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Incidence and Predictors of Secondary Fibromyalgia in an Early Arthritis Cohort

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Abstract

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Each individual named as an author contributed to either the conception and design, acquisition of data or analysis and interpretation of data. All authors helped draft the article and/or revised it critically for important intellectual content. All authors provided final approval of the submitted version of the manuscript. No other individuals met these criteria for authorship.

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Objectives—Secondary fibromyalgia (FM) is common among patients with inflammatory arthritis, but little is known about its incidence and the factors leading to its development. We examined the incidence of secondary FM in an early inflammatory arthritis cohort and assessed the association between pain, inflammation, psychosocial variables and the clinical diagnosis of FM.

Methods—We analyzed data from 1487 patients in the Canadian Early Arthritis Cohort, a prospective, observational Canadian cohort of early inflammatory arthritis patients. Diagnoses of FM were determined by rheumatologists. Incidence rates were calculated, and Cox regression models were used to determine hazard ratios for FM risk.

Results—The cumulative incidence rate was 6.77 (95% CI 5.19–8.64) per 100 person years during the first 12 months after inflammatory arthritis diagnosis and decreased to 3.58 (95% CI 1.86–6.17) per 100 person years 12–24 months after arthritis diagnosis. Pain severity (HR 2.01, 95% CI 1.17–3.46) and poor mental health (HR 1.99, 95% CI 1.09–3.62) predicted FM risk. CCP positivity (HR 0.48, 95% CI 0.26–0.88) was associated with decreased FM risk. Serum inflammatory markers and swollen joint count were not significantly associated with FM risk.

Conclusions—The incidence of FM was from 3.58 to 6.77 cases per 100 person years and was highest during the first 12 months after diagnosis of inflammatory arthritis. Although inflammation was not associated with the clinical diagnosis of FM, pain severity and poor mental health were associated with the clinical diagnosis of FM. Seropositivity was inversely associated with the clinical diagnosis of FM.

Keywords

Early Rheumatoid Arthritis; Fibromyalgia/Pain Syndromes; Epidemiology

Fibromyalgia (FM) is common among patients with systemic inflammatory disease, affecting 14–20% of rheumatoid arthritis (RA) patients.[1–4] It is characterized by deficits in central pain processing that lead to heightened pain sensitivity. Many FM patients also report other symptoms, including sleep problems and psychiatric distress.[5–8] In comparison to RA patients who do not have FM, RA patients with secondary FM have worse quality of life and higher hospitalization rates.[1]

Little is known about the course of FM and the effects of pain and inflammation on FM risk among inflammatory arthritis patients. Studies in other pain states suggest that there may be a “window of opportunity,” during which aggressive pain management may prevent the development of chronic pain.[9] It is not clear whether this concept may apply to secondary FM among inflammatory arthritis patients.

Researchers have hypothesized that the transition between acute peripheral pain and chronic central pain may be mediated by prolonged exposure to inflammation and pain.[8, 10] In animal models, proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α), have been implicated in the development of aberrant central pain processing, leading to widespread pain sensitivity.[11–14] In humans, the link between inflammation and alterations in central pain processing is not well established. Clinical studies have reported that populations with elevated systemic inflammation have lower pain thresholds in a widespread distribution than healthy controls.[15–17] However, in a case-only study of 59 RA patients, serum C-reactive protein (CRP) was not associated with widespread pain sensitivity.[18] These data were derived from patients with established RA. It is not clear whether the effects of inflammation on widespread pain may have occurred earlier in the disease course.[19]

In this study, we sought to examine the course of secondary FM development in an early inflammatory arthritis cohort. We also assessed the association between inflammation, pain, sleep and psychosocial variables on the clinical diagnosis of FM. We hypothesized that inflammation and pain would be associated with the clinical diagnosis of FM.

