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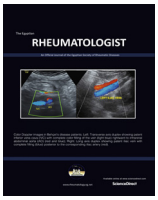

Original Article

Anti-carbamylated protein antibodies in psoriatic arthritis patients: Relation to disease activity, severity and ultrasonographic scores

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ABSTRACT

Background: Anticarbamylated proteins (anti-CarP) are a novel family of antibodies recently identified in patients with inflammatory arthritis.

Aim of the work: To investigate the anti-CarP serum levels in psoriatic arthritis (PsA) patients. The relation of anti-CarP to disease activity and severity as well as to the ultrasonographic findings and scores were well thought-out.

Patients and methods: Forty-five PsA patients diagnosed according to the classification of psoriatic arthritis (CASPAR) criteria. 45 matched controls were included. The erythrocyte sedimentation rate (ESR), C-reactive protein and serum anti-CarP antibody were measured. PsA disease activity was recorded according to the modified disease activity score (DAS28). The severity and extent of psoriasis was assessed by the psoriasis area severity index (PASI). Musculoskeletal ultrasound (US) of the small hand joints was performed using grey scale (GS) and power Doppler (PD) to derive composite scores based on abnormal counts and severity.

Results: The mean age of the patients was 44.58 ± 6.76 years, 40 females and 5 males (F:M 8:1), disease duration 4.93 ± 3.17 years. Serum levels of anti-CarP antibody were increased in PsA patients (33.48 ± 14.05) compared to controls (12.21 ± 4.71 ng/ml) ($p < 0.001$). The mean DAS28 was 4.61 ± 1.59 There was a significant correlation between anti-CarP antibody and each of DAS28, ESR, CRP, PASI, the GS and PD joint counts ($r = 0.97$, $r = 0.97$, $r = 0.97$, $r = 0.97$, $r = 0.96$, $r = 0.9$ respectively) as well as with the US joint scores; GSJS and PDJS ($r = 0.98$, $r = 0.97$ respectively) denoting severity.

Conclusions: Anti-CarP antibody might represent a promising marker to predict joint damage and disease activity in PsA patients.

1. Introduction

Psoriatic arthritis (PsA) belongs to the group of seronegative spondyloarthropathies (SpA) and is characterized by inflammation of joints, tendons, and/or entheses associated with psoriatic skin and/or nail lesions [1]. Endothelial dysfunction and hyperuricemia account for a high frequency of comorbidities in Egyptian PsA patients [2]. Clinical presentation and course are highly variable, ranging from pain at tendon insertions to mutilating arthritis [3]. The arthropathy generally begins several years after the commencement of the disease [4] and subclinical arthritis has been reported [5,6]. Serological investigations for PsA are negative in most of the patients. Unfortunately, there are no specific laboratory markers for the disease [4] even though a role for cytokines as tumor necrosis factor-α [7] and interleukins [8,9] has been reported in patients with PsA; moreover, conventional radiography is of limited value for early diagnosis [10]. Therefore, there is still a continuous demand for new biomarkers which could be useful for prediction, diagnosis or follow-up of the patients with PsA.

Antibodies against post-translationally modified proteins have gained considerable interest in rheumatoid arthritis (RA). The antibodies directed against citrullinated proteins (ACPAs) have become a specific early serological marker of the disease and crucial for patient stratification [10]. In addition to citrulline, carbamyl adducts have also been shown to act as neoepitopes in RA [11] and juvenile idiopathic arthritis [12] resulting in the production

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of antibodies specifically targeting carbamylated residues (anti-CarP). The presence of anti-CarP correlated with joint destruction and was reported to be predictive of RA development, independent of the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies [13].

Protein carbamylation is a cyanate-dependent, non-enzymatic conversion of lysine residues and N-terminal amino groups to ε-carbamyl-lysine (homocitrulline) and α-carbamyl amino acids, respectively. Recent studies demonstrated a novel pathway connecting carbamylation with inflammation via the activation of myeloperoxidase (MPO). MPO is a haem peroxidase released by activated neutrophils. It catalyses the formation of cyanate from thiocyanate in the presence of hydrogen peroxide, leading to homocitrulline formation [14]. This discovery attracted attention to carbamylation in the context of chronic inflammatory and autoimmune diseases.

Imaging techniques are new attractive tools supporting diagnosis and management in PsA. Among various imaging modalities, ultrasound (US) is routinely accessible, inexpensive, and noninvasive diagnostic imaging tool. It has been shown to be a sensitive method, particularly when compared to clinical examination, for assessing both disease activity and damage in inflammatory arthritis, including PsA [15]. It provides measures of synovial morphology and vascularity. Grayscale (GS) ultrasound visualizes the structures of the joint and can discriminate between synovial hypertrophy and various other sources of perceptible swelling of the joint such as tenosynovitis or edema in subcutaneous plane [16]. Power Doppler (PD) sonography shows increased soft tissue vascularity with superior sensitivity and hence differentiates inflamed from noninflamed synovial swelling.

