Factors Associated with a Longer Time to Access Pediatric Rheumatologists in Canadian Children with Juvenile Idiopathic Arthritis

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ABSTRACT. *Objective.* The Research on Arthritis in Canadian Children Emphasizing Outcomes (ReACCh Out) cohort is a prospective inception cohort of patients with newly diagnosed juvenile idiopathic arthritis (JIA) seen in 16 Canadian pediatric rheumatology (PR) centers. We used data from this cohort to explore factors associated with longer time from symptom onset to the first visit to PR, and with longer time from first visit to a diagnosis of JIA.

Methods. We included children enrolled in ReACCh Out within 6 months of JIA diagnosis, for whom the dates of symptom onset and first PR visit were recorded. We used Cox proportional hazard modeling to investigate the effects of history, physical examination, and laboratory evaluation on the interval from JIA symptom onset to first PR assessment.

Results. In total, 319 children from the cohort were included. Having a fever (hazard ratio 1.80, 95% CI 1.10, 2.93), any part South Asian ethnicity (HR 1.75, 95% CI 1.04, 2.95), highly educated parents (HR 1.69, 95% CI 1.18, 2.44), and limp (HR 1.55, 95% 1.16, 2.06) were significantly associated with shorter time from symptom onset to first PR assessment, while a history of heel pain or enthesitis (HR 0.61, 95% 0.38, 0.97) was significantly associated with a longer time to first PR visit.

Conclusion. Children with a history of a fever, limp, any part South Asian ethnicity, or highly educated parents were more likely to see PR sooner than patients without these features, while children with a history of enthesitis received PR care later than those without enthesitis. (First Release August 15 2010; J Rheumatol 2010;37:2415–21; doi:10.3899/jrheum.100083)

Key Indexing Terms:
PEDIATRIC RHEUMATOLOGY   JUVENILE IDIOPATHIC ARTHRITIS
ACCESS TO CARE   HEALTH SERVICES DELIVERY

Chronic childhood inflammatory arthritis is a common pediatric rheumatic disease that affects from 16 to 150 per

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Accepted for publication June 16, 2010.

100,000 children less than 16 years of age[1], yet children who develop this condition often are not recognized by primary and community healthcare providers, and frequently take a long time to be seen by a pediatric rheumatologist. Recent studies have shown median time from arthritis symptom onset to first pediatric rheumatology (PR) assessment was 13 weeks in Tübingen, Germany[2], 20 weeks in the United Kingdom (UK)[3], 24.4 weeks in British Columbia, Canada[4], and a mean of 39.9 weeks in Australia[5]. Although definitive guidelines for referral times do not exist in Canada, the Alliance for the Canadian Arthritis Program (an alliance of arthritis patients, caregivers, volunteer associations, healthcare providers, researchers, government, and industry) recommends that new patients with inflammatory arthritis should be identified and treated within 4 weeks of seeing a healthcare professional[6]. In the UK, guidelines recommend all patients with suspected inflammatory arthritis should be seen by a rheumatologist within 6 weeks of referral from a general practitioner[7]. Factors associated with a longer time to assessment by a pediatric rheumatologist have been described in the UK[8], and comparable data are emerging for children in Canada[9].

The International League of Associations for Rheumatology (ILAR) classification system for juvenile idiopathic arthritis (JIA) is the most recent classification

system for chronic childhood inflammatory arthritis[10]. We investigated factors associated with a longer time from arthritis symptom onset to first visit to a pediatric rheumatologist in children diagnosed with JIA, as well as those associated with longer time from first PR visit to diagnosis of JIA. We used data from a national prospective cohort of Canadian children with newly diagnosed JIA, the Research on Arthritis in Canadian Children Emphasizing Outcomes cohort (ReACCh Out). The process leading to a diagnosis and enrolment into the study cohort was divided into 2 models: the first used information available prior to the first PR assessment to examine factors associated with a longer time to the initial PR visit, and the second used information available at this initial assessment to examine factors associated with a longer time from first PR visit to a definitive diagnosis of JIA. We included only variables that we felt could conceptually influence the time intervals being examined in each particular model, as these variables could potentially be the focus of efforts to reduce the time from arthritis symptom onset to the first PR visit.