METHODS

Study population

Data were analyzed from 1487 patients in the Canadian Early Arthritis Cohort (CATCH), a prospective, observational, cohort of early inflammatory arthritis patients. The study population included all patients recruited between July 2007 and March 2011 from 18 centers across Canada. Inclusion criteria included: age >16 years, 6–52 weeks of persistent synovitis, 2 swollen joints or 1 swollen metacarpophalangeal/proximal interphalangeal joint and 1 of the following: positive rheumatoid factor (RF), positive anti-citrullinated peptide (CCP) antibodies, morning stiffness >45 minutes, response to non-steroidal anti-inflammatory drugs or painful metatarsophalangeal squeeze test. For the primary analyses, we focused on the 1198 participants who had follow-up data and did not have FM at baseline (Figure 1). Participants who were lost to follow-up did not contribute data beyond their last study visit. Additional details regarding this cohort may be found in a previous publication.[20] Written informed consent was obtained from all patients. Research ethics boards representing all investigative sites approved the study.

Study procedures

Participants were followed every three months for the first 12 months, every six months for the next 12 months and annually thereafter. At every visit, clinical data, including medications, were recorded. Synthetic disease-modifying anti-rheumatic drugs (DMARDs) were defined as hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide. Biologic DMARDs were defined as anti-TNF agents, abatacept, rituximab and tocilizumab. Corticosteroids were defined as oral corticosteroids or intra-articular injections of methylprednisolone or triamcinalone. Pain severity and sleep problems were assessed using numeric rating scales.[21] Mental health was assessed using the mental component summary of the 12-item Short Form Health Survey (SF-12).[22] Blood samples were collected for a standard laboratory panel, including erythrocyte sedimentation rate (ESR) and CRP, at every visit. Rheumatologists also assessed tenderness in 68 joints and swelling in 66 joints.

The outcome, diagnosis of secondary FM, was determined based on the clinical judgment of the participants' rheumatologists. The rheumatologists answered a "yes/no" question asking whether participants had FM. If this question was not answered, it was assumed that the participant did not have FM. A subsequent question asked the rheumatologist to provide the number of tender points if the participant had FM. Prevalent FM was defined as participants who had FM at study entry. Incident FM was defined when participants who were not categorized as FM at study entry were later diagnosed with FM.

Statistical analyses

Prevalence, cumulative incidence and incidence rates of secondary FM were calculated. The outcome of FM was considered static, in that once a diagnosis of FM was made, future fluctuations in and out of the diagnosis were not included in the analyses.

Cox proportional hazards models were used to assess the independent effect of baseline patient characteristics (gender, race, RF and CCP status) and time-varying covariates (joint counts, ESR, CRP, mental component summary score, pain numeric rating scale, sleep numeric rating scale, medications) on the clinical diagnosis of FM. For ease of

interpretation, continuous variables were dichotomized based on previously defined clinical thresholds or, if these thresholds did not exist, based on the most severe quartile vs. the remainder of the population. Time-varying covariates were updated at each point before the diagnosis of FM. We used stratified Cox proportional hazards models to adjust for heterogeneity across study centers.

Initially, the association between each variable and the clinical diagnosis of FM was assessed separately. Each Cox proportional hazards model was adjusted for age, gender and race because previous studies documented an association between these variables and FM diagnosis.[23–26] All variables associated with the development of FM at $P \leq 0.1$ were considered for inclusion in the final multivariable model. A backward selection process was employed, with $P \leq 0.1$ as the threshold for inclusion. Statistical significance was defined as $P < 0.05$.

A secondary analysis was performed, excluding CCP status as a covariate, given the high number of missing values. To assess biases introduced by including participants who may not have had RA, a secondary analysis was performed among participants who met 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for RA.[27] All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

Clinical characteristics for the 1487 CATCH participants and the subset of 1198 participants in the incidence and Cox proportional hazards analyses are provided in Table 1. Data on CCP status were missing for 36% of participants, and data on ACR/EULAR 2010 criteria for RA was missing for 34% of participants. Out of 6200 possible data points, 287 (4.63%) were missing a yes/no answer for the outcome of FM.

