses on genetic and serological biomarkers and of comorbidity

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Akademisk avhandling

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Abstract
Psoriatic Arthritis (PsA) is a heterogonous inflammatory arthritis associated with psoriasis. The disease leads to inflammation of peripheral joints, axial skeleton and/or enthesites, and can result in severe destruction of affected joints. In contrast to rheumatoid arthritis (RA), most individuals with PsA are sero-negative for rheumatoid factor (RF) and/or anti-citrullinated protein/peptide antibodies (ACPA) and the distal interphalangeal (DIP) joints are often involved. Dactylitis, a diffuse swelling of an entire digit (finger or toe), is also common. Traditional markers of systemic inflammation, such as erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) are elevated in only 50% of the individuals with PsA.
Underlying genetic factors are considered important for the aetiology, disease expression and prognosis of PsA. To date no specific biomarker for PsA disease or disease activity/severity is available and there is a need for diagnostic and prognostic tools to meet the challenge of early diagnosis and assessment of disease severity.
An increased risk of co-morbidity, particularly cardiovascular disease (CVD), has been demonstrated in patients suffering from different rheumatic diseases, *e.g.* systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Corresponding data for patients with PsA are more limited, but evidence exists for an increased risk of mortality and cardiovascular morbidity. However, published results are conflicting and heterogeneity among studies makes interpretation of data difficult.
The aim of this study was to investigate genetic and serological biomarkers, and also mortality and cardiovascular comorbidity, in different phenotypes of PsA and in comparison with healthy controls. Patients with PsA were included between 1995 and 2015, the majority from the county of Västerbotten, except for two cohorts from Örnsköldsvik (n=55) and Östersund (n=98).
The genetic polymorphism *PTPN22*+1858C/T, previously found to be associated with several autoimmune diseases, was also found associated with PsA, the results were later confirmed in a genome wide association study (GWAS). Additionally, among PsA patients, the minor allele, T, was associated with the number of deformed joints and dactylitis (Paper I).
Genetic polymorphisms in genes related to the inflammasome were also investigated, both in comparison with healthy controls and in relation to different phenotypes of PsA (Paper II). An association was identified between patients with PsA and the polymorphism *CARD8*-C10X in comparison with controls. In addition, associations between various inflammasome polymorphisms and different clinical phenotypes of PsA were detected.
To investigate the relation of serological biomarkers and PsA, individuals with blood samples collected in conjunction with clinical investigation were selected (Paper III). Associations with different biomarkers and different clinical phenotypes of PsA were identified In addition, associations were found with different biomarkers and patients with moderate/high disease activity at clinical investigation, confirming the inflammatory nature of the disease.
Mortality and incidence of acute cardiovascular disease were investigated with standardized mortality rate-ratio (SMR) and standardized incidence ratio (SIR) compared with the general population of Västerbotten (Paper IV). An increased SMR for diseases of the circulatory system in PsA compared with controls was found. Among PsA patients, death was associated with a composite disease activity index (DAI) and with a disease phenotype including both axial- and peripheral joint involvement.
In conclusion, associations were found with different clinical phenotypes of PsA, both with genetic polymorphisms and serological biomarkers that confirm the inflammatory nature of the disease and illustrate the disease heterogeneity. As in many other inflammatory diseases, an increased cardiovascular mortality was found that highlights the importance of considering cardiovascular risk factors in patients with PsA.

Keywords
Psoriatic Arthritis, genetics, inflammasomes, polymorphisms, biomarkers, disease expression, disease activity, cardiovascular diseases, mortality, epidemiology

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