MATERIALS AND METHODS

Study population. The ReACCh Out cohort is a multicenter inception cohort of newly diagnosed children with JIA being followed by pediatric rheumatologists in 16 Canadian centers. Data collection for this cohort is described in detail elsewhere[11]. Briefly, the cohort includes patients diagnosed with JIA according to ILAR criteria[10] within 12 months prior to enrolment[11]. Standardized data collection occurs at enrolment, every 6 months for 2 years, and then yearly. Information collected includes demographics, family and patient histories, medication histories, as well as laboratory data available at enrolment and followup. Additionally, the juvenile rheumatoid arthritis (JRA) core set measures[12], the Juvenile Arthritis Quality of Life Questionnaire[13], and the Quality of My Life Questionnaire[14] are completed at study visits. This study included only those subjects enrolled into ReACCh Out within 6 months of JIA diagnosis between January 1, 2005, and June 30, 2007. Additional criteria for inclusion into this study were: (1) the month and year of symptom onset and (2) the date of the first PR assessment. JIA subtype diagnoses were checked against criteria data submitted by site investigators for each patient as described[11].

Statistical modeling. We used multivariable regression with Cox proportional hazard modeling to model the primary and secondary outcomes of interest: days from symptom onset to first PR assessment (model 1, primary outcome), and days from first PR assessment to definitive diagnosis of JIA (model 2, secondary outcome). As only the month and year of symptom onset were collected, the 15th day of the month was imputed as the day of symptom onset. We chose the 15th of the month and not the 1st of the month in order to avoid artificially increasing subsequent time intervals, which would increase potential bias. If the imputation resulted in a negative number of days from symptom onset to first PR assessment, then the first day of the month was imputed as the day of symptom onset.

All variables that had a conceptual rationale for inclusion were forced into the regression model. Rationale and categorization of these variables are listed in Table 1. Independent variables included in model 1 were clinical history (joint pain, joint swelling, limp, morning stiffness, enthesitis, fever, and systemic rash), family history of inflammatory arthritis, demographic information (age, sex, ethnicity), socioeconomic information (highest level of parental education), and distance to the PR center (based on the first 3 digits of the postal code). Independent variables in model 2 included clinical history (enthesitis, fever, systemic rash, psoriasis), physi-

cal examination findings at baseline (enthesitis, psoriasis, systemic rash, number of active joints), and laboratory features at enrolment [HLA-B27 status and rheumatoid factor (RF) status], as well as family history (psoriasis, inflammatory bowel disease, ankylosing spondylitis, and uveitis). Antinuclear antigen was not included as it does not influence the clinical diagnosis of arthritis, nor subtype classification.

We used the hazards ratios (HR) as measures of strength of association between dependent and independent variables. HR were considered statistically significant if p values were less than 0.05. The suitability of the assumption of proportional hazards was verified using the Schoenfield test. Although each participating province was initially part of model 1, no HR for the provinces were significant, and province was excluded from the final model to maintain an adequate number of events per variable.

Statistical analyses were performed using Stata version 10.1 (Stata Corp., College Station, TX, USA).

RESULTS

A total of 437 patients were enrolled during the period of time covered by this report, and 356 met the criterion for enrolment within 6 months after diagnosis. Of the latter a further 35 patients were excluded because of missing dates of symptom onset or first PR visit. Patients excluded were similar to included patients in age at symptom onset, sex and subtype distributions, interval from symptom onset to diagnosis, and distance from PR center (data not shown). Thus a total of 319 patients were included in this study, and patient characteristics are listed in Table 2. The JIA subtype distribution was as follows: 41.1% oligoarticular JIA, 21.3% RF-negative polyarticular JIA, 3.4% RF-positive polyarticular JIA, 6.3% psoriatic arthritis, 10.0% enthesitis related arthritis, 7.5% systemic arthritis, and 10.3% undifferentiated JIA.

The distribution of the time from symptom onset to the first PR assessment is shown in Figure 1. Overall, the median time from symptom onset to first PR visit was 115 days [interquartile range (IQR) 45, 219]. There were 52 patients for whom time from symptom onset to first PR visit was > 365 days (1 year). The median time from first PR visit to diagnosis of JIA was 0 days (IQR 0, 20), indicating that JIA was frequently diagnosed on the day of the first rheumatology assessment (Table 3). The median distance travelled to a PR center was 38.2 km (IQR 17.9, 117.3). Although the majority (59.2%) of patients lived within 50 km, 130 (40.8%) lived > 50 km, 68 (21.3%) > 150 km, and 49 (15.4%) > 300 km from a PR center.