Prevalent fibromyalgia at study entry

Sixty-eight participants (4.6%) had a diagnosis of FM at entry into CATCH. Compared to participants without a prevalent diagnosis of FM, participants with prevalent FM had a longer duration of RA symptoms at study entry (median 7.2 vs. 5.5 months, $P = 0.008$). Participants with prevalent FM also had higher HAQ scores (median 1.4 vs. 0.9, $P < 0.0001$) and higher pain scores (median 6.0 vs. 5.5, $P = 0.02$) than participants without FM. Participants with prevalent FM had higher disease activity scores (DAS28) (median 5.4 vs. 4.9), though this was not statistically significant ($P = 0.06$).

Cumulative incidence and incidence rates

During the follow-up period (mean 16.3 months, maximum 72 months), 74 participants (6.2%) developed FM. Among these participants, the mean tender point count was 10.1 ± 4.4 . The frequency of incident FM ranged from 0% to 23.4% across study centers. These frequencies varied depending on the size of the center, with the five smallest centers (each enrolling < 30 patients) all reporting zero cases of incident FM. The cumulative incidence of FM was 5.9% at 12 months and increased to 9.2% at 36 months (Figure 2). The cumulative incidence rate was highest during the first 12 months after inflammatory arthritis diagnosis (6.77 cases per 100 person years) and decreased to 3.58 cases per 100 person years during months 12–24.

Clinical variables associated with the clinical diagnosis of fibromyalgia

In individual, time-varying models adjusted for age, gender and race, ESR, CRP and swollen joint count were not significantly associated with the clinical diagnosis of FM (Table 2). Tender joint count > 20 and pain numeric rating score 4 were associated with the clinical diagnosis of FM. Corticosteroid use, mental component summary score 35 and sleep numeric rating scale score 8 were also associated with the clinical diagnosis of FM. CCP-positivity was inversely associated with the clinical diagnosis of FM.

In the final multivariable model, pain numeric rating score 4 (HR 2.01, 95% CI 1.17–3.46) and mental component summary score 35 (HR 1.99, 95% CI 1.09–3.62) remained significantly associated with the clinical diagnosis of FM. CCP positivity was negatively associated with the clinical diagnosis of FM (HR 0.48, 95% CI 0.26–0.88). Tender joint count, corticosteroid use and sleep problems were no longer significantly associated with the clinical diagnosis of FM (Table 2). Similar results were obtained in a secondary analysis excluding CCP status as a covariate.

Secondary analyses among participants meeting 2010 ACR/EULAR classification criteria for rheumatoid arthritis

In analyses examining the subset of patients who met 2010 ACR/EULAR classification criteria for RA (N = 760), the prevalence of FM was 5.2% at entry into CATCH. The cumulative incidence was 6.6% at 12 months and increased to 9.3% at 36 months. In a multivariable model, pain numeric rating score 4 and corticosteroid use were significantly associated with the clinical diagnosis of FM. CCP positivity was negatively associated with the clinical diagnosis of FM. Although the mental component summary score was no longer significantly associated with the clinical diagnosis of FM, the HR remained the same as the HR derived from the full population.

Fluctuations in fibromyalgia diagnosis

Among the 56 participants with *prevalent* FM who contributed data beyond baseline, 28 (50.0%) had at least one other diagnosis of FM during follow-up. Among the 62 participants with *incident* FM who had follow-up data beyond the initial point of FM diagnosis, 29 (46.8%) had at least one subsequent diagnosis of FM during follow-up.

