BRIEF REPORT

Dactylitis and Early Onset Psoriasis in Psoriatic Arthritis: Are they Markers of Disease Severity? A Clinical Study

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ABSTRACT

Objectives: To stratify psoriatic arthritis (PsA) patients based on psoriasis (PsO) onset age: early onset psoriasis (EOP) vs. late onset psoriasis (LOP), and to assess if there are differences in disease characteristics, activity/function/impact of the disease, and comorbidity indices.
Methods: Cross-sectional analysis of a longitudinal PsA cohort. Patients were stratified based on PsO onset age.
Results: One hundred and sixty PsA patients were enrolled (84 in EOP and 76 in LOP group) in the study. EOP PsA patients seem to have an increased probability to have dactylitis rather than LOP ones, OR 9.64 (3.77–24.6). Comorbidity indices (Rheumatic Disease Comorbidity Index and Charlson Comorbidity Index) were higher in LOP PsA patients, but these data were not confirmed when adjusted by age and sex. There are also differences in the treatment regimen: EOP PsA patients were more frequently treated with anti-interleukin (IL) 17; instead, LOP patients were more frequently treated with non-steroid anti-inflammatory drugs and conventional synthetic disease-modifying antirheumatics drugs. There were no differences in the disease activity, function, or impact of the disease.
Conclusions: There are some clinical and therapeutic differences in PsA patients linked to the PsO onset age, namely dactylitis in EOP. Other characteristics found were: a "comorbidities trend" in LOP patients and a more frequent use of anti-IL17 in EOP.

Keywords: Psoriatic arthritis; Early onset psoriasis; Late onset psoriasis; Comorbidity indices; Dactylitis

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Key Summary Points

Why carry out this study?

Among PsO patients, the PsO onset age distinguishes two different patterns: early onset psoriasis (0–40 years) and late-onset psoriasis (over 40 years). EOP has been identified as a more severe skin disease. Moreover, LOP in PsA patients has been associated with a higher cardiovascular risk.

The aim of the present study was to assess any differences in clinical characteristics, disease activity, impact of the disease, function, and comorbidities indices in a group of PsA patients when stratified by EOP and LOP.

What was learned from the study?

In our group of PsA patients, EOP is associated with a higher probability of dactylitis and a more frequent use of anti-IL17. In the LOP group, the assessed comorbidities indices tended to have a higher score, but these data were not confirmed when corrected by age and sex.

It could be useful to stratify PsA patients according to the PsO onset age for a clinical patients profiling. This, in turn, could help physicians in the disease severity assessment and in the clinical patients profiling. However, larger studies are needed to confirm these preliminary results.

INTRODUCTION

Psoriatic arthritis (PsA) and psoriasis (PsO) are chronic inflammatory diseases characterized by a wide phenotypic heterogeneity [1–3].

In 1985, Hensler and Christophers described two PsO phenotypes [4]:

- Early onset PsO (EOP) (or type 1 or "hereditary" form), a phenotype characterized by: onset at age 0–40 years, more extensive and severe skin involvement, association with human leukocyte antigen (HLA) Cw*06 and a PsO family history;
- Late-onset PsO (LOP) (or type 2), a phenotype characterized by: onset over 40 years, mild skin involvement, and the lack of both genetic association and PsO family history [4].

A recent analysis in PsO patients confirmed that HLA alleles explain a larger heritability of EOP, moving towards a genetic profiling to predict the PsO risk of a more severe phenotype [5]. The PsO stratification age among PsA patients was also assessed, showing that it could play a role in the clinical and genetic features of PsA patients [6, 7]. Furthermore, in PsA patients, LOP was described as an independent cardiovascular disease-associated factor [8].

Looking at this intriguing topic, the aim of the present study was to assess any differences in clinical characteristics, disease activity, impact of the disease, function, and comorbidities indices in a group of PsA patients when stratified by EOP and LOP.

METHODS

This is a cross-sectional analysis of a longitudinal PsA cohort, in which all PsA patients referred to the Rheumatology Unit of the University of Molise from January 1, 2019 to September 1, 2019 were considered eligible.

Inclusion criteria were:

- Age ≥ 18 years old,
- PsA, satisfying ClASsification criteria for Psoriatic ARthritis (CASPAR) [9],
- PsO confirmed by a dermatologist.

For each patient, age, sex, body mass index (BMI), smoking habits, PsO and PsA disease duration, predominant PsA subset at the time of the visit, PsO at the time of the visit (yes/no), body surface area (BSA) [10], uveitis, Crohn's disease, ulcerative colitis, were collected.

