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Palindromic Rheumatism Frequently Precedes Early Rheumatoid Arthritis: Results From an Incident Cohort

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Background. This multicenter incident cohort aimed to characterize how often early rheumatoid arthritis (ERA) patients self-report episodic joint inflammation (palindromic rheumatism) preceding ERA diagnosis and which characteristics differentiate these patients from those without prior episodic symptoms.

Methods. Data were from patients with early confirmed or suspected RA (more than 6 weeks and less than 12 months) enrolled in the Canadian Early ArThritis CoHort (CATCH) between April 2017 to March 2018 who completed study case report forms assessing joint pain and swelling prior to ERA diagnosis. Chi-square and *t* tests were used to compare characteristics of patients with and without self-reported episodic joint inflammation prior to ERA diagnosis. Multivariable logistic regression was used to identify sociodemographic and clinical measures associated with past episodic joint inflammation around the time of ERA diagnosis.

Results. A total of 154 ERA patients were included; 66% were female, and mean (SD) age and RA symptom duration were 54 (15) years and 141 (118) days. Sixty-five (42%) ERA patients reported a history of episodic joint pain and swelling, half of whom reported that these symptoms preceded ERA diagnosis by over 6 months. ERA patients with past episodic joint inflammation were more often female, had higher income, were seropositive, had more comorbidities, fewer swollen joints, and lower Clinical Disease Activity Index (CDAI) around the time of ERA diagnosis ($P < 0.05$). These associations remained significant in multivariable regression adjusting for other sociodemographic and RA clinical measures.

Conclusion. Almost half of ERA patients experienced episodic joint inflammation prior to ERA diagnosis. These patients were more often female, had higher income, and presented with milder disease activity at ERA diagnosis.

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SIGNIFICANCE & INNOVATION

What is already known about this subject?

- Palindromic rheumatism is considered an at-risk phenotype for the development of rheumatoid arthritis (RA).
- The prevalence of palindromic rheumatism, how frequently it precedes RA, and traits of patients with palindromic rheumatism preceding RA are largely uncharacterized.

What does this study add?

- More than 40% of early RA patients report experiencing episodic joint inflammation prior to RA diagnosis (palindromic rheumatism).
- Patients with prior episodes of inflammatory joint symptoms are more likely female, seropositive, have higher income, more comorbidities, and lower disease activity.

How might this impact clinical practice?

- Study findings have implications for earlier recognition of RA in routine clinical practice, particularly for patients with more insidious or milder disease activity at RA onset.

INTRODUCTION

Palindromic rheumatism (PR) constitutes transient acute attacks of self-resolving articular and/or periarticular inflammation without radiographic damage (1–4). Although it is debated whether PR is part of the spectrum of rheumatoid arthritis (RA), estimated rates of PR progression to RA range from 50% to 67%, and PR is widely considered an at-risk phenotype for development of RA (5–7).

The prevalence of PR and how frequently it precedes RA is largely uncharacterized, and the median length of time before RA diagnosis is unknown. In one study, less than 3% of patients with musculoskeletal disorders seen by rheumatologists had PR (8). PR may be more common than previously recognized. In a Canadian retrospective study of 145 newly referred rheumatology patients, 51 were diagnosed with PR and 94 with RA, providing a relative estimate (9). Another study from the United Kingdom found that of 100 RA patients, 1 in 4 had transient symptoms for more than 6 months, often over a year, before definite RA (10). The purpose of this study was to determine how frequently patients with early RA (ERA) experience episodic joint inflammation prior to ERA diagnosis and to compare characteristics of patients with ERA who did versus did not report past episodes of joint inflammation.

METHODS

Data source. The present study was an analysis of an incident cohort of early classifiable or suspected RA according to their rheumatologist enrolled in the Canadian Early ArThritis CoHort (CATCH) from April 2017 to March 2018 (11). The CATCH study involves 16 sites. CATCH inclusion criteria are age over 18 years; between 6 weeks and 12 months of persistent synovitis at enrollment; two or more swollen joints or one swollen metacarpophalangeal or proximal interphalangeal joint; and one or more of the following: positive rheumatoid factor (RF), positive anti-citrullinated protein antibodies (ACPA), morning stiffness of at least 45 minutes, response to nonsteroidal anti-inflammatory drugs, or painful metatarsophalangeal squeeze test. All CATCH participants provided signed informed consent, the data were anonymmized, and the CATCH study was approved by each local site's research ethics board. Additionally, the study was conducted according to the Declaration of Helsinki. Summary data are available upon request.