Forty-eight participants had a diagnosis of FM at baseline but not three months; 17 participants had a diagnosis of FM at three months but not baseline. The difference between patient global and physician global increased among those who gained a diagnosis of FM (patient global > physician global), whereas the difference between patient and physician global decreased among those who lost the diagnosis of FM (mean 19.7 vs. -8.2, $P = 0.01$). Participants who gained the diagnosis of FM had smaller decreases in numeric pain scores compared to those who lost the diagnosis of FM (mean 0.6 vs. 2.6, $P = 0.04$). However, changes in physician global assessment of disease activity and changes in DAS28 were not significantly different between these groups.

DISCUSSION

Secondary FM is a common problem among patients with inflammatory arthritis.[1–4] It is associated with high disease activity and poor functional status.[1] In this study, we examined the development of FM in an early inflammatory arthritis cohort. The incidence rate was highest during the first 12 months after inflammatory arthritis diagnosis. The variables most significantly associated with the clinical diagnosis of FM were pain severity and poor mental health. CCP positivity was inversely associated with the clinical diagnosis

of FM. Inflammatory markers and joint counts were not significantly associated with the clinical diagnosis of FM.

Our study is the first to describe the development of FM in an early inflammatory arthritis cohort. We ascertained that the incidence rate is highest during the first 12 months after diagnosis, consistent with the hypothesis that the development of chronic, central, non-inflammatory pain occurs early. These results are similar to studies of patients with acute back pain,[28, 29] which have reported that the establishment of chronic pain may occur as early as 3–6 months after injury. This period may represent a critical window, during which the transition from acute to chronic pain may be prevented.

The prevention of FM rests upon knowledge regarding potential risk factors. Studies in the general population have reported that sleep problems,[30] depression,[31] and severe pain intensity[32] [33] predict the development of chronic widespread pain syndromes. Only one study, including established RA patients in the National Data Bank for Rheumatic Diseases, has examined the predictors of FM in RA.[34] Similar to our study, this study reported an incidence rate of 5.3 cases per 100 person years. Anti-depressants, patient global assessment, prednisone, functional status, fatigue, widespread pain and symptom count were associated with increased FM risk.[34]

In our study, a pain numeric rating score $\geq 4/10$ was associated with the clinical diagnosis of secondary FM. Moderate to severe pain may induce central nervous system sensitization, leading to the development of FM. Central sensitization has been described in studies of primary fibromyalgia,[35–37] and a few studies of RA have reported widespread decreases in pain thresholds compared to controls.[38, 39] Given that the incidence rate of FM was highest within the first year of inflammatory arthritis diagnosis, our data may reveal an opportunity to identify at-risk patients through routine pain assessments during the first year. A prospective study is needed to determine whether effective early pain treatment may prevent later development of FM.

Objective inflammatory measures, such as ESR, CRP and swollen joint count, were not associated with the clinical diagnosis of FM, suggesting that inflammation does not predict FM diagnosis. These results should be viewed cautiously, however, as our outcome, physician diagnosis of FM, does not provide direct information about the mechanisms underlying this diagnosis. Other factors, including factors affecting physician decision-making, may impact these results.

CCP positivity was the only variable inversely associated with the clinical diagnosis of FM. This association may reflect a protective biologic mechanism or physician decision-making. Physicians may be more likely to treat CCP-positive patients aggressively and achieve disease control earlier. Alternatively, when presented with a CCP-positive patient, physicians may be more likely to attribute pain to inflammatory arthritis than to FM. Future studies, involving surveys and focus groups, are needed to understand decision-making processes when diagnosing FM in patients with systemic inflammatory disease.