To assess PsA disease activity, Patient Global Assessment, Physician's global evaluation of disease activity [11], patient 'pain on Visual Analogue Scale (VAS), tender/68 (TJC) and swollen/66 joint count (SwJC), Leeds Enthesitis Index [12], dactylitis (past, present, never) and C-reactive protein (CRP) were collected. Moreover, the following indices were calculated: Disease Activity for Psoriatic Arthritis and Minimal Disease Activity [13]. Finally, Health Assessment Questionnaire-Disability Index [14], Psoriatic Arthritis Impact of the Disease [15] and Patient Acceptable Symptoms State [16] were also performed.

For each patient, the current rheumatological therapy was collected. The Charlson Comorbidity Index (CCI), the Rheumatic Disease Comorbidity Index (RDCI) and the Functional Comorbidity Index (FCI) [17] (see Table S1 in the electronic supplementary material for details) were also calculated. Comorbidities were recorded based on previous diagnosis.

PsA patients were stratified in EOP (0–40 years) or LOP (over 40 years) and then compared to evaluate the potential differences in PsA disease characteristics, disease activity, impact of the disease, function, and comorbidity indices.

The study protocol followed the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Molise (protocol n. 0002-09-2017).

Statistical Analysis

Statistical analysis was performed using the R software (version 3.6.2). All demographic and clinical characteristics were summarized by using descriptive statistics. Normally distributed variables were reported by mean ± standard deviation (SD), and non-normally distributed variables by median and inter-quartile range (IQR). The distribution of normality was evaluated by Kolmogorov–Smirnov test. Categorical data are shown as number ($n.$) and percentage (%) of valid data.

To compare EOP and LOP PsA patients, the χ^2-test for independence and Student's t test or Mann–Whitney U test were used.

Univariate logistic regression models were performed to analyze the association between EOP/LOP (independent factors), with all the clinical characteristics and comorbidity indices that showed a statistically significant difference between the two groups.

Multivariate logistic regression models were performed to adjust the significant association by sex and age when appropriate. Odds ratios (OR) were used as a measure of association and a statistical significance was defined as a two-tailed p value ≤ 0.05.

RESULTS

Data of 160 PsA patients were considered for the study, 84 in the EOP group and 76 in the LOP one (Table 1). The proportion of females and males between the EOP and LOP PsA patients was similar, while the mean age (SD), as expected, was different: EOP PsA patients were younger, 51.9 (11.6), than LOP PsA ones, 62.3 (9.92), $p < 0.001$.

The only PsA clinical feature that statistically differed between EOP and LOP was dactylitis: $n = 38$ (45.2%) patients had dactylitis (present or past) among EOP patients vs. $n = 6$ patients (7.9%) among LOP patients, $p < 0.001$ (Table 1). These data were confirmed in the simple regression model (Table 2): EOP PsA patients have an increased probability of more than nine times to have dactylitis rather than LOP PsA patients, OR (CI95%) 9.64 (3.77–24.6), $p < 0.001$.

Another difference in the treatment was found: EOP PsA patients treated with anti-interleukin (IL) 17 drugs were statistically more numerous than LOP patients, respectively $n = 22$ (26.8%) and $n = 10$ (13.5%), $p = 0.039$. On the other hand, LOP PsA patients' number on non-steroidal anti-inflammatory drugs (NSAIDs) and on conventional synthetic disease-modifying anti-rheumatics drugs (csDMARDs) was statistically higher, respectively $n = 22$ (29.7%) vs. 10 (12.2%), $p = 0.016$, and $n = 16$ (21.6%) vs. 6 (7.3%), $p < 0.01$.

Table 1 Demographic, clinical characteristics, therapy, and comorbidity indices of the PsA enrolled patients stratified in early onset PsO and late-onset PsO

