Risk factors of persistent synovitis development in early undifferentiated arthritis patients

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Background

Persistent synovitis (PS) may lead to erosive joint damage and result in functional disability.

Objectives

The aim of the study was to identify the risk factors for development of PS in early undifferentiated arthritis patients (EUA) attending Al Sharqia Governorate Hospitals, Egypt.

Patients and methods

A total of 80 EUA patients comprised the patients group. Assessment was performed twice (baseline and after 1 year) using clinical, laboratory, functional, and radiological [high resolution ultrasonography (HRUS) and power Doppler (PD)] assessments.

Results

Among 80 patients assessed, 20 (25%) showed evidence of self-limiting arthritis and 60 (75%) had PS (PS):16 (27%) developed rheumatoid arthritis, 14 (23%) progressed to spondyloarthropathy, and 30 (50%) remained undifferentiated (UA). Baseline tender and swollen Joint Counts (TJC and SJC) and anti-CCP2 titer were significantly evident in PS patients. Baseline HRUS total score of synovitis and PD total score were significantly higher in PS patients. Family history of any specific rheumatic disease, SJC, anti-CCP2 titer, HRUS total synovitis score, and PD total score were the significant risk factors of PS development. The most significant risk factor of PS (logistic regression analysis) was the baseline PD total score.

Conclusion

Baseline PD total score is the most significant risk factor for development of PS in EUA patients.

Recommendation

PD examination of all patients presenting with EUA should be performed.

Keywords:

early undifferentiated arthritis, persistent synovitis, power Doppler, predictors, ultrasonography

Introduction

Patients with early arthritis are meant to be those with the potential for development of persistent synovitis (PS) but in whom a recognized clinical pattern does not exist [1]. Most patients with early arthritis cannot be diagnosed as a defined disease entity. Early arthritis may evolve into rheumatoid arthritis (RA) or other well-defined diseases and may resolve on its own or may remain undifferentiated [2]. It has been suggested that very early inflammatory disease may differ immunologically from disease of longer duration, and intervention at this stage, before the development of PS, offering a unique opportunity for a qualitative improvement in outcome [3,4]. Management of inflammatory arthritis on the basis of suppression of synovitis to minimize damage would seem to be an appropriate aim of therapy in this patient group [5]. As distinct clinical or laboratory risk factors have not yet been well declared, the diagnosis of PS currently relies on clinical features [6]. Ultrasonography (US) is a relatively cheap and noninvasive imaging modality; multiple joints in a short period of time and bone structure as well as soft tissue can be examined. Moreover, it has a better sensitivity than physical examination in the detection of synovitis in early arthritis [7].

The aim of this study was to the identify risk factors for PS development in early undifferentiated arthritis (EUA) patients attending Al Sharqia Governorate hospitals, Egypt.

Patients and methods

This study was carried out at Rheumatology & Rehabilitation and Radiodiagnosis Departments of Zagazige University Hospitals in Al Sharqia Governorate, Egypt.

The study included all EUA patients who attended Zagazig University hospitals, Al-Ahrar hospital as well as insurance hospitals of Zagazig (the main hospitals that offer full assessment and follow-up as well as free treatment for patients in Al

Sharqia Governorate, Egypt) during the period from December 2011 to December 2012. EUA patients were defined as those with clinical profile, examination, or laboratory data suggesting the presence of an inflammatory arthritic disorder but in whom a specific rheumatic disease has not been diagnosed [8]. Disease duration ranged from 6 weeks to 6 months. At the end of recruitment period, 100 patients were recruited; 20 patients were lost/did not wish to continue the follow-up or participate in the study. The remaining 80 (56 women/24 men) patients completed the study. All patients signed informed consent to be included in the study, and the ethics committee approved the study protocol.

Exclusion criteria

Patients satisfying the American College of Rheumatology classification criteria for RA [9] and the European Spondyloarthropathy Study Group criteria for spondyloarthropathry [10] were excluded. Patients who were found to have a specific rheumatic diagnosis were also excluded.

Assessment and outcome measures

Assessment was performed twice (baseline and after 1 year). At each assessment, different clinical and laboratory parameters were assessed in addition to radiographic assessment, including conventional Plain radiograph and Ultrasonography (High Resolution Ultrasonography (HRUS) and power Doppler (PD)].