Measures. History of joint symptoms was assessed with the following questions: 1) Have you had other similar episodes of pain and swelling in your joints in the past (Yes/No)? 2) How long ago did the past episode(s) happen? (within the past 6 months, more than 6 months ago); and 3) Did the other episode(s) come and go (Yes/No)?

Other variables included sociodemographic variables: age, sex, ethnicity (Caucasian or minority), annual household income, smoking, and education (above high school); clinical variables: RA symptom duration in months, fulfilment of 2010 ACR/European League Against Rheumatism (EULAR) classification criteria, ACPA and RF serology, physician and patient global assessments, 28 swollen and tender joint counts, the composite Clinical Disease Activity Index (CDAI), Multi-Dimensional Health Assessment Questionnaire (MD-HAQ), comorbidity was collected for the composite rheumatic disease comorbidity index (RDCI) and also for osteoarthritis (OA), fibromyalgia, and back or spine arthritis.

Analysis. Descriptive, chi-square, and *t* tests were used to compare differences in baseline characteristics in patients with versus without a reported history of PR as defined by prior transient inflammatory joint symptoms. Simple and multivariable logistic regression with backward selection ($P < 0.2$) were used to identify crude and adjusted predictors of episodic symptoms. SAS version 9.4 and SPSS version 25.0 were used.

RESULTS

Over the course of 1 year, 201 patients were recruited and 47 of those were excluded because of missing data for joint symptom questions, leaving 154 patients for analyses. Included patients had similar demographic and RA clinical characteristics as those excluded except that those excluded were less likely to be Caucasian and had more comorbidities (Supplemental Table 1).

Table 1. Baseline characteristics of ERA patients who did vs did not report transient joint episodes prior to ERA diagnosis[a]

Variable	Total Sample (n = 154)	ERA Patients Who Did NOT Report Prior Transient Joint Episodes (N = 89)	ERA Patients Who Reported Prior Transient Joint Episodes (N = 65)	*P* value
MD-reported symptom duration (days), median (IQR)	141 (118)	142 (130)	140 (118)	0.549
Age (years), mean (SD); range	54 (15); 18-80	54 (15); 18-80	54 (15); 22-80	0.971
Female (%)	101 (66)	51 (57)	50 (77)	**0.011**
Caucasian (%)	124 (80)	73 (82)	51 (78)	0.582
Education (>high school) (%)	84 (55)	46 (52)	38 (58)	0.447
Household income (>$50 000) (%)	69 (59)	33 (52)	36 (68)	0.073
Smoking (%)				
Never	66 (44)	42 (49)	24 (38)	0.167
Current smoker	28 (19)	12 (14)	16 (25)	0.086
Past smoker	56 (37)	32 (37)	24 (38)	0.971
Rheumatic disease comorbidity index (SD)	1.4 (1.5)	1.1 (1.3)	1.7 (1.7)	**0.021**
Fibromyalgia (%)	4 (3)	1 (1)	3 (5)	0.311
Osteoarthritis (%)	33 (24)	13 (16)	20 (32)	**0.017**
Back/spine symptoms (%)	42 (29)	14 (17)	28 (45)	**<0.001**
2010 ACR/EULAR criteria (%)	127 (83)	74 (83)	53 (82)	0.713
Seropositivity (RF or ACPA)	101 (67)	50 (58)	51 (79)	**0.009**
RF positive (%)	81 (59)	38 (49)	42 (70)	**0.012**
ACPA positive (%)	79 (64)	40 (56)	39 (74)	**0.048**
Patient global assessment (SD) (0-10)	6 (3)	5 (3)	6 (3)	0.345
MD global assessment (SD) (0-10)	5 (2)	6 (2)	5 (3)	**<0.001**
Swollen joint count (SD) (0-28)	7 (5)	8 (6)	5 (4)	**0.001**
Tender joint count (SD) (0-28)	8 (6)	8 (6)	6 (6)	0.063
CDAI (SD)	25.2 (12.5)	27.5 (12.4)	22.1 (12.0)	**0.011**
MD-HAQ (SD)	0.9 (0.6)	0.8 (0.6)	0.9 (0.6)	0.198
Oral corticosteroids (%)	24 (16)	15 (17)	9 (14)	0.611
Parenteral corticosteroids (%)	38 (25)	20 (23)	18 (28)	0.458

Bold indicate stat significant values ($P < 0.05$).
Abbreviation: ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; ERA, early rheumatoid arthritis; EULAR, European League Against Rheumatism; IQR, intraquartile range; MD, medical doctor; MD-HAQ, Multi-Dimensional Health Assessment Questionnaire.
[a]Chi Square and *t* test were used where appropriate.