	PsA patients	
	Overall, *n* = 160	
	Early onset PsO *n* = 84 (52.5%)	Late-onset PsO *n* = 76 (47.5%)
Demographic, physical characteristics, and smoking habits		
Sex, F, *n* (%)—M, *n*. (%)	30 (35.7)—54 (64.3)	30 (39.5)—46 (60.5)
Age, mean (SD)	51.9 (11.86)**	62.3 (9.92)**
Weight (kg), median (IQR)	72.5 (64–81)	79 (72–82)
Height (cm), median (IQR)	166 (163–175)	169 (160–173)
BMI (kg/h^2), median (IQR)	25.2 (23.3–29.6)	27.6 (24.3–30)
BMI ≥ 30, *n* (%)	22/84 (26.2)	22/76 (28.9)
Smoke, *n* (%)		
Never smoke	42/70 (60)	34/60 (56.6)
Current smoke	14/70 (20)	14/60 (23.2)
Past smoke	14/70 (20)	14/60 (23.2)
Clinical PsA characteristics		
Disease duration (months), median (IQR)	62 (24–120)	74 (19.2–129.5)
PsA subset		
Axial, *n* (%)	12 (14.4)	8 (10.5)
Monoarticular, *n* (%)	6 (7.1)	4 (5.3)
Oligoarticular, *n* (%)	24 (28.6)	24 (31.6)
Polyarticular, *n* (%)	32 (38.1)	32 (42.1)
Enthesitic, *n* (%)	10 (11.9)	8 (10.5)
Prevalent DIP involvement, *n* (%)	0 (0)	0 (0)
Mutilans, *n* (%)	0 (0)	0 (0)
Dactylitis, *n* (%)	38 (45.2)**	6 (7.9)**
Uveitis present or past, *n* (%)	6 (7.1)	0 (0)
Crohn's disease, *n* (%)	2 (2.9)	0 (0)
Ulcerative colitis, *n* (%)	0 (0)	0 (0)
Psoriasis at the visit moment (yes), *n* (%)	56/82 (68.3)	46/64 (71.8)
BSA, median (IQR)	1 (0–2)	1 (0–3)
Patient Global Assessment, median (IQR)	4 (1–6)	4 (2–6.25)
Patient pain on VAS, median (IQR)	5 (2–7)	5 (2.75–7)

Table 1 continued

	PsA patients	
	Overall, $n = 160$	
	Early onset PsO$n =$ 84 (52.5%)	Late-onset PsO$n =$ 76 (47.5%)
Tender joints/68, median (IQR)	1 (0–4)	1.5 (0–5.25)
Swollen joints/66, median (IQR)	0 (0–1)	0 (0–0.25)
LEI, mean (± SD)	0 (0–1)	0 (0–1)
CRP (mg/dl), mean (± SD)	0.2 (0.2–0.3)	0.2 (0.2–0.6)
PsA activity, function and impact		
DAPSA, median (IQR)	13 (5.1–17.6)	10.28 (5.0–17.4)
MDA 5/7, n %	36/78 (46.1)	26/78 (38.2)
MDA 7/7, n %	12/78 (15.38)	8/78 (11.8)
PsAID, median (IQR)	2.70 (1–5.27)	2.32 (1.1–4.14)
PASS yes, n (%)	48/76 (63.15)	36/54 (66.6)
HAQ-DI, median (IQR)	0.5 (0.125–0.687)	0.5 (0.125–0.812)
Therapy		
NSAIDs, n (%)	10/82 (12.2)*	22/74 (29.7)*
Oral corticosteroids, n (%)	4/82 (4.9)	2/74 (2.7)
csDMARDs, n (%)	6/82 (7.3)*	16/74 (21.6)*
Methotrexate, n (%)	6/82 (7.3)*	14/74 (18.9)*
Sulfasalazine, n (%)	0/82 (0)	2/74 (2)
Anti-TNF-α, n (%)	28/82 (34.1)	30/74 (40.5)
Anti-IL-17, n (%)	22/82 (26.8)*	10/74 (13.5)*
Anti-IL12-23, n (%)	6/82 (7.3)	4/74 (5.4)
iPDE4, n (%)	8/82 (9.7)	6/74 (8.1)
Comorbidities indices		
CCI $\geq$ 1	14/84 (16.6)*	26/76 (34.2)*
FCI $\geq$ 1	36/84 (42.8)	44/76 (57.9)

Table 1 continued

	PsA patients	
	Overall, $n = 160$	
	Early onset PsO$n =$ 84 (52.5%)	**Late-onset PsO$n =$ 76 (47.5%)**
RDCI $\geq$ 1	36/84 (42.8)**	54/76 (71.0)**

SD standard deviation, *IQR* inter quartile range, *BSA* body surface area, *LEI* Leeds Enthesitis Index, *CRP* C-reactive protein, *DAPSA* disease activity for psoriatic arthritis, *MDA* minimal disease activity, *PsAID* Psoriatic Arthritis Index of the Disease, *PASS* patient acceptable symptom state, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *NSAIDs* non-steroid anti-inflammatory drugs, *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs, *TNF* tumor necrosis factor, *IL* interleukin, *iPDE4* inhibitors of phosphodiesterase type 4, *CCI* Charlson Comorbidity Index, *FCI* Functional Comorbidity Index, *RDCI* Rheumatic Disease Comorbidity Index

*p value $\leq$ 0.05
**p value $\leq$ 0.001

Table 2 Univariate logistic regression analysis to assess the association between EOP and dactylitis (present or past)

	Dactylitis	
	OR (CI 95%)	**p value**
EOP (vs. LOP)	9.64 (3.77–24.6)	< 0.001

With regard to comorbidities, the patients with CCI $\geq$ 1 and a RDCI $\geq$ 1 were numerous in LOP group: CCI $\geq$ 1: $n = 26$ (34.2%) vs. $n = 14$ (16.6%), $p = 0.01$, respectively, in LOP and EOP; RDCI $\geq$ 1: $n = 54$ (71%) vs. $n = 36$ (42.8%), respectively, in LOP and EOP, $p < 0.001$ (Table 1).

