Clinical comparison of early-onset psoriatic and non-psoriatic oligoarticular juvenile idiopathic arthritis

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Abstract

Objective

Among the seven subtypes of juvenile idiopathic arthritis (JIA), oligoarticular JIA (oJIA) and psoriatic JIA (psJIA) display a predilection for onset in early childhood. We examined whether meaningful differences in clinical phenotype justify the distinction between these conditions.

Methods

We performed a chart review to identify children with psoriatic and non-psoriatic oligoarticular-onset JIA. Clinical and demographic features of the two groups of children were compared.

Results

Of the 390 children included in the study, 303 met the criteria for oJIA and 87 met the criteria for oligoarticular-onset psJIA. Both groups had a peak age of onset at 2–3 years, though psJIA had appreciable incidence into adolescence. Onset before 5 years of age was observed in 215 (71%) and 38 (44%) children respectively ($p<0.001$). Within this age category, children with psJIA demonstrated similar gender ratio and anti-nuclear antibody status to those with oJIA but exhibited a distinctive clinical pattern, with a tendency to involve the wrists and small joints of the hands and feet. Conversely, among all children presenting with oligoarthritis in early childhood, those with wrist or small joint involvