

Risk Factors for the Development of Psoriatic Arthritis: a Population Based Nested Case Control Study

JULIAN THUMBOO, KRISTINE URAMOTO, MOHAMMED I. SHBEEB, W. MICHAEL O'FALLON, CYNTHIA S. CROWSON, LAWRENCE E. GIBSON, CLEMENT J. MICHET Jr, SHERINE E. GABRIEL

ABSTRACT Objective. To identify factors influencing the development of psoriatic arthritis (PsA) in a population-based, inception cohort of psoriasis (PS) patients.

Methods. Using the population-based data resources of the Rochester Epidemiology Project, which ensures virtually complete ascertainment of all clinically defined conditions, we previously identified all incident cases of PsA and prevalent cases with PS from 1/1/1982 to 12/21/1991. In this nested case-control study, we assessed potential factors influencing the development of PsA in this cohort using medical record and patient survey information. Each case of PsA was matched with 2 PS controls on age, gender and PS duration/date of onset. Factors influencing the development of PsA were identified, adjusting for the influence of other variables using conditional logistic regression for medical record data and logistic regression for survey data.

Results. Sixty incident PsA cases were matched with 120 controls with PS. The median age at onset of PS was 31.7 (3.0–78.3) years, and 49% of subjects were male. There were 67% (n = 40) survey responders among cases and 48% (n = 58) among controls. Corticosteroids were used by 10 cases and 6 controls in the 2 years prior to onset of PS through to the development of PsA, and increased the risk of developing PsA (odds ratio 4.33, 95% CI = 1.34–14.02). Pregnancy occurred in 2 cases and 12 controls in the same period, and decreased the risk of developing PsA (odds ratio 0.19, 95% CI = 0.04–0.95). These associations remained significant after adjusting for the influence of gender, age, and duration of psoriasis.

Conclusion. Corticosteroid use and pregnancy, both of which modulate the immune response, may influence the development of PsA in patients with PS. (J Rheumatol 2002;29:757–62)

Key Indexing Terms:

PSORIATIC ARTHRITIS
PREGNANCY

RISK FACTORS

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CASE-CONTROL STUDIES

Psoriatic arthritis (PsA) affects 5 to 8% of patients with psoriasis (PS)¹ and has been associated with substantial morbidity in some studies^{2,4}. Factors associated with the development of PsA have largely been identified from case reports or case series, which are subject to bias and cannot establish a cause and effect relationship. Identifying factors that influence the development of PsA in patients with PS may provide insights into the etiology of PsA, and may lead to strategies to reduce the rate of PsA in patients with PS. We hypothesized that demographic, environmental, socio-economic, co-morbidity, disease or therapy related factors might influence the development of PsA, and studied the

influence of these factors on the development and time to onset of PsA in an existing population based cohort of patients with PS in Olmsted County, Minnesota using a nested case control study design.

MATERIALS AND METHODS

Study design and population. Using the resources of the Rochester Epidemiology Project (REP), we conducted a nested case control study using a previously assembled database of all incident cases of PsA and all prevalent cases of PS resident in Olmsted County at diagnosis of PsA or PS from 1982 to 1991. The methods used to identify patients for inclusion in this database have been described⁵. The REP record linkage system contains information on virtually all medical care provided to residents of Olmsted County for as long as they reside in the county. Diagnoses made in clinics, hospitals, home visits, or at autopsy are entered into a centralized index, which enables the identification and retrieval of pertinent medical records. This system ensures virtually complete ascertainment and followup of all clinically defined disease among residents in Olmsted County.

Matching of cases and controls. Of the 66 incident PsA cases identified through our previous epidemiologic studies, 6 were excluded from this analysis because they developed PsA before PS. Each remaining case was matched with 2 controls from the same cohort. Controls were selected from all PS patients without PsA who fulfilled the following matching criteria applied in sequence: case duration of PS at onset of PsA (± 2 yrs), age of case (± 2 yrs) at onset of PsA, gender, date of onset of PS (± 2 yrs) and Mayo Clinic registration number, which controlled approximately for opportunity of care in Olmsted county (Table 1).

From the Department of Health Sciences Research; Division of Rheumatology and Department of Dermatology, Mayo Clinic, Rochester, Minnesota, USA.

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J. Thumboo, FRCP(Edin); K. Uramoto, MD; M.I. Shbeeb, MD; W. M. O'Fallon, PhD; C.S. Crowson, BS; L.E. Gibson, MD; C.J. Michet Jr, MD, MPH; S.E. Gabriel, MD, MSc, Department of Health Sciences Research and Department of Dermatology.

Address reprint requests to Dr. S.E. Gabriel, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: gabriel.sherine@mayo.edu

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Medical record abstraction and questionnaire design. Data from an existing database of all patients with PS in Olmsted county, MN from January 1, 1982 to December 31, 1991 was utilized⁵. In assembling this database, 1056 cases of PS were identified from 1844 potential cases of PS, and the entire medical record was reviewed using a pretested data collection form to collect information on demographics, clinical manifestations, laboratory findings, treatment, and outcome. Additional data on possible risk factors for the development of PsA including surgical procedures, trauma, streptococcal infections, psychological stress, diabetes mellitus, hypertension and treatments for PS (topical or oral medications and phototherapy) were collected by a physician abstractor (JT) using a pretested data collection form and encompassing the period up to the diagnosis of PsA. A pre-tested, self-administered survey questionnaire with a single mailing was utilized to obtain information not usually recorded in the medical record. This included information on family members with PS or PsA, ethnicity, number of years of education, tobacco, alcohol and medication use, pregnancies, and menopause. To minimize recall bias, the questionnaire inquired about the patient's PS and health in general, and did not specifically mention PsA as a focus of the study. None of the 66 cases declined research authorization at the time of medical record abstraction. Three controls declined research authorization and 3 alternative control patients with PS were therefore selected. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Definitions and diagnostic criteria. The diagnosis of PS was based on documentation of typical skin changes of PS in the medical record by a dermatologist. All questionable cases of PS were reviewed with our dermatologist co-investigator (LEG). Skin severity of PS was defined as limited (≤ 2 sites) or generalized (> 2 sites) based on involvement of the scalp, elbows, knees, other flexural areas, palms/soles or other sites. The diagnosis of peripheral joint involvement due to PsA was based on documentation in the medical record of inflammatory synovitis with objective joint swelling noted by a physician in any upper or lower limb joint in a patient with PS. Patients with seropositive rheumatoid arthritis, Reiter's syndrome, crystalline arthritis, arthritis of inflammatory bowel disease, and inflammatory osteoarthritis were excluded, as were patients with uncharacterized

inflammatory arthritis who were persistently rheumatoid factor positive. Axial disease was defined as involvement of the cervical, thoracic, or lumbosacral spine with documented inflammatory spinal pain, sacroiliac tenderness, reduced chest expansion or radiographic changes consistent with PsA (sacroiliitis or syndesmophytes).

Potential risk factors for PsA. We studied risk factors associated with the development of either PsA or PS, as evidence suggests that shared genetic and environmental factors may influence the development of both the articular⁶⁻⁹ and cutaneous¹⁰⁻¹² manifestations of PS. As these factors may influence the development of PsA before or after the onset of PS, their influence was studied in both time intervals. The presence of potential risk factors prior to the onset of PsA was determined from medical record and/or patient survey data. The time period during which individual risk factors might influence the development of PsA (summarized in Table 2) was determined by the plausibility of cause and effect over a period of time, anticipated accuracy of patient recall, and the literature on trigger factors¹³⁻¹⁸. Risk factors whose influence on the development of PsA was unlikely to vary with time (e.g., menopause, diabetes mellitus) were included in the analysis if they were present at any time before the development of PsA. Risk factors whose influence was likely to be time dependent (e.g. smoking or use of medications) were included if they were present in the 2 years prior to the onset of PS through to the onset of PsA. Medical record ascertained risk factors were defined as follows: trauma as a documented motor vehicle accident, fracture, sprain/ contusion, surgical procedure (including minor surgical procedures) or burn; psychological stress as a documented physician/psychiatrist diagnosis of a depressive illness (major depressive disorder, dysthymic disorder, depressive disorder not otherwise specified), adjustment disorder, anxiety (panic attacks, agoraphobia, acute stress disorder, post-traumatic stress disorder, general anxiety disorder, anxiety related to a general medical condition or substance abuse); hypertension as a blood pressure of $> 140/90$ on 3 separate occasions¹⁹; diabetes mellitus as 2 consecutive outpatient fasting plasma glucose values ≥ 140 mg/dl (7.8 mmol/l) or 1 oral glucose tolerance test for which the 2 hour and one other value were both > 200 mg/dl (11.1 mmol/l); streptococcal infection as positive bacteriological culture of *Streptococcus* from a