In the univariate model, LOP showed a positive association with CCI $\geq$ 1 and RDCI $\geq$ 1: LOP PsA patients, rather than EOP ones, have an increased probability of 2.6 times to have a CCI $\geq$ 1 and of 3.27 times to have a RDCI $\geq$ 1 (Table 3). However, when these data were corrected by age and sex, the association was not confirmed (Table 3).

DISCUSSION

In this study, we compared EOP and LOP PsA patients; in the first group, dactylitis seems to be more prevalent. Moreover, focusing on comorbidities indices, CCI and RDCI scores tend to be higher in LOP PsA patients, but these results could be related to the patients' age.

The PsO onset age is considered as a severity marker in PsO patients. In fact, EOP is associated with extensive skin disease, strong family aggregation, and HLA-Cw*06 positivity, when compared to the LOP [18]. However, for PsA, a definition of severity is still lacking; in 2005, Brockbanck et al. proposed dactylitis as a clinical marker of disease severity because of its association with a greater degree of radiological damage [19]. This concept is in keeping with a recent study in which early PsA patients (DMARDs-naïve) with dactylitis seem to have a greater burden of disease (greater SwJC, TJC, CRP, ultrasound synovitis and erosive damage) [20] when compared to early PsA patients without dactylitis. Therefore, it could be supposed that EOP is also a marker of severity in PsO, due to the association that we found between EOP and dactylitis. The early onset of PsO could be a potential clinical marker of PsA severity. If other future larger studies will confirm this association, EOP and dactylitis could be considered as potential additional factors to take into account for a tight control in a treat-to-target strategy [21, 22].

Moreover, while the assessment of PsA disease activity is standardized and well defined, the way to collect comorbidities is still an

Table 3 Univariate logistic regression analysis to assess the association between LOP and RDCI ≥ 1 and CCI ≥ 1; multivariate logistic regression analysis in which these results were adjusted for sex and age

	Univariate		Multivariate	
	OR (CI 95%)	p value	OR (CI 95%)	p value
RDCI ≥ 1				
LOP (vs. EOP)	3.27 (1.70–6.32)	< 0.001	1.83 (0.88–3.81)	0.104
Sex (F)	–	–	1.37 (0.67–2.81)	0.387
Age (years)	–	–	1.07 (1.03–1.10)	< 0.001
CCI ≥ 1				
LOP (vs. EOP)	2.60 (1.23–5.47)	0.012	2.10 (0.92–4.76)	0.075
Sex (F)	–	–	0.61 (0.27–1.36)	0.231
Age (years)	–	–	1.02 (0.99–1.06)	0.167

EOP early onset psoriasis, *LOP* late-onset psoriasis, *RDCI* Rheumatic Disease Comorbidity Index, *OR* (CI 95%) odd ratio (confidence interval 95%)

unmet need [17]. In our study, we assessed comorbidities through three different comorbidity indices (CCI, RDCI, and FCI), finding an association between LOP with CCI ≥ 1 and RDCI ≥ 1, but these results were not confirmed when adjusted for patients' age and sex. These data probably suggest that in our group of patients, there is a "comorbidity trend" in LOP patients, but other factors (like age) could have an influence.

Another intriguing point to consider is that EOP PsA patients were more frequently on anti-IL 17 therapy, underlying that EOP PsA patients often require a more robust "skin-driven" treatment. In fact, these patients, having a long-standing history of skin disease, had more previous systematic treatments, including tumor necrosis factor-α inhibitors (data not shown) when compared to LOP. This difference could also be linked to a different management between EOP and LOP patients because it is more likely that EOP patients had a first evaluation carried out in a dermatological setting, as previously shown [23].

The main limitation of our study is due to the monocentric and cross-sectional design of the analysis.

CONCLUSIONS

This study confirmed that there are some clinical differences in PsA patients linked to the PsO onset age, namely dactylitis in EOP, "comorbidities trend" in LOP patients and a more frequent use of anti-IL17 in EOP.

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acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted.

Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study was approved by the Institutional Review Board of the University of Molise.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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