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Pediatric psoriatic arthritis: a population-based cohort study of risk factors for onset and subsequent risk of inflammatory comorbidities

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Abstract

Background: Relatively little is known about the epidemiology of juvenile psoriatic arthritis (PsA), including clinical features associated with the development of arthritis among children with psoriasis and subsequent risk of inflammatory comorbidities.

Objective: To identify the overall risk of arthritis among children with psoriasis and subsequent risk of inflammatory comorbidities.

Methods: Using Clinformatics™ DataMart (OptumInsight, Eden Prairie, MN) de-identified US administrative claims data from 2000–2013, we identified children 0–16 years with an incident diagnosis of psoriasis or PsA using ICD-9-CM diagnostic, procedure and pharmacy billing codes. Cox proportional hazard regression was performed to assess clinical features associated with development of arthritis in children with psoriasis. Incidence rate ratios were used to compare the relative frequency of co-morbid diagnoses.

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Results: We identified 212 children with PsA, 4,312 with psoriasis-only, and 45,240 controls. Approximately 33% of children with PsA received a diagnostic code for psoriasis before arthritis. Median time to index code for arthritis after index code for psoriasis was 17.6 months (IQR 4.1–38.1). Older age and uveitis were associated with a significantly increased risk of developing arthritis in children with psoriasis. Children with PsA had a significantly increased risk of uveitis, diabetes, and depressive disorder when compared to patients with psoriasis and inflammatory bowel disease, uveitis, diabetes, and depressive disorder when compared to controls.

Conclusion: Most children with PsA developed arthritis first. Older age and uveitis were risk factors for arthritis among children with psoriasis. PsA was associated with increased risk of several clinically relevant inflammatory comorbidities.

Keywords

Psoriatic Arthritis; Psoriasis; Pediatric; Comorbidity; Diagnosis

Introduction

Psoriatic arthritis (PsA) is one of seven categories of juvenile idiopathic arthritis (JIA) as defined by the International League of Associations for Rheumatology (ILAR). Juvenile PsA is clinically diverse in its presentation and is diagnosed according to the ILAR criteria when a child presents with arthritis and psoriasis or with arthritis plus at least two of the following: family history of psoriasis in a first-degree relative, dactylitis, or nail pitting. Studies have found that psoriasis, a major criterion for diagnosing PsA, affects 0–1.4% of children globally^{1,2}, but relatively little is known about the epidemiology of pediatric PsA, including risk factors for development of PsA among children with psoriasis. In one population-based study of 440 children with JIA, the presence of psoriasis or a psoriasis-like rash with at least two of the following variables significantly decreased the odds of attaining remission after eight years: dactylitis, nail pitting, enthesitis, first-degree relative with psoriasis or PsA³. Additionally, in comparison to other categories of JIA, with the exception of systemic JIA, children with PsA have a greater risk of disease flare after attaining inactive disease and stopping treatment⁴. There remains a critical need to better characterize the disease course and treatment of children with PsA, including description of the overall risk of arthritis in children with psoriasis and the time period during which psoriasis patients are most at risk of developing arthritis.

Not all children or adults with psoriasis develop PsA. In adults, severity of psoriasis, smoking, obesity, hypercholesterolemia, trauma, uveitis, and depression have been identified as clinical risk factors in the development of PsA^{2,5–10}. These triggers may stimulate an inflammatory cascade, ultimately leading to arthritis, enthesitis, and dactylitis. Studies have not yet examined risk factors for development of arthritis in children with psoriasis.

After diagnosis of PsA, there is also increased risk of cardiometabolic comorbidities in comparison to the general population without PsA. In a population-based study, adults with PsA had increased incidence rates of Crohn's disease, uveitis, osteoporosis and fibromyalgia compared to patients with psoriasis without arthritis¹¹. In another UK population based cohort study, patients with PsA had increased risk of uveitis and Crohn's disease when

compared to the general population and psoriasis controls¹². Incidence of these clinically relevant comorbidities have not been evaluated in the pediatric PsA population. In this population-based pediatric study, we aimed to identify the overall risk of arthritis and clinical features associated with the development of arthritis among children with psoriasis and subsequent risk of inflammatory comorbidities.

Methods

Study Design

Retrospective population-based cohort study.