Table 1. Characteristics of cases and controls.

	Cases, n = 60		Controls, n = 120	
	n	%	n	%
Entire Cohort				
Male	29	(48.3)	59	(49.2)
White	59	(98.3)	118	(99.2)
Median age (range) at onset of PS, yrs*	31.6	(3.0–76.5)	31.7	(4.5–78.3)
Median age (range) at onset of PsA, yrs*	41.2	(19.8–82.3)	40.6	(16.2–82.4)
Median duration (range) of PS at onset of PsA, yrs*	5.8	(0–52.2)	6.2	(–2.4–49.0)
	Responders n (%)	Non-responders n (%)	Responders n (%)	Non-responders n (%)
Survey responders and non-responders				
Number	40 (66.7)	20 (33.3)	58 (48.3)	62 (51.7)
Male	21 (52.5)	8 (40.0)	27 (46.6)	32 (51.6)
White	39 (97.5)	20 (100.0)	58 (100.0)	60 (98.4)
Median age (range) at onset of PA, yrs*	39.7 (24.0–65.3)	53.1 (19.8–82.3)	42.4 (16.2–77.3)	40.4 (22.9–82.4)
Median duration (range) of PS at onset of PsA, yrs*	4.6 (0–52.2)	9.5 (0–37.9)	6.0 (–2.4–49.0)	7.0 (–2.2–47.3)

* For controls, the date corresponding to the matched case's date of onset was used.

Table 2. Distribution of potential risk factors for psoriatic arthritis in cases and controls.

Risk Factor	Number (%)		Odds Ratio	95% Confidence Interval	p
	Cases, n = 60	Controls, n = 120			
Medical record data					
Family history of PS*	19 (31.7)	32 (26.7)	1.27	0.65, 2.50	0.486
Family history of PsA*	2 (3.3)	0	—	—	—
Trauma†					
All causes of trauma	40 (66.7)	71 (59.2)	1.58	0.73, 3.41	0.248
Fractures only	9 (15.0)	13 (10.8)	1.50	0.58, 3.91	0.407
Streptococcal infection‡	10 (16.7)	24 (20.0)	0.74	0.29, 1.90	0.528
HIV infection‡	0	0	—	—	—
Psychological stress†	9 (15.0)	19 (15.8)	0.93	0.36, 2.36	0.874
Medication use†					
Lithium	1 (1.7)	2 (1.7)	1.00	0.09, 11.03	1.000
Beta blockers	7 (11.7)	9 (7.5)	1.61	0.58, 4.49	0.366
Corticosteroids	10 (16.7)	6 (5.0)	4.33	1.34, 14.02	0.015
Antimalarials	0	1 (0.8)	—	—	—
White	59 (98.3)	118 (99.2)	1.41	0.35, 5.66	1.000
Generalized PS at presentation	25 (41.7)	46 (38.3)	1.18	0.59, 2.34	0.642
Skin type at presentation					
Papulosquamous, plaque or other	60 (100.0)	114 (95.0)	—	—	—
Erythroderma	0	2 (1.7)	—	—	—
Pustular	0	4 (3.3)	—	—	—
Nail involvement ‡	12 (24.0)	23 (25.6)	1.16	0.46, 2.92	0.752
Iritis, enthesitis or dactylitis‡	8 (13.3)	20 (16.7)	0.78	0.33, 1.85	0.572
Treatments for PS‡					
Coal tar preparations	27 (45.0)	59 (49.2)	0.82	0.42, 1.62	0.567
Methotrexate	0	1 (0.83)	—	—	—
Phototherapy	2 (3.3)	12 (10.0)	0.33	0.08, 1.49	0.150
Hypertension‡	15 (25.0)	23 (19.2)	1.51	0.67, 3.43	0.325
Diabetes mellitus‡	1 (1.7)	5 (4.2)	0.40	0.05, 3.42	0.403
	Cases, n = 40 (%)	Controls, n = 58 (%)			
Survey data					
College graduate*	14 (35.0)	21 (36.2)	0.95	0.41, 2.20	0.902
Smoking*	18 (45.0)	34 (59.7)	0.55	0.24, 1.25	0.156
Alcohol use# (≥ weekly)	11(29.0)	19 (34.6)	0.77	0.32, 1.89	0.571
Use of HRT or oral contraceptives‡	15 (83.3)	19 (63.3)	2.90	0.68, 12.28	0.149
Pregnancy†	2 (10.5)	12 (38.7)	0.19	0.04, 0.95	0.044
Menopause‡	6 (35.3)	11 (37.9)	0.89	0.26, 3.10	0.858

*Present at any time;

†Present in the 2 years before onset of psoriasis (PS) through to the onset of psoriatic arthritis (PsA);

‡Present at any time before the onset of PsA; Only 1 control had a diagnosis of 'dactylitis.' This individual had no documented evidence of synovitis.

Present 1 year before the onset of PS. HRT: hormone replacement therapy. Data on nail involvement not available for 10 cases and 30 controls.

clinically infected site; HIV infection as Western blot confirmed HIV infection. The patient survey was used to obtain data on ethnicity, use of tobacco (smoked at least 100 cigarettes), alcohol, or specified medications (for which generic and commercial names were stated), number and dates of pregnancies, date of menopause, and the presence of parents or siblings with PsA (defined as "arthritis caused by psoriasis") or PS. Data on topical corticosteroid use was not collected.

Statistical analyses. Dates of onset of PS and PsA were used to define time intervals for analysis. Demographic characteristics and possible risk factors influencing the development of PsA of interest in cases and controls were described using appropriate summary statistics. Conditional logistic regression comparing cases and matched controls was used to assess possible risk factors obtained from the medical record (Table 2). Each factor was assessed individually in a model. The stepwise process was used to build a multivariable model to identify factors independently important as risk

factors for PsA among patients with PS. A p value < 0.05 was considered statistically significant. Possible risk factors obtained from the patient survey were analyzed using logistic regression models, with data on predictor variables incorporating both medical record and patient survey data (in contrast to the medical record analysis, which used data on predictor variables from the medical record only). Each factor was assessed univariately. A multivariate model was developed using the stepwise process and adjusting for significant medical record factors. Matched analyses of patient survey data were not feasible as some subjects did not respond to the survey.

RESULTS

Cohort characteristics and survey response rates. The gender and ethnic distribution of patients with PsA was

similar to that of the Olmsted County population, with equal numbers of males and females of largely white ethnicity with a wide range of ages. Subjects had PS for up to 52 years at the time of the study (Table 1), with a median age at onset of PS of 31.7 (3.0 to 78.3) years. By design, cases (PsA patients) and controls (PS patients) were similar in gender and duration of PS. Thirty-two percent of cases and 27% of controls gave a family history of psoriasis, while 3% of cases and no controls gave a family history of PsA. However 2% of cases gave a family history of RA, Reiter's syndrome, and/or connective tissue disease, while 12.5% of controls gave such a history. No cases or controls gave a family history of ankylosing spondylitis or iritis. Of the 60 cases and 120 controls, 67% and 48%, respectively, returned survey forms after a single questionnaire mailing in October 1998. Responders and non-responders generally had similar demographic characteristics, with responders among patients with PsA being younger, with a shorter disease duration than non-responders (Table 1).

Risk factors for psoriatic arthritis: medical record data. Characteristics of cases and controls for potential risk factors for PsA using data obtained from medical records are summarized in Table 2. Univariate analysis showed that corticosteroid use in the period beginning 2 years prior to onset of PS through to the development of PsA was associated with an increased risk of developing PsA [odds ratio (OR) 4.33, 95% confidence interval (CI) 1.34–14.02, $p = 0.015$]. This association remained significant after adjusting for the influence of gender, age, and duration of psoriasis using conditional logistic regression, in which corticosteroid use was the only factor significantly associated with the development of PsA (OR 5.54, 95% CI 1.54–19.87, $p = 0.009$). During this period, corticosteroids were used in 16.7% of cases and 5% of controls. Ethnicity, documented trauma or infection, co-morbidity, and extent, type of and therapy for psoriasis did not show a significant relationship with the development of PsA, with $p \geq 0.15$ in all cases. No subjects were treated with azathioprine, cyclosporin A, etretinate, cyclophosphamide, or chlorambucil in the time period of interest.

Risk factors for psoriatic arthritis: patient survey data. Characteristics of cases and controls for potential risk factors for PsA obtained from the patient survey are summarized in Table 2. Univariate analysis showed that pregnancy in the 2 years prior to onset of PS through to the development of PsA was associated with a decreased risk of developing PsA (OR 0.19, 95% CI 0.04–0.95, $p = 0.05$). As in the case of corticosteroid therapy, this association also remained significant after adjusting for the influence of gender, age, duration of psoriasis, and corticosteroid use using logistic regression (OR 0.16, 95% CI 0.02–0.99, $p = 0.05$). Two cases and 12 controls became pregnant in this period, with one pregnancy each for the 2 cases, and a median of 1.5 pregnancies (range 1–4) for the 12 controls. The two cases

developed PsA 5.7 years and 8.4 years after the end of their pregnancies. In contrast, the total number of pregnancies at any time in cases ($n = 40$) and controls ($n = 58$) was not significantly different [median (range) = 1.5 (0–6) in cases and 2.0 (0–6) in controls, RR 0.86, 95% CI = 0.63 - 1.16]. Educational status, use of alcohol or cigarettes, exposure to oral contraceptive pills or hormone replacement therapy, and menopause did not show a significant relationship with the development of PsA, with again $p \geq 0.15$ in all cases.

DISCUSSION

In this population based, inception cohort study, we assessed the influence of demographic, environmental, disease, comorbid, and therapy related factors on the development of PsA in patients with PS. We found that corticosteroid use in the period beginning 2 years prior to onset of PS through to the development of PsA was associated with an increased risk of developing PsA, while pregnancy in the same period was associated with a decreased risk of developing PsA. To the best of our knowledge, this is the first population based study of risk factors for developing PsA in patients with PS. Our findings may provide insights into the etiology of PsA, and may lead to the development of new strategies to reduce the incidence of PsA in PS patients.

Our findings that corticosteroid use and pregnancy influenced the subsequent development of PsA suggest that modulation of the immune system may be important in the pathogenesis of PsA. Corticosteroids are potent immunosuppressives that are effective in treating PS, but are rarely used because corticosteroid withdrawal may cause a rebound worsening of PS²⁰, possibly by aggravating the underlying immune dysfunctions present in PS. It is possible that a similar mechanism may contribute to the development of PsA in PS patients receiving corticosteroids. Pregnancy involves modulation of the host immune system to allow tolerance of foreign antigens in the fetus²¹. It is possible that pregnancy-induced changes in the immune system may reduce the subsequent risk of developing PsA, as seen in this study. This is supported by observations suggesting that PS²¹, PsA²² and also rheumatoid arthritis²³ improve during, and worsen after, pregnancy. Interestingly, the risk of developing RA is higher in the 1st year postpartum and thereafter decreases²³. As PsA and RA share the same improvement during and worsening after pregnancy, this observation may account for our finding that pregnancy reduces the risk of PsA, while McHugh and colleagues found that PsA developed soon after pregnancy in several patients with PS²⁴.

We adopted several measures to minimize bias and confounding in this study. Using a population based cohort of PS patients reduced the possibility of prevalence-incidence and admission rate bias²⁵, and made it likely that cases and controls had the same baseline risk of developing PsA. We minimized recall bias by not stating our interest in

PSA in the survey questionnaire. Further, questionnaire items are not generally known as risk factors for the development of PsA or PS and would therefore not lend themselves to recall bias. Bias in data abstraction is unlikely as the variables abstracted were objectively documented in the medical record, and data in the original database were abstracted prior to planning this study. Ascertainment bias for trauma and streptococcal infections is also unlikely, unless patients who eventually developed PsA were more likely to seek medical attention than controls. As male gender is associated with more axial PsA²⁶, and age with more skin involvement⁶ and a family history of PS²⁷, we minimized potential confounding by matching cases and controls on these variables. As severe skin disease is associated with PsA and is more likely to be treated with oral medications or phototherapy, we adjusted statistically for possible confounding by skin severity on any relationship between medication use and the development of PsA. Although pregnancy was assessed by patient report, it is likely that these data are accurate as subjects would generally be able to recall the dates and number of pregnancies.

As with all research, our results should be viewed in the light of our study limitations. The retrospective study design did not allow standardized ascertainment of potential risk factors. In particular, ascertainment of trauma, streptococcal infection, and psychological stress might have been incomplete, as medical record review only identifies episodes that were clinically recognized or were severe enough to come to medical attention. Likewise, while we did review the medical records of all subjects for evidence of inflammatory arthritis prior to index date, we cannot rule out the possibility that non-specific musculoskeletal symptoms may have been present which either did not reach medical attention or were not documented in the medical record. Further, medical records may not reliably document enthesitis, given that this is a relatively common form of soft tissue rheumatism. While this may affect the magnitude of an association, it is unlikely to cause bias as the extent of medical record documentation was similar for both cases and controls²⁸. Although the survey response rate was only 54% after the single questionnaire mailing (64% response rate for cases and 48% for controls), characteristics of responders and non-responders were generally similar, suggesting that our results are likely to be representative of the entire cohort. A family history of PS or PsA may be a marker for genetic or shared environmental factors predisposing to the development of PsA. The relative contributions of these factors could not be separated in this study. As Caucasians form 96% of the Olmsted county population, study results may not be applicable to subjects of other ethnicities. The relatively small sample size may have limited the power of this study to identify risk factors with a small influence on the development of PsA. This study had 80% power to detect an OR of 3.2 for the medical record

data analyses and 4.0 for the survey data analyses (assuming $\alpha = 0.05$). Thus, the power to detect risk factors with smaller associations was modest. The use of repeated significance testing in univariate analyses of medical record and survey data raises the possibility that observed differences were due to chance rather than actual differences between cases and controls. This is unlikely to be of concern, as multivariate models for medical record and survey data, respectively, each identified only one factor as being significantly associated with the development of PsA. Given the difficulty of studying our research question prospectively, we feel that, despite these limitations, our results are clinically useful and may provide insights into the etiology of PsA.

In conclusion, we found in a population-based, inception cohort study of patients with PS that corticosteroid use was associated with an increased risk of developing PsA, while pregnancy was associated with a decreased risk of developing PsA. Given that corticosteroids and pregnancy are known to affect the immune system, our findings may provide insight into the etiology of PsA, and may lead to the development of new strategies to reduce the incidence of PsA in PS patients. Additional research is needed to elucidate the determinants of PsA and to devise strategies to prevent psoriatic arthritis in patients with psoriasis.

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