HR of 1 indicates equal likelihood of first PR visit in the presence of the variable in question compared to its absence, while HR > 1 indicates increased likelihood, and < 1 indicates a reduced likelihood. Cox proportional hazard modeling of time from symptom onset to first PR visit in the 272 patients with complete data for all variables showed significant HR > 1 for a history of fever (1.80, 95% CI 1.10, 2.93), any part South Asian ethnicity (HR 1.75, 95% CI 1.04, 2.95), highest parental education at a university or postgraduate level (HR 1.69, 95% CI 1.18, 2.44), and history of a limp (HR 1.55, 95% CI 1.16, 2.06); while the HR was < 1 for a history of heel pain or enthesitis (HR 0.61, 95% CI 0.38, 0.97), as shown in Table 4. The likelihood ratio test for

Table 1. Definitions and rationale for study variables. Family history of psoriasis, inflammatory bowel disease, ankylosing spondylitis, and uveitis were also included.

Variable	Definition in Model	Rationale
Distance from PR center	First 3 digits of the postal code used to map approximate distance (≤ 50 km, 51 to 150 km, > 150 km; reference: ≤ 50 km)	Longer distance could make transportation difficult and reduce access to care, increasing time to first PR visit
Features on history and physical examination (except joint count)	Present or absent	Pain, gait abnormalities, and systemic features likely to be associated with shorter time to seeking subspecialty care
Ethnicity	A subset of self-identified ethnicities, grouped and entered as dichotomous variables (present/absent). Categories neither mutually exclusive nor exhaustive; based on those from Statistics Canada as per the ReACCh Out protocol: (i) First Nations; (ii) Chinese, Korean, or Japanese; (iii) South Asian; (iv) European	Culture-specific healthcare beliefs could affect how and when the families access healthcare. A small subset of ethnicities was chosen in order to maintain an appropriate number of events per variable
Age	Continuous variable; log-transformed due to non-normal distribution	Older age has been reported to be associated with a longer interval to PR visit
Highest level of parental education	Categorized as secondary or less, some postsecondary, and university/postgraduate degree; > 12 years considered some postsecondary education; ≥ 16 yrs considered obtained a university degree; secondary or less was the reference category	Higher parental education could be associated with increased parental awareness of resources and ability to advocate for their child
Family history of inflammatory arthritis	Single dichotomous variable (yes or no); included any family history of rheumatoid arthritis, JIA, psoriatic arthritis, or ankylosing spondylitis	May be associated with increased awareness of arthritis and earlier assessment
No. of active joints	Continuous variable; log-transformed due to non-normal distribution	MD assessment of disease severity

PR: pediatric rheumatology. JIA: juvenile idiopathic arthritis.

this model was 53.37, p < 0.0001, 18 df, with 15 events per variable.

The second Cox proportional hazard model examined the time from first PR assessment to a final diagnosis of JIA. Only patients whose diagnoses were not made at the first PR assessment were included in this model. Rheumatoid factor and HLA-B27 status were excluded from the model because these tests were not available for each patient. None of the HR in the reduced model were significant, although there was a trend toward a shorter time from first PR visit to a diagnosis of JIA with a family history of inflammatory bowel disease (HR 0.62, CI 0.38, 1.03; p = 0.064).

DISCUSSION
Children with JIA take a long time to see a pediatric rheumatologist in a variety of healthcare systems, with median or mean times from symptom onset varying from 13 to 40 weeks[2,3,4,5,8]. Identifying risk factors associated with a longer time to first PR visit will help focus efforts to minimize this time interval for children with JIA. The median interval of 115 days in our study (16.5 weeks) is within the variation previously reported[2,3,4,5,8]. The time from symptom onset to the first assessment by a pediatric rheumatologist can be divided into several components: the interval from symptom onset to presentation to a primary healthcare provider; time from first visit to a primary healthcare provider to referral to a pediatric rheumatologist; and time between referral and first assessment by a pediatric rheumatologist. In our study the variables assessed were primarily historical and could be related to both initial phases. For

example, systemic symptoms, pain, functional limitations, cultural, and socioeconomic status are variables that may affect both a patient's presentation to a primary healthcare provider and the time to referral. In our model we used ethnicity as a proxy for cultural influences and parental education as proxy for socioeconomic status.