Outcome of PS was detected by clinical, laboratory, and radiological (HRUS or PD) assessments.

Control group: Forty apparently healthy volunteers (28 women/12 men) proved by clinical and laboratory investigations and having age-matched and sex-matched with the patients were recruited from persons attending the dental clinic.

Clinical assessment
Complete history taking, complete general and local examinations, and functional assessment by health assessment questionnaire-20 [11] were performed.

The health assessment questionnaire (HAQ-20) [11]: The HAQ-20 assesses a patient's level of functional ability. There are 20 questions in eight categories of functioning. The stem of each item asks over the past week. For each item, there is a four-level difficulty scale that is scored from 0 to 3. The highest component score in each category determines the score for the category.

Laboratory assessment
Each patient underwent the following:

(1) Complete blood count.
(2) Liver and kidney functions tests.
(3) Erythrocyte sedimentation rate (the Westergren method), C-reactive protein (ELISA).
(4) Rheumatoid factor (ELISA), antinuclear antibodies.

Anticyclic citrullinated peptide 2 (anti-CCP2) using anti-CCP second-generation enzyme-linked immunosorbent assay (ELISA) was performed for the determination of IgG CCP in human serum [12] (Distal™ ANTI-CCPFCCP 200 Axis-Shield, Dundee, Scotland, UK). Cutoff value for positivity was greater than 25 U/ml.

Radiological assessment
Conventional plain radiograph of the hands and feet were available for all patients. Osteopenia, joint space narrowing, and erosions, if present, were evaluated. An erosive joint is defined as the joint having, at least, one erosion (erosion means a lesion with an interrupted cortex) [13]. Radiographs of other joints were also obtained as clinically indicated.

Ultrasonography: US assessment was performed for all participants using a Toshiba Nemu 20 (Toshiba Corporation Medical System Company, Model: SSA-550A, Japan) using linear transducer with a frequency of 5–10 MHz. US assessment was performed both longitudinally and transversely by high-frequency US and PD with constant B-mode setting. Each patient underwent an US assessment by two expert radiographers who were blinded to the clinical and laboratory findings, on the day of entry into the study and 12 months later for all of the patients. A systematic multiplanar gray scale and PD ultrasound examination of 38 joints (both metacarpophalangeal joints 1–5; metatarsophalangeal joints 2–5; proximal interphalangeal joints 1–5, both wrists, elbows, shoulders, knees, and ankles) was performed on the basis of standard EULAR reference scans [14]. PD parameters were adjusted at the lowest permissible pulse repetition frequency to maximize the sensitivity (50–1000 Hz). Low wall filters were used. The dynamic range was 20–40 dB. Color gain was set just below the level at which color noise appeared (no flow should be visualized at bony surface). This setting resulted in gain from 18–30 dB Doppler spectrum to exclude artifacts. Joints were scored on a four-grade semiquantitative scale for joint effusion, synovitis, bone erosions, and PD signal [15].

Joint effusion was scored as follows: A score of 0 = no effusion, 1 = minimal amount of joint effusion, 2 = moderate amount of joint effusion (without distension of the joint capsule), and 3 = extensive amount of joint effusion (with distension of the joint capsule).

Synovitis was defined as the presence of abnormal hypoechoic material within joint recesses, tendon sheaths, or bursae. Intra-articular synovitis, tenosynovitis, and bursitis were graded semiquantitatively from 0 to 3 and it was scored as follows:

A score of 0 = no synovial thickening, 1 = minimal synovial thickening (filling the angle between the periarticular bones, without bulging over the line linking tops of the bones), 2 = synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis, and 3 = synovial thickening bulging over the line linking tops of the periarticular bones with extension to at least one of the bone diaphyses.

Bone erosions were defined as changes in the bone surface of the area adjacent to the joint and scored as follows:

A score of 0 = regular bone surface, 1 = irregularity of the bone surface without formation of a defect seen in two planes, 2 = formation of a defect in the surface of the bone seen in two planes, and 3 = bone defect creating extensive bone destruction.

PD signal was used to display flow signal in the synovium and scored as follows:

A score of 0 = no flow in the synovium, 1 = single vessel signals, 2 = confluent vessel signals in less than half of the area of the synovium, and 3 = vessel signals in more than half of the area of the synovium.

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 11.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were given as mean ± SD and categorical variables as frequencies and percentages. The t-test or the Wilcoxon rank-sum test were used according to the distribution of the variable, and the χ^2-test was used for categorical variables. P value less than 0.05 was considered statistically significant. Exact test was used if less than 20% of cells demonstrated less than 5 expected observations. Variables that show a significance level were subjected to Logistic regression analysis to identify the risk factors of PS. Intraobserver and interobserver agreement was assessed using the κ coefficient. κ value for intraobserver reproducibility was 0.73, indicating high reproducibility.

Results

Baseline clinical, laboratory, and radiological features of participants included in the study are depicted in Table 1.

At the end of the study, 20 (25%) of the 80 patients showed evidence of self-limiting arthritis (SLA). Sixty (75%) had PS: 16 (27%) developed RA, 14 (23%) developed spondyloarthropathy, and 30 (50%) had undifferentiated inflammatory arthritis (Fig. 1).

Baseline data of the SLA group and PS patients showed that family history of any specific rheumatic disease, TJC, SJC, and anti-CCP2 titer were significantly

Table 1 Baseline clinical, laboratory, and radiological features of participants included in the study

	Patients ($N = 80$)	Controls ($N = 40$)
Age (years)	45.5 ± 13.5	49.1 ± 11.5
Sex (female/male)	56/24	28/12
History of [n (%)]		
Smoking	17 (21)	8 (20)
FH	10 (13)	4 (10)
RF positivity	32 (40)	13 (33)
HAQ-20	2.1 ± 0.2	0
HRUS		
Total score of synovitis	72 ± 12	0
Total score of effusion	20 ± 3	0
Total score of erosion	18 ± 5	0
PD total score	84 ± 7	0
Radiograph [n (%)]		
Periarticular osteopenia	12 (15)	–
Diminished joint space	10 (13)	–
Erosions	5 (6)	–

Continuous data are expressed as mean ± SD; categorical data are expressed as number and percentage. FH, family history of any specific rheumatic disease; HAQ-20, health assessment questionnaire; HRUS, high resolution ultrasonography; PD, power Doppler; RF, rheumatoid factor.

Figure 1
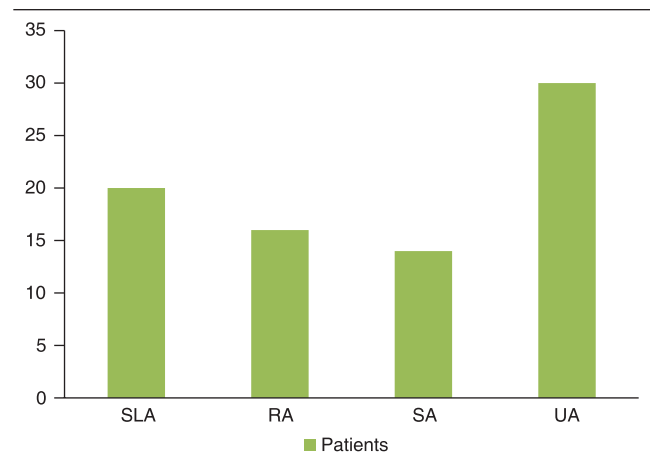
Outcome of early undifferentiated arthritis patients after 1 year (at the end of the study). SLA, self-limiting arthritis; RA, rheumatoid arthritis; SA, spondyloarthropathy; UA, undifferentiated arthritis.

more evident in the PS group. Synovitis was estimated significantly in the PS group according to HRUS total score of synovitis and PD total score (Table 2).

There were significant positive correlations between PS detection and the following risk factors: FH, anti-CCP2 titer, SJC, HRUS total synovitis score, and PD total score (P = 0.04, 0.02, 0.01, 0.04, and 0.01, respectively). PS was detected independently of sex, age, smoking, disease duration, erythrocyte sedimentation rate, CRP, TJC, baseline HAQ-20, HRUS total score of effusion, and HRUS total score of erosion (Table 3).

According to logistic regression analysis, the most significant risk factor for PS development in EUA patients was the baseline PD total score [odds ratio and 95% confidence interval was 0.376 (0.215–0.613)] (Table 4 and Figs. 2 and 3).

Discussion

The aim of this study was to identify the risk factors for PS development in EUA patients attending Al Sharqia Governorate hospitals, Egypt. After 1 year, 25% of 80 EUA patients showed evidence of spontaneous remission (SLA). SLA was defined as the absence of arthritis and synovitis on the examination of a patient who has not taken DMARDs or glucocorticoids in the last 3 months [16]. Seventy-five (75%) had PS: 27% had RA, 23% had spondyloarthropathy, and 30% remained undifferentiated (UA). Thabet *et al.* [17] agreed with our finding that UA has a variable disease course, as 40% of their patients had spontaneous remission, 30% had RA, and 30% remained UA.

In the present study, family history, TJC, SJC, and anti-CCP2 titer were significantly evident in the PS group. This is in agreement with the finding of El Miedany *et al.* [1], as they found that arthritis of the small joints of the hands and anti-CCP were significantly detected in persistent inflammatory arthritis patients.

Furthermore, results of the present study did not support the findings reported by Jansen *et al.* [18] who found that sex and rheumatoid factor are significantly related to the development of PS. The patients included in their study were clinically suspected to have RA, which is one of the exclusion criteria of patients of the present study, and this could be considered an explanation for this finding.

Synovitis was significantly more detected in the PS group according to HRUS total score of synovitis and PD total score. This is in accordance with the findings

of Raissouni *et al.*'s study [19]. In the present study, family history of any specific rheumatic disease, SJC, anti-CCP2 titer, HRUS total synovitis score, and PD total score were the baseline significant risk factors for

Table 2 Baseline clinical and laboratory findings of the self-limiting arthritis and the persistent synovitis groups

| Variables	SLA (20)	PS (60)	P value
Age	47.9 ± 6.2	49 ± 6.2	0.86
Sex (female/male)	15/5	41/19	0.66
DD (months)	3.8 ± 1.4	4.3 ± 1.6	0.64
Morning stiffness>1 h [n (%)]	7 (35)	25 (41)	0.18
History of smoking [n (%)]	4 (20)	13 (22)	0.12
FH [n (%)]	2 (10)	8 (13)ᵃ	0.03
Polyarthritis [n (%)]	7 (35)	28 (46)	0.17
Bilateral affection [n (%)]	5 (25)	18 (30)	0.34
Systemic manifestations [n (%)]	6 (30)	18 (30)	0.755
TJC	20 ± 4	30 ± 5ᵃ	0.03
SJC	9 ± 2	36 ± 6ᵃ	0.01
HAQ-20	1.99 ± 0.3	2.2 ± 0.9	0.14
Anti-CCP 2 titer	18 ± 3.2	29 ± 4.2ᵃ	0.03
CRP	17 ± 5	18 ± 4	0.12
ESR	40 ± 5	39 ± 7	0.42
RF positivity [n (%)]	7 (35)	25 (41)	0.28
Radiograph erosions [n (%)]	1 (5)	4 (6)	0.12
HRUS total score of synovitis	15 ± 2	77 ± 9ᵃ	0.01
HRUS total score of effusion	18 ± 5	19 ± 4	0.14
HRUS total score of erosion	16 ± 3	19 ± 1	0.06
PD total score of synovitis	25 ± 1	88 ± 2ᵃ	0.01

Continuous data are expressed as mean ± SD; categorical data are expressed as number and percentage, anti-CCP2, anticyclic citrullinated peptide2; DD, disease duration before baseline evaluation; FH, family history of any specific rheumatic disease; HAQ-20, health assessment questionnaire; HRUS, high resolution ultrasonography; PD, power Doppler; PS, persistent synovitis; RF, rheumatoid factor; SJC, swollen joint counts; SLA, self-limiting arthritis; TJC, tender joint counts. ᵃSignificant difference.

Table 3 Correlation between different baseline risk factors and evolution into persistent synovitis after 1 year of follow-up

	R	P
Sex	0.015	0.23
Age	0.035	0.24
FH	0.215	0.04ᵃ
Smoking	0.117	0.64
Duration of disease	0.127	0.21
ESR	0.091	0.11
CRP	0.045	0.28
Anti-CCP2 titer	0.230	0.02ᵃ
TJC	0.110	0.06
SJC	0.404	0.01ᵃ
HAQ-20	0.109	0.54
HRUS total score of synovitis	0.328	0.04ᵃ
HRUS total score of effusion	0.112	0.07
HRUS total score of erosion	0.013	0.09
PD total score	0.375	0.01ᵃ

anti-CCP2, anticyclic citrullinated peptide2; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FH, family history of any specific rheumatic disease; HAQ-20, Health assessment questionnaire; HRUS, high resolution ultrasonography; PD, power Doppler; SJC, swollen joint counts; TJC, tender joint counts. ᵃSignificant.

Figure 2
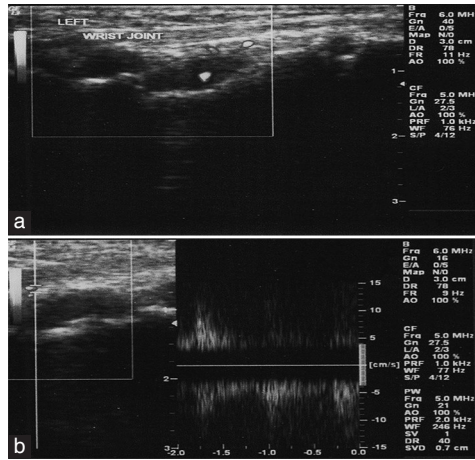
(a) Radiocarpal joint reveals moderate synovial thickening. (b) Two color Doppler signal and continuous diastolic flow.

Figure 3

First metacarpophalangeal joint displaying moderate synovial thickening in the ventral recess with no color Doppler signal.

Table 4 Multiple logistic regression analysis for baseline risk factors of early undifferentiated arthritis evolving into persistent synovitis after 1 year

Variables	Odds ratio (95% CI)	*P* value
PD total score	0.376 (0.215–0.613)	0.001
HRUS total synovitis score	0.699 (0.115–1.541)	0.07
SJC	2.243 (0.573–1.723)	0.14
Anti-CCP2 titer	1.228 (0.055–2.946)	0.39
FH	3.228 (0.935–1.846)	0.36

anti-CCP2, anticyclic citrullinated peptide2; FH, family history of any specific rheumatic disease; HRUS, high resolution ultrasonography; PD, power Doppler; SJC, swollen joint count.
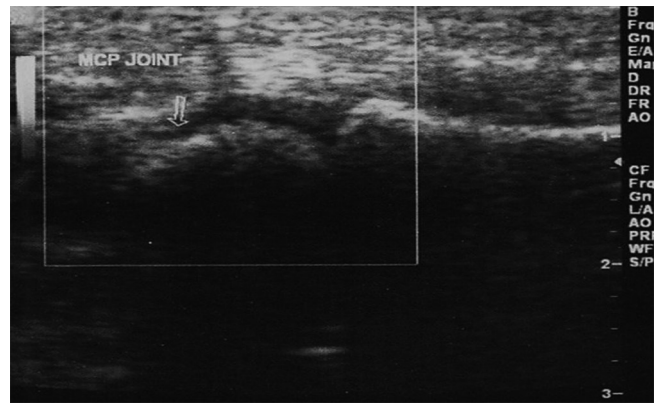
PS development after 1 year of follow-up. This is in agreement with other previous studies [18,20,21].

In addition, CRP and radiograph were not the significant baseline risk factors for PS development in patients of the present study. These data confirmed the findings of two earlier reports [5,22].

The authors of this study found that baseline CRP and radiograph were not the significant risk factors of PS detection after 1 year of follow-up. This may be explained by the notion that EUA may differ immunologically and radiologically from disease of longer duration UA as stated by two previous studies [5,23].

Moreover, in the present study, baseline HRUS total synovitis score and PD total score were the significant risk factors for development of PS. The most significant risk factor was the baseline PD total score ($P < 0.001$). This is in agreement with two other previous studies, which stated that US is a promising diagnostic tool in predicting arthritis and recommended extensive US scoring in all patients with artheralgia or subclinical disease [24,25].

Conclusion
Baseline PD total score is a significant risk factor for PS development in EUA patients.

Recommendation
PD examination of all patients presenting with EUA should be performed.

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