Table 1 summarizes baseline characteristics comparing patients with and without PR prior to ERA diagnosis. Two-thirds of patients were female, mean (SD) age was 54 (15) years, and mean (SD) physician-reported symptom duration was 141 (118) days; 83 (54%) reported having previous joint pain and swelling prior to current episode; 65 (42%) endorsed prior joint pain and swelling that would "come and go," of whom 31 (48%) reported joint symptoms that occurred more than 6 months prior to ERA diagnosis. Patients reporting PR (history episodic inflammatory joint symptoms) were more often female, seropositive, had higher average RDCI scores, and OA and back or spine arthritis. They had lower swollen joint counts, physician global assessment, and baseline CDAI ($P < 0.05$). There were no significant differences in physician-reported RA symptom duration.

Results of regression models are summarized in Tables 2 and 3. Unadjusted predictors of prior episodic inflammatory joint symptoms included female sex, higher income, seropositivity, comorbid OA, back/spine arthritis, higher RDCI, and lower swollen joint count, physician global assessment, and CDAI ($P < 0.05$). Female sex, higher income, seropositivity, back or spine arthritis, and lower CDAI remained significant in multivariable regression.

DISCUSSION

In this study of patients with ERA, patients frequently reported PR prior to RA. Sociodemographic and clinical measures associated with past inflammatory joint symptoms in adjusted models were female sex, higher income, seropositivity, comorbid back or spine arthritis, and lower CDAI disease activity. There were no differences in RA symptom duration between those with and without PR.

Results of the present study (20% reported PR more than 6 months prior to ERA and more than 40% within 1 year prior to diagnosis) are consistent with a previously reported rate of 23% and 50% (9,10) but higher than two other studies (15% of 158 patients with RA had PR (12) and 5% in another study (2)).

Consistent with the reported associations with seropositivity and female sex in the present study, seropositivity has been associated with PR progression to RA (3,13–15); in a 10-year prog-

Table 2. Univariable logistic regression examining associations between ERA baseline characteristics and history of transient joint episodes prior to ERA diagnosis

Variable	Odds Ratio	95% CI	*P* Value
Age	1.000	0.978, 1.021	0.971
Female	2.484	1.217, 5.070	**0.012**
Caucasian	0.798	0.358, 1.780	0.582
Education (>high school)	1.316	0.690, 2.508	0.405
Income (>$50 000)	2.107	1.098, 4.040	**0.025**
Current smoker	2.095	0.914, 4.804	0.081
Rheumatic disease comorbidity index	1.303	1.044, 1.626	**0.019**
OA	2.601	1.174, 5.763	**0.019**
Back/spine	4.118	1.923, 8.815	**<0.001**
RA symptom duration	1.001	0.997, 1.005	0.547
Seropositivity (RF or ACPA)	2.623	1.264, 5.444	**0.010**
RF positive	2.452	1.207, 4.981	**0.013**
ACPA positive	2.159	1.000, 4.663	0.050
Patient global assessment	1.065	0.935, 1.213	0.343
MD global assessment	0.771	0.668, 0.891	**<0.001**
Swollen joint count	0.893	0.830, 0.961	**0.002**
Tender joint count	0.950	0.899, 1.003	0.065
CDAI	0.963	0.935, 0.992	**0.014**
MD-HAQ	1.495	0.811, 2.757	0.197

Bold indicate stat significant values ($P < 0.05$).
Abbreviation: ACPA, anticitrullinated protein antibodies; CDAI, Clinical Disease Activity Index; CI, confidence interval; ERA, early rheumatoid arthritis; MD, medical doctor; MD-HAQ, Multi-Dimensional Health Assessment Questionnaire; OA, osteoarthritis; RF, rheumatoid factor.

nostic study of PR, female patients with positive RF and hand involvement had an 8-fold risk of developing connective tissue disease relative to patients with one or fewer of these traits (8). Seropositive RA is also associated with progression to more erosive and severe disease (16–19); thus, early clinical recognition of this patient group has important prognostic implications.