The aim of this study was to investigate the anti-CarP serum levels in PsA patients. In addition, the relation of anti-CarP to disease activity and severity as well as to the ultrasonographic findings and scores were well thought-out.

2. Patients and methods

The present case control study was carried out on 45 PsA patients who attended the outpatient clinics of Rheumatology and Rehabilitation and Internal Medicine Departments of Ain Shams University Hospitals. PsA patients fulfilled the diagnostic criteria defined by the classification of psoriatic arthritis (CASPAR) study [17]. 45 healthy volunteers matching in age and sex served as a control group. Written informed consent was obtained from every patient and control. The study was approved by Ain Shams medical ethical committee. Patients with evidence of anti-citrullinated protein antibody (ACPA) positivity, on biologic treatments or gave history of biologic treatments, malignancy or active infectious disorders were excluded from the study. 32 patients were receiving methotrexate either alone or in combination with sulfasalazine or oral cyclosporine; 14 were treated with prednisone (≤5 mg/day).

All patients and controls were subjected to full medical history taking and thorough clinical examination. The severity of psoriasis was assessed by the psoriasis area severity index (PASI) created by Fredriksson and Pettersson in 1978 to evaluate the clinical efficacy of a new treatment for psoriasis [18]. Disease activity was assessed using the Disease activity score in 28 joints (DAS 28) for PsA patients with predominant peripheral arthritis [19]. Routine laboratory investigations were carried out including erythrocyte sedimentation rate (ESR), complete blood count (CBC), quantitative C-reactive protein (CRP), rheumatoid factor (RF) by latex method and anti-CCP by enzyme-linked immunosorbent assay (ELISA) (Euro-Diagnostica, the Netherlands).

Serum anti-CarP antibody level was measured by enzyme-linked immunosorbent assay (ELISA), using the commercial anti-CarP antibody kits (Novatein biosciences, UK).

2.1. Musculoskeletal ultrasound (MSKUS) assessment

On the same day of clinical evaluation, a radiologist with 5+ years of MSKUS experience performed bilateral US examination of the metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints using Philips HD 10 system equipped with a 12 MHZ linear array transducer at the Radiodiagnosis Department, Ain Shams University Hospitals. For PD, "low flow" settings with a medium to low wall filter (to minimize flash artifact) were used. Each joint was scanned in both transverse and longitudinal planes for GS and PD studies.

In every patient, scanning of 28 hand joints (10 MCP, 8 PIP, and 10 DIP joints) was done and the presence of synovial thickening, soft tissue thickening, tendonitis, periosteal reaction, joint effusion, erosions, and PD abnormality was noted. US images (from both longitudinal and transverse planes) from MCP and PIP joints were further scored according to the degree of synovial hypertrophy (SH) on GS as 0 (absent SH and PD signal); 1 (mild SH and single vessel dots on PD); 2 (moderate SH and confluent vessel dots over ≤50% of the synovial area) and 3 (marked SH with confluent vessel dots over >50% of the synovial area) [20]. Interphalangeal joint of first digit was considered as DIP joint. The severity grade of GS score was determined according to the following grading of synovial thickness [21]: Grade 0: no/minimal synovial thickening (considered normal); Grade 1: synovial thickening bulging over the line joining the tops of the bones forming the joint without extension along the bone diaphyses; Grade 2: synovial thickening extending to one of the metadiaphyses and Grade 3: extension to both metadiaphyses.

Separate GS and PD subjective score were documented for each joint which ranged from 0 to 3. Scores of 1, 2, and 3 were considered abnormal, and 0 was considered as normal. These scores were used to derive the US joint count (JC) and joint score (JS) where the GSJC and PDJC represent the number of joints scoring either 1, 2, or 3, out of a total of 28 while the GSJS and PDJS form the sum of the scores in all 28 joints, out of a total of 84. Accordingly, the GSJC and PDJC represented number of normal or abnormal joints, similar to TJC and SJC system employed in the DAS28, whereas the GSJS and PDJS suggested an assessment of severity [22].

2.2. Statistical analysis

IBM SPSS statistics (V. 22.0, IBM Corp., USA, 2013) was used for data analysis. Variables are given as mean ± SD. Student t test were used to compare two quantitative variables with each other. Pearson correlation coefficient (r) was used to test correlation between two quantitative variables. In all tests, p value <0.05 is considered significant.

3. Results

This study included 45 PsA patients (40 females, 5 males; F:M 8:1). The control group was 45 healthy individuals of matched age (44 ± 6.71 years; 33–55 years) and gender (37 females and 8 males; F:M 4.6:1). There was no significant difference for age and sex.

Eighteen patients had moderate disease activity, 17 had high DAS28, 6 had low disease activity and 4 were in remission. The clinical, laboratory and radiological findings of PsA patients are shown in Table 1. Abnormal synovial thickening was observed in the joints of 43 (95.5%) patients by GS US. Soft tissue thickening

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