The observation that heel pain increased time to first rheumatology assessment suggests that heel pain may be underrecognized both by families and by primary healthcare providers as a possible manifestation of enthesitis related arthritis. Other diagnoses such as Sever's syndrome or Osgood Schlatter disease have findings that are often indistinguishable from enthesitis due to enthesitis related arthritis, especially in the absence of arthritis. This similarity may be a cause for the delay.

Our analysis showed patients with some South Asian ethnicity were seen sooner by a pediatric rheumatologist. This was true when holding factors such as education (our proxy for socioeconomic status) and distance from PR center constant. There are several possible explanations for this trend. First, as hypothesized (Table 1), it is possible that families with South Asian ethnicity have cultural expectations that lead them to seek earlier care. Second, it is possible that children with South Asian ethnicity have an overrepresentation of more severe types of arthritis, as differences in relative frequencies of subtypes have been reported[15]. We did not perform a statistical comparison of subtypes of JIA diagnosed in this ethnic group compared to the rest of the study population due to the small number of patients with some South Asian ethnicity (n = 21). We did not have data about

Table 2. Characteristics of the 319 ReACCh Out patients included in this study.

Characteristic*	Number (%) or Median (IQR)
Demographics	
Female	207 (64.9)
Median age at onset (IQR), yrs	8.0 (2.9, 12.0)
Ethnicity, n = 313[†]	
Aboriginal	22 (7.0)
Chinese, Korean, or Japanese	21 (6.7)
South Asian	21 (6.7)
European	211 (67.4)
Distance to pediatric rheumatology center	
< 50 km	189 (59.2)
50.1–150 km	62 (19.4)
150.1–300 km	19 (6.0)
> 300 km	49 (15.4)
Maximum level of parental education (n = 304)	
Elementary or secondary school	58 (19.1)
Some postsecondary training	99 (32.6)
University degree or postgraduate training	147 (48.4)
History	
Joint pain, n = 318	296 (93.1)
Swelling	272 (85.3)
Limp, n = 315	199 (63.2)
Heel pain or enthesitis (n = 314)	31 (9.9)
Morning stiffness (n = 316)	225 (71.2)
Fever, n = 317	45 (14.2)
Systemic JIA rash	26 (8.2)
Family history	
Inflammatory arthritis, n = 299	98 (32.3)
Inflammatory bowel disease, n = 311	30 (9.7)
Ankylosing spondylitis, n = 304	13 (4.3)
Uveitis, n = 299	4 (1.3)
Physical examination at enrolment	
Systemic JIA rash, n = 318	12 (3.8)
Enthesitis, n = 261	22 (8.4)
Psoriasis, n = 317	16 (5.1)
Median number of active joints[††]	2 (1.6)
JIA subtype at enrolment	
Oligoarticular	131 (41.1)
Polyarticular rheumatoid factor+	11 (3.4)
Polyarticular rheumatoid factor–	68 (21.3)
Psoriatic	20 (6.3)
Enthesitis related arthritis	32 (10.0)
Systemic	24 (7.5)
Undifferentiated	33 (10.3)
Laboratory data	
Rheumatoid factor-positive at enrolment, n = 276	19 (6.9)
HLA-B27-positive, n = 139	35 (25.2)

* Where data were unavailable for all study patients, n represents total number of patients for whom that characteristic was recorded, and percentage value corresponds to percentage of n. [†] Ethnicities were not mutually exclusive, and only a subset of ethnicities was included in the model; percentage values for this characteristic will not total 100%. [††] range: 0 to 63. IQR: interquartile range. JIA: juvenile idiopathic arthritis.

the number of joints affected prior to the initial PR visit, and we cannot exclude an association between ethnicity and the number of joints involved between symptom onset and initial PR assessment[15]. Third, it is also possible that patients
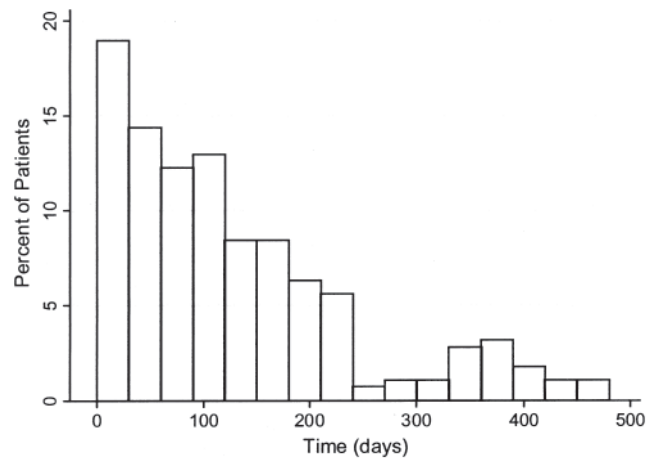