Poor mental health was strongly associated with the clinical diagnosis of FM. This association has been reported in previous studies of primary FM and may reflect similarities in the pathophysiologic basis of FM and depression. Some studies suggest that proinflammatory cytokines are linked to both FM and depression.[40] One study reported that induction of sadness leads to lower pain thresholds, indicating that negative affect amplifies pain.[41]

Corticosteroid use was significantly associated with the clinical diagnosis of FM in partially adjusted analyses and in adjusted analyses involving patients meeting 2010 ACR/EULAR

criteria for RA. Corticosteroid use may reflect enhanced disease activity undetected by inflammatory markers due to suppression by treatment. Alternatively, corticosteroid use may reflect the consequences of centralized pain. Pain centralization may lead to increased pain reports and overestimates of disease activity. Studies have reported that the DAS28 is falsely elevated among RA patients with FM.[2, 3, 42, 43] Higher assessments of disease activity may lead to more aggressive corticosteroid treatment, even when it is unwarranted.[44, 45]

Interestingly, the stability of the FM diagnosis was variable. This observation may reflect some cases that were originally misclassified as FM. Alternatively, these data may reflect the natural course of FM. As noted in the National Data Bank for Rheumatic Diseases, the severity of secondary FM symptoms varies over time, causing many RA patients to fluctuate in and out of a discrete diagnosis of FM. This observation was noted even among a population with FM defined according to strict adherence to the ACR 2010 diagnostic criteria for FM, rather than physician diagnosis.[34]

This study has several limitations. The number of patients followed for over 24 months was small. Because outcomes were assessed every three months during the first year but only every six to 12 months thereafter, an ascertainment bias may have occurred, leading to underestimation of FM after the first year. Data required for the ACR 1990 classification criteria and the ACR 2010 diagnostic criteria for FM were not systematically collected for all patients, so the outcome was defined by a rheumatologist's diagnosis of FM. While it would be ideal to estimate inter-observer variability in the diagnosis of FM, each patient was seen by only one provider, and tender point counts were not recorded routinely. In addition, data regarding FM severity were not collected, though changes in severity commonly occur over time.[46, 47]

Although the number of missing data points was low, some FM cases may have been overlooked (and coded as "no") due to under-recognition of FM, particularly at baseline when rheumatologists had limited information regarding disease course and treatment response. Conversely, some participants may have been misdiagnosed as early inflammatory arthritis rather than FM at entry into the study. Future studies examining the consistency of RA diagnosis in this cohort will be informative. Narvaez et al. reported that 72–78% of patients with an initial diagnosis of seronegative inflammatory arthritis had a final diagnosis of RA at one-year, based on magnetic resonance imaging to assess synovitis, bone marrow edema and erosions.[48]

The strengths of this study include its generalisability. Data were obtained from 18 centers across eight provinces in Canada. Rates of FM diagnosis varied across centers, possibly due to instability in estimates at small centers and differences in diagnostic methods. To avoid bias by excluding centers, we used stratified Cox proportional hazards models to account for heterogeneity when obtaining overall risk estimates.

In summary, this study describes the development of secondary FM in an early inflammatory arthritis cohort. The cumulative incidence of FM increased over time, with the greatest increase during the first 12 months after diagnosis. Pain severity was significantly associated with the clinical diagnosis of FM, but inflammation was not significantly associated with the clinical diagnosis of FM. CCP positivity was inversely associated with the clinical diagnosis of FM, whereas poor mental health was positively associated with the clinical diagnosis of FM. Given the limitations in FM assessment, these results should be considered exploratory. Future studies are needed to better understand the mechanisms driving these associations.

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Figure 1.

Flow diagram documenting numbers of participants in this study. The primary cohort, used for incidence rates and predictors of fibromyalgia, included 1198 participants. †359 patients did not have sufficient data to determine rheumatoid arthritis classification based on criteria defined by Aletaha et al.[27]

Figure 2.
Cumulative incidence of fibromyalgia over 36 months.

Table 1

Baseline characteristics of the entire CATCH cohort and the primary analysis cohort, including only participants who did not have a diagnosis of FM at study entry.

Clinical Characteristic	Total Cohort (N = 1487)	Incidence Cohort (N = 1198)
Demographic Variables		
Age, mean $\pm$ SD years	52.7 (15.3)	52.9 (15.2)
Female sex, n (%)	1055 (72.8%)	856 (71.5%)
Non-Caucasian, n (%)	261 (17.6%)	203 (16.9%)
RA-related Variables		
Met 2010 ACR/EULAR criteria for RA, n (%)	982 (90.2%)	760 (92.9%)
Symptom duration, mean $\pm$ SD months	6.4 (6.9)	6.3 (6.6)
CCP positive, n (%)	506 (53.5%)	425 (53.5%)
RF positive, n (%)	674 (56.6%)	571 (54.3%)
Erosive disease, n (%)	289 (25.9%)	259 (27.4%)
68-swollen joint count, mean $\pm$ SD	9.4 (8.0)	9.6 (8.0)
68-tender joint count, mean $\pm$ SD	12.7 (9.9)	12.6 (9.8)
ESR, mean $\pm$ SD mm/hr	26.4 (23.2)	27.1 (23.6)
CRP, mean $\pm$ SD mg/L	13.7 (17.8)	14.1 (18.2)
DAS28-ESR, mean $\pm$ SD	4.9 (1.6)	4.9 (1.6)
Physician global assessment (0–10 cm), mean $\pm$ SD	4.7 (2.5)	4.8 (2.5)
Patient global assessment (0–100 mm), mean $\pm$ SD	56.7 (29.7)	56.5 (29.9)
Pain numeric rating scale (0–10 cm), mean $\pm$ SD	5.5 (2.8)	5.5 (2.8)
Corticosteroid use, n (%)	402 (27.0%)	359 (30.0)
High dose corticosteroid use ($\geq$ 40 mg prednisone, or its equivalent, daily), n (%)	40 (2.7%)	33 (2.8%)
Synthetic DMARD use, n (%)	1042 (70.1%)	964 (80.5)
Biologic DMARD use, n (%)	28 (1.9%)	22 (1.8)
Combination DMARD use, n (%)	460 (30.9%)	426 (35.6%)
Psychosocial variables		
SF-12 mental component score, mean $\pm$ SD	46.1 (11.7)	46.2 (11.6)
Sleep numeric rating scale, mean $\pm$ SD	4.9 (3.3)	4.9 (3.3)

Table 2

Cox proportional hazards models for the association between clinical characteristics and diagnosis of FM.

Clinical Characteristics	Partially Adjusted Models [†]		Final Multivariable Model [‡]	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
RA-related Variables				
Met 2010 ACR/EULAR criteria for RA	1.01	0.35–2.93	-	-
Symptom duration (months) 8.0	0.90	0.53–1.53	-	-
CCP positive	0.43	0.25–0.76	0.48	0.26–0.88
RF positive	0.69	0.40–1.19	-	-
Erosive disease	0.84	0.44–1.60	-	-
68-swollen joint count > 14	1.76	0.85–3.62	-	-
68-tender joint count > 20	2.15	1.11–4.17	-	-
ESR (mm/hr) 40	0.66	0.25–1.71	-	-
CRP (mg/L) > 20.0	0.70	0.27–1.83	-	-
Physician global assessment 7.0	0.95	0.43–2.11	-	-
Patient global assessment > 80	0.66	0.26–1.71	-	-
Pain numeric rating scale 4.0	2.40	1.43–4.03	2.01	1.17–3.46
Corticosteroid use	1.93	1.00–3.73	1.83	0.93–3.63
Synthetic DMARD use	1.62	0.79–3.33	-	-
Biologic DMARD use	1.69	0.80–3.57	-	-
Psychosocial variables				
SF-12 mental component score 35	2.18	1.23–3.88	1.99	1.09–3.62
Sleep numeric rating scale 8.0	2.25	1.26–4.03	-	-

[†]For the partially adjusted models, each row is a separate model, adjusted for age, gender and race.[‡]All variables in this column are included in the same multivariable model.

* High scores on the physician global assessment and the patient global assessment indicate higher disease activity. High numeric rating scale scores indicate more severe pain and worse sleep problems. Low mental component summary scores indicate worse mental health.