Data Source

Clinformatics™ Data Mart (OptumInsight, Eden Prairie, MN) is an administrative de-identified claims database derived from a large national commercial health insurance and Medicare Advantage (C and D) database. It contains de-identified data on approximately 64 million unique patients, representing approximately twenty percent of United States residents. Available data include demographics, prescription drug claims, medical diagnoses specified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes, procedure codes, and provider specialty.

Participants

The source population for this study was children diagnosed with psoriasis (PsO) or psoriatic arthritis (PsA) between 1 May 2000 and 30 Jun 2013 (N=26,710) who were 0–16 years old at time of diagnosis. To ensure that the cohort represented children with an incident code of psoriasis or PsA, any subjects with a code for psoriasis or arthritis within the first 12 months of enrollment in the database were excluded. For the analysis, children with incident psoriasis were defined as children with at least two ICD-9-CM codes indicating psoriasis separated by a minimum of 7 days but no more than 183 days during the enrollment period. The first code for psoriasis was considered the index date for psoriasis. Children with PsA were identified by 1 of four algorithms: 1) at least two ICD-9-CM codes indicating PsA (696.0) separated by a minimum of 7 days but no more than 183 days^{13,14}; 2) at least one code indicating PsA (696.0) plus at least one of the following: (a) pharmacy claim for a systemic medication used to treat juvenile arthritis (csDMARDs: methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, mycophenolate, cyclosporine, azathioprine; bDMARDs: infliximab, adalimumab etanercept, abatacept, tocilizumab, certolizumab pegol, ustekinumab, rituximab, golimumab, tofacitinib; NSAIDs: diclofenac, naproxen, ibuprofen, piroxicam, celecoxib, ketorolac, nabumetone, indomethacin, meloxicam, sulindac, ketoprofen, etodolac, flurbiprofen, oxaprozin, mefenamic acid, tolmetin, salsalate, diflunisal); (b) medication code for intraarticular glucocorticoid (triamcinolone, hydrocortisone, methylprednisolone, dexamethasone, and betamethasone); or (c) procedure code indicating intraarticular injection (Current Procedural Terminology (CPT) codes 20600, 20605, 20610); 3) 2 codes indicating psoriasis *plus* 2 codes indicating juvenile arthritis (codes 714.0, 714.1, 714.2, 714.30–714.33, 716.50, 719.00–719.09, 720.00–720.02, 720.8, 720.9); 4) 2 codes indicating psoriasis *plus* 1 code indicating arthritis and at least one of the qualifying criterion from algorithms 2. Approximately 50 records of those

excluded were manually reviewed to search for possible errors or missed codes to confirm the diagnosis and none were identified. Children from the source population without PsA or psoriasis were matched on age and sex at a 10:1 ratio to patients with psoriasis and PsA. The index date was identified as the date of first ICD-9-CM code for arthritis for PsA patients, first ICD-9-CM code for psoriasis for the psoriasis only group, and match date for controls. Only enrollment periods with continuous coverage were used for outcome diagnoses (arthritis and psoriasis). Additional periods of enrollment were included if the gap in coverage did not exceed 90 days. These expanded enrollments were used to capture comorbid conditions (inflammatory bowel disease (IBD), uveitis, diabetes, hypertension, hyperlipidemia and depressive disorder) not expected to be impacted by a gap in coverage.

Statistical Analysis

Clinical and demographic characteristics were summarized by mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables and count and percentage for categorical variables. Univariate cox proportional hazard regression analysis was performed to identify risk factors for development of arthritis in children with psoriasis. Variables with a p-value <0.20 in univariate analysis were considered in multiple regression analysis. Incidence rate ratios (IRR) were computed to evaluate the relative frequency of comorbid diagnoses of inflammatory bowel disease (IBD), uveitis, diabetes, hypertension, hyperlipidemia and depressive disorder in children with psoriasis with and without arthritis and in controls.

Human Protections

The protocol for this study was reviewed and approved by the Children's Hospital of Philadelphia Committee for the Protection of Human Subjects (IRB 14–011409). Waivers of consent and assent were granted for this retrospective study of de-identified data.

Results

During the study period, 25,346 children had at least one code for psoriasis. One thousand three hundred twenty-seven children had at least one code for PsA or psoriasis plus at least one code indicating juvenile arthritis. Restricting the cohort to patients with incident diagnoses (clean period of 365 days) reduced the eligible study population to 14,612 psoriasis patients and 714 PsA patients. Of this source population, only 4,312 children met inclusion criteria for the psoriasis cohort and 212 met inclusion criteria for PsA. The median time for continuous enrollment in the database was 63.9 months (IQR: 41.5–93.3). Patients who had a single code for PsA or arthritis but did not meet the more stringent inclusion criteria for PsA (n=400) were most commonly seen by providers in the following specialties: dermatology (n=136; 34.0%), orthopedics (n=85; 21.3%), family practice/pediatrics (n=84; 21.0%), rheumatology (n=39; 9.8%), general acute-care hospital (n=14; 3.5%), emergency care/emergency medicine (n=12; 3.0%), and ophthalmology (n=10; 2.5%). The remainder of the cases came from providers in specialties not included in the above categories (n=20; 5.0%).

The overall prevalence of arthritis in children with psoriasis was approximately 2%. Of the 212 children with PsA, 44% never had a documented code indicating psoriasis. Of the 93 children with diagnosis codes meeting our inclusion criteria for both psoriasis and arthritis, the index date for arthritis preceded the index date for psoriasis in 22 (23.7%) children. For the 70 (33.0%) patients who developed psoriasis first, the median time to development of arthritis was 17.6 months (IQR: 4.1–38.1). The median time to development of psoriasis in patients who had arthritis first was 5.4 months (IQR: 1.4–13.5). Demographics of children with psoriasis and PsA are presented in Table 1.

Clinical Features Associated With Development of Arthritis in Children With PsO

Results of univariate and multiple regression modeling of clinical features associated with development of arthritis in children with psoriasis are presented in Table 2.

Disease-Related Comorbidities

The incidence of disease-related comorbidities is presented in Table 3.

Discussion

This is the first study to examine risk factors for development of arthritis in children with psoriasis and subsequent risk of comorbid diagnoses in a population-based cohort. We found that 44% of children with PsA had at least 1 code for psoriasis and only 2% of children with psoriasis received a code for arthritis within the follow-up period (5.25 years on average). The demographics of this cohort, other than a slightly older age of diagnosis, are consistent with prior reports^{15,16}. Uveitis and older age at the time of first psoriasis code were associated with a significantly increased risk of developing arthritis in children with psoriasis. Children with PsA had a significantly increased risk of clinically important comorbidities, including inflammatory bowel disease, uveitis, diabetes, and depressive disorder, when compared to controls. PsA patients also had a greater risk of developing uveitis, diabetes, and depressive disorder when compared to children with psoriasis without arthritis. We also found psoriasis patients without arthritis had a higher risk of hyperlipidemia than controls which is in line with the results from Tollefson et al¹⁷. However, we were unable to find statistically significant increased risk of diabetes or hypertension children with psoriasis compared to controls, likely due to the differences in inclusion criteria and sample sizes between the studies.

In this study, we found that children with psoriasis or PsA had a significantly increased risk of developing inflammatory bowel disease. Limited data exists on the connection between IBD and psoriasis or PsA in children. Most literature to date focuses on the the development of psoriasis secondary to treatment with anti-tumor necrosis factor alpha agents^{18–20}. We demonstrated that the risk of IBD was higher in children with PsA than in patients with psoriasis and no arthritis. This finding is concordant with recent work from the Netherlands that demonstrated that risk of IBD was higher in adults with PsA than adults with psoriasis and no arthritis²¹. Genome-wide association studies have shown shared susceptibility loci in patients with psoriasis and IBD²², so these associations are not surprising. This, however, is the first study to demonstrate these associations in pediatric-onset disease. These findings

have important implications for clinical care. While many pediatric rheumatologists maintain a high index of suspicion for concomitant IBD in children with enthesitis related arthritis, the same is not necessarily the case for children with PsA.

We aimed to identify a robust cohort of patients with psoriasis and PsA. As such, documentation of a single ICD-9-CM code for psoriasis or PsA was not considered sufficient for inclusion in the analytic cohort; the requirement for at least 2 diagnostic codes is consistent with prior well-performing validated algorithms in other administrative^{23,24} and integrated health care databases²⁵. Applying these algorithms to our cohort, we felt that excluding patients who technically did not meet ILAR criteria for PsA due to the exclusionary criteria (i.e. acute anterior uveitis, inflammatory bowel disease) was not necessary because we feel our algorithms capture cases that represent the clinical nature and pathogenesis of PsA. Restricting to patients with at least two diagnostic codes for psoriatic arthritis or one diagnostic code plus a medication used to treat psoriatic arthritis ensured physicians were diagnosing and treating their patients as if they had PsA. Other patients had at least two codes for arthritis and psoriasis, the major criteria for diagnosis of PsA. One study comparing the Vancouver criteria²⁶ to the ILAR criteria found that within a cohort of 139 patients meeting the Vancouver criteria for PsA, statistical analysis found almost no clinical differences between the group who met ILAR criteria versus those who did not²⁷. The majority of patients who were excluded under ILAR (76%) were reclassified as another subtype of JIA but were phenotypically similar to the patients included under ILAR criteria for PsA²⁷. The adult classification system for psoriatic arthritis, Classification criteria for Psoriatic Arthritis (CASPAR)²⁸, does not employ any exclusionary criteria. Applying CASPAR to a JIA cohort of 6,043 patients within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) legacy registry identified 52 patients who were classified as some JIA subtype other than juvenile PsA that would have been diagnosed as PsA by an adult rheumatologist¹⁶. These patients exhibited less psoriasis but more enthesitis, IBD, uveitis, and inflammatory back pain¹⁶, all characteristics of the clinically similar umbrella of spondyloarthritis that can begin as juvenile disease and carry into adulthood²⁹. CASPAR has been suggested as a potential diagnostic tool for use in defining juvenile PsA that could improve the transition from pediatric to adult care teams¹⁶.

Surprisingly, even though we used 4 different algorithms to identify children with PsA that included not only diagnostic codes but also procedure and medication codes, only 19% of those with one code for PsA (or one code for juvenile arthritis in the background of psoriasis) met our more stringent inclusion criteria. The vast majority (90%) of single codes for PsA or arthritis were made by providers who do not typically diagnose or treat arthritis. The presence of only a single code for arthritis could mean one of the following: 1) providers are using the code(s) for PsA or arthritis in children with psoriasis non-specifically, perhaps for arthralgia but not “true” arthritis (including as “rule-out” codes when a patient is in the process of being evaluated for possible arthritis), 2) children with psoriasis are being diagnosed with arthritis and not receiving further diagnostic evaluation or longitudinal care for the arthritis, 3) arthritis is occurring with reasonably high prevalence but resolves in the majority of the cases, perhaps due to systemic therapy that patients are receiving for psoriasis, or 4) providers are only coding the diagnosis at first encounter and not at subsequent visits. Unfortunately, due to the administrative nature of the data we

cannot obtain clinical information to further examine the reason for the presence of a single code. Of the possibilities, the second is most concerning as longitudinal care for children with PsA is not only important to preserve joint integrity and function but also to monitor for and treat uveitis, which can be vision-threatening.

One of the strengths of this study is the large patient population that includes a broadly representative group of children across the United States. It is important, however, to interpret our study in light of potential limitations. First, this study was conducted utilizing a large retrospective administrative database. As such, we are limited to assessment of diagnoses and symptoms that can be coded. In particular, this may result in an underestimation of the prevalence and incidence of arthritis in children with psoriasis. Second, the duration of continuous enrollment was limited to under 6 years for the majority of subjects. Therefore, detection of arthritis in children with psoriasis and comorbidities after diagnosis was limited to a relatively short period of time, likely leading to underestimation of the prevalence of comorbidities and biasing our results towards the null. However, the fact that there were still significant findings suggests that these associations are even stronger than we are able to demonstrate with this data. Third, as with any administrative database, there is risk of misclassification given the use of diagnostic codes. The diagnosis of PsA in children is challenging; children with psoriasis may be coded as PsA or non-specific arthritis. In order to address this concern for misclassification, we examined several algorithms for identifying PsA.

This is the first study to assess risk factors associated with the development of arthritis in children with psoriasis, and the first to demonstrate that this group of children is at increased risk for inflammatory bowel disease and other clinically important comorbidities including uveitis, diabetes, and depressive disorder. Additional studies are needed to identify the mechanisms underlying these associations and the impact on long-term outcomes into adulthood.

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Table 1.
Patient characteristics at index date.

Index date = date of diagnosis for psoriasis or arthritis (whichever came first) and first encounter for controls.

	PsA n=212	Psoriasis n=4312	Controls n=45240
Age at index date	13.2 (9.7–15.0)	10.9 (7.8–13.5)	11.8 (8.5–14.5)
Female, N (%)	139 (65.6%)	2380 (55.2%)	25190 (55.7%)
Race, N (%)			
Asian	6 (2.8%)	169 (3.9%)	1280 (2.8%)
Black	14 (6.6%)	279 (6.5%)	4081 (9.0%)
White	158 (74.5%)	3085 (71.5%)	29894 (66.1%)
Unknown	34 (16.0%)	779 (18.1%)	9985 (22.1%)

Table 2.
Clinical features associated with development of arthritis in children with psoriasis.

Results of univariate and multivariate analysis of risk factors for development of psoriatic arthritis in children with psoriasis. HR = Hazard ratio, CI = confidence interval

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at psoriasis index date	1.25 (1.14–1.36)	<0.01	1.24 (1.14–1.35)	<0.01
Male sex	0.77 (0.47–1.24)	0.28		
Race				
Asian	1.02 (0.32–3.26)	0.98		
Black	1.02 (0.41–2.55)	0.97		
Inflammatory bowel disease	1.22 (0.17–8.77)	0.85		
Uveitis	7.26 (2.27–23.17)	<0.01	5.54 (1.73–17.74)	<0.01
Hyperlipidemia	1.13 (0.41–3.12)	0.81		
Depression	1.24 (0.66–2.31)	0.50		

In multivariate analysis, age at psoriasis index date and preceding diagnosis of uveitis were significantly associated with a diagnostic code of arthritis in children who had psoriasis ($p < 0.01$).

Table 3.
Incidence rates (IR) and incidence rate ratios (IRR) of incident codes for co-morbid diagnoses after index date of psoriatic arthritis (PsA) or psoriasis (PsO), or match date for controls.

Pys = person-years, IBD= inflammatory bowel disease

	PsA IR, cases/ 1000 pyrs	PsO IR, cases/ 1000 pyrs	Control IR, cases/1000 pyrs	PsA/PsO IRR (95% CI)	PsA/Control IRR (95% CI)	PsO/Control IRR (95% CI)
IBD	5.73	1.64	0.64	3.49 (0.66–11.85)	8.98 (1.82–27)	2.57 (1.49–4.23)
Uveitis	9.94	0.60	0.44	16.52 (4.13–60.47)	22.36 (7.04–54.75)	1.35 (0.52–2.94)
Diabetes	7.51	1.56	1.56	4.83 (1.19–14.66)	4.82 (1.3–12.51)	1 (0.58–1.61)
Hyperlipidemia	3.91	8.08	4.18	0.48 (0.06–1.8)	0.94 (0.11–3.39)	1.93 (1.53–2.41)
Hypertension	9.52	4.08	3.09	2.33 (0.72–5.84)	3.09 (1–7.25)	1.32 (0.96–1.79)
Depressive disorder	60.12	23.15	25.28	2.6 (1.68–3.87)	2.38 (1.56–3.47)	0.92 (0.8–1.04)

The incidence rate of IBD was significantly increased in patients with PsA and psoriasis compared to controls, with the highest risk being in patients with PsA (PsA/controls IRR 8.98, 95% CI: 1.82–28.0, PsO/controls IRR 2.57, 95% CI 1.49–4.23). Children with PsA had a significantly increased risk of incident uveitis, diabetes, and depressive disorder compared to controls (uveitis IRR 22.36, 95% CI 7.04–54.75; diabetes IRR 4.82, 95% CI 1.30–12.51; depressive disorder IRR 2.38, 95% CI 1.56–3.47) and compared to patients with psoriasis without arthritis (uveitis IRR 16.52, 95% CI 4.13–60.47; diabetes IRR 4.83, 95% CI 1.19–14.66; depressive disorder IRR 2.60, 95% CI 1.68–3.87). Psoriasis alone was not statistically associated with incident uveitis, diabetes, or depressive disorder when compared to controls (diabetes IRR 1.0, 95% CI 0.58–1.61; depressive disorder IRR 0.92, 95% CI 0.80–1.04; uveitis IRR 1.35, 95% CI 0.52–2.94).