Patients with prior episodic inflammatory joint symptoms also had more comorbidities with higher RDCI comorbidity counts, more frequent OA, and self-reported back or spine arthritis. Although cervical spine involvement is thought to be rare at onset of RA, it may be an early manifestation of RA and has been reported as a presenting symptom (20). Moreover, the presence of a concomitant musculoskeletal condition such as OA or fibromyalgia has previously been identified as the most significant predictor of prolonged time from RA symptom onset to treatment (21). A larger sample size is required to further assess the likely association of OA and RDCI with palindromic symptoms.

Additionally, markers of disease activity were lower in this subset of patients, suggesting a possible insidious onset or milder disease activity at RA diagnosis, including lower swollen joint count, physician global assessment, and CDAI. In another Canadian cohort study comparing PR patients with new RA patients, inflammatory markers were generally higher in new-onset RA but were often also elevated in PR (9). Our findings suggest that patients with self-reported transient symptoms have relatively lower disease activity at study enrollment. In clinical practice, the finding that ERA patients frequently experience transient initial joint symptoms can help inform early recognition of disease, which initially may be more insidious or milder in this patient group.

Few studies have quantified patient symptoms preceding ERA diagnosis (22,23) or characterized PR preceding ERA (5–7). The strengths of this study are its unique quantitative characterization of episodic inflammatory symptoms prior to ERA and inclusion of ERA patients from multiple centers. A limitation of this study is the exclusion of 47 patients for missing data for joint symptom questions. Another limitation is that previous joint pain and swelling was reported by patients rather than physician-verified episodes of inflammatory arthritis; we are thus unable to verify whether patient-reported symptoms constituted inflammatory arthritis, previous PR, or may be attributable to comorbid musculoskeletal conditions such as OA. Our findings suggest that half of the patients with early onset RA had an episodic prodrome of inflammatory arthritis symptoms before the onset of RA.

As defined by Pasero and Barbieri (2), PR involves more than five recurrent attacks over 2 years of sudden onset monoarthritis, with physician verification of one attack; negative radiographs, RF, and inflammatory markers; attacks in three or more different joints; and exclusion of other arthritides. Hannonen et al expanded their definition to include mono- or polyarthritis and periarticular tissue inflammation lasting anywhere from a few hours to 1 week and excluded radiographic and serologic criteria (3); similar criteria were proposed by Guerne and Weisman (4), including a 6-month history of these brief symptoms and no radiographic damage. Diagnostic criteria for

Table 3. Multivariable logistic regression examining associations between ERA baseline characteristics and history of transient joint episodes prior to ERA diagnosis[a]

	N = 133	
Variable	OR	95% CI
Age (years)	0.997	0.966, 1.029
Female	3.303	**1.165, 9.366**
Household income (>$50 000)	2.539	**1.063, 6.063**
Rheumatic disease comorbidity index	1.347	0.994, 1.825
Osteoarthritis	3.102	0.996, 9.658
Back/spine symptoms	2.974	**1.145, 7.723**
Seropositivity	3.641	**1.343, 9.873**
CDAI	0.949	**0.912, 0.988**

Bold indicate stat significant values ($P < 0.05$).
Abbreviation: CDAI, Clinical Disease Activity Index; CI, confidence interval; ERA, early rheumatoid arthritis; MD, medical doctor; OR, odds ratio.
[a]Nonsignificant variables: current smoker, MD global assessment. Twenty-one patients were excluded from multivariate analysis because of missing data.

PR were not included in the current study of patient-reported transient symptoms of joint pain and swelling that would come and go. Despite this, there are differences for patients with episodic symptoms by self-report such as more seropositivity. Further research is required to characterize physician-diagnosed PR and its relationship with RA onset.

Recently, cases of RA have been described with overlapping autoimmune and autoinflammatory clinical phenotypes characterized by abrupt inflammatory attacks with fever, joint swelling, erythema, and elevated inflammatory markers (24). Our finding that patient-reported episodic inflammatory joint symptoms are prevalent amongst patients with ERA further highlights the importance of characterizing the phenotypic variability of ERA.

Patients with ERA frequently reported experiencing transient episodes of inflammatory arthritis prior to RA diagnosis. ERA patients who endorsed a history of joint symptoms that come and go prior to RA diagnosis were more likely female and seropositive with higher income and lower CDAI at ERA cohort entry, but median ERA duration did not differ. These findings have implications for earlier RA recognition in routine clinical practice, particularly for patients with more insidious or milder disease activity at RA onset.

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APPENDIX A: CATCH INVESTIGATORS

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