Figure 1. Distribution of time from symptom onset to first pediatric rheumatology (PR) visit for all patients seen in the first 500 days after symptom onset. The median for this interval was 115 days. There were 52 patients for whom time from symnptom onset to first (PR) assessment was > 365 days (1 year).

Table 3. Duration of time intervals from symptom onset to study enrolment.

| | Time (days) | |
	Median	IQR
Symptom onset to first PR visit	115	45, 219
First PR visit to diagnosis of JIA*	0	0, 20
Symptom onset to study enrolment	167	97, 296

* Zero days indicates that diagnosis of JIA was made on the same day as the first PR visit. IQR: interquartile range; PR: pediatric rheumatology; JIA: juvenile idiopathic arthritis.

with South Asian ethnicity tend to reside in urban or suburban areas, thus facilitating access to subspecialty care. Although our model included distance to the PR center as a proxy for access, it was not able to distinguish reliably between urban and rural areas. The effect of ethnicity on accessing healthcare for children with arthritis requires further study, especially in a culturally diverse country such as Canada. The observation that highest parental education at a university level also decreased the delay is in keeping with reports of earlier referral of children with higher socioeconomic status[9] and adults with higher education[16] to rheumatologists.

Other independent variables that may affect the length of time to referral to PR originate from the primary healthcare provider's assessment, the provider's knowledge about the condition being considered, and accessibility of specialist services. Direct information about primary healthcare provider knowledge was not collected in this study; but studies have suggested that the source of referral may affect referral time[3,8]. In our study, distance to PR center had no effect on time to first PR assessment, but due to our sample size a moderate effect of distance cannot be definitively

Table 4. Hazard ratios (HR) for the model of time from symptom onset to first pediatric rheumatology assessment. All variables in the model and corresponding hazard ratios are listed. Likelihood ratio test for the model was 53.37, p < 0.0001, 18 df, with 15 events per variable.

Feature	HR	95 % CI	p
History of heel pain or enthesitis	0.61	0.38, 0.97	0.035
History of fever	1.80	1.10, 2.93	0.019
South Asian ethnicity	1.75	1.04, 2.95	0.036
Parental university degree or postgraduate education	1.69	1.18, 2.44	0.005
History of limp	1.55	1.16, 2.06	0.003
Distance to rheumatology center 51–150 km	1.03	0.74, 1.44	0.87
Distance to rheumatology center > 150 km	0.82	0.47, 1.41	0.47
History of joint pain	0.76	0.46, 1.27	0.29
History of joint swelling	1.07	0.73, 1.56	0.74
History of morning stiffness	0.98	0.73, 1.33	0.90
History of systemic JIA rash	1.72	0.94, 3.12	0.077
Highest parental education, some postsecondary studies	1.27	0.86, 1.88	0.23
First Nations ethnicity	0.87	0.52, 1.45	0.59
Chinese, Korean, or Japanese ethnicity	1.30	0.74, 2.27	0.36
European ethnicity	1.00	0.74, 1.36	0.99
Family history of arthritis	1.23	0.93, 1.64	0.16
Sex	1.04	0.78, 1.39	0.79
Age (log-transformed)	1.09	0.92, 1.28	0.33

JIA: juvenile idiopathic arthritis.

excluded (hazard ratio 0.82, 95% CI 0.47 to 1.41 for distances more than 150 km). This contrasts with the experience of one center in Germany, where greater distance to the regional PR center increased delay to referral[2]. In another study, local availability of rheumatologists in Ontario was also an important factor associated with utilization of specialist services for musculoskeletal complaints in adults[17]. Our findings are remarkable since a considerable proportion of patients, 21.3%, lived more than 150 km from a PR center, and the median distance to a PR center was 38.2 km (IQR 17.9, 117.3), which is similar to the median of 38.8 km in the German study[2]. Although some of our patients are followed in outreach clinics in British Columbia and Saskatchewan, none of the patients in this study were seen for their initial assessment in traveling clinics. This observation suggests that accessibility to the network of PR clinics in Canada is not impeded by travel for patients who are referred to subspecialty care. However, patients who are not referred to a pediatric rheumatologist could not be included in this study, and therefore a possible bias cannot be excluded.

The final interval prior to PR assessment is the time from referral to the first visit with a pediatric rheumatologist. The duration of this interval may be affected by the information received during the triage process and subspecialist availability; but this information was not identified in our study.

Our analysis differs from that reported by the Childhood Arthritis Prospective Study (CAPS), a multicenter cohort of children with new onset inflammatory arthritis in the UK[8]. In the CAPS study, disease activity and demographic characteristics at enrolment were assessed, but only erythrocyte sedimentation rate (ESR) had a significant effect on duration of symptoms prior to the first PR assessment in their regression model of the entire cohort, and both lower ESR and older age at symptom onset had significant effects when analysis was limited to children with oligoarticular JIA[8]. Our first model focused specifically on features available prior to the first PR assessment as these were variables that may have initiated a referral and were available for analysis.

Our second model, in which we included historical features and physical examination findings at enrolment to model factors associated with a longer time from PR assessment to a definitive diagnosis of JIA, failed to show any significant hazard ratios. A high number of patients received their JIA diagnosis at the first PR visit and were therefore excluded from the model. We did not have enough patients with HLA-B27 and RF status in the remaining patients to include these in our model as these tests were not part of our study protocol, but rather were performed selectively to assign JIA subtype diagnoses. Consequently they were not available for the entire study population.

Our distribution of JIA subtypes is similar to that in studies that used the ILAR classification criteria for JIA, although our proportion of patients diagnosed with oligoarticular JIA is closer to the lower end of the reported range of 46%–51%[3,8]. Although unlikely, we cannot exclude the possibility of a referral bias affecting the proportion of our study patients with oligoarticular JIA. Since only 67% of our patient population were of European background, it is also possible that the multiethnic distribution of our patients affected the proportions of ILAR subtypes[15].

We used data collected for an inception cohort of patients with JIA that focuses on outcomes and was not originally

designed to track referral processes. Accordingly, some data that might have permitted an examination of causes for delayed referral were not collected. For example, date of referral and data relating to the primary healthcare provider's assessment and investigations were not identified in our study. Our study included only patients ultimately seen at a PR center. Although Canada has a universal healthcare system and PR centers are available in all provinces, we cannot rule out that selection bias may be present in our results. We did not collect data about the number and types of healthcare providers seen prior to the initial PR visit, and therefore cannot comment on the pathways to care followed by these patients. Despite these shortcomings our study identified previously unreported variables that affected time from symptom onset to first PR assessment. These included history of limping and high parental education, which decreased time to assessment, and a history of heel pain, which lengthened this time interval.

Children with JIA are at risk for complications such as uveitis, erosions, growth abnormalities, and flexion contractures[18]. Although acceptable length of time of symptom duration prior to first PR assessment has not been universally established, the longterm effects of untreated disease can be devastating, and current standard practice includes early treatment of JIA[18]. Our preliminary analyses suggest that patients with longer delay to inital PR assessment have greater disability and poorer quality of life during their early disease course[19]. Further followup of this cohort will be critical to answer questions about the longterm effects of longer time to the first PR assessment.

In summary, in our study of patients from the ReACCh Out cohort, patients with traditional features associated with inflammatory arthritis, such as a limp and fever, were seen by a pediatric rheumatologist sooner than patients without these symptoms. The children of parents with a university degree or postgraduate training were also more likely to be seen sooner, suggesting that these parents may be either more aware of abnormalities or better able to navigate the healthcare system and advocate for their children. It is less clear why patients with South Asian ethnicity had shorter times from onset of symptoms to first PR assessment. Patients with enthesitis, on the other hand, were seen later than those without enthesitis. Future advocacy and education efforts that include promoting awareness of the presenting symptoms and signs of JIA will hopefully improve access to PR care for these patients. Our results suggest the possibility that such advocacy and awareness of JIA may be more important than physical barriers to accessibility, such as distance to a PR center, at least in Canada. Prospective cohort studies such as ReACCh Out and CAPS will continue to provide important data about the short- and longterm influence of delays in diagnosis on eventual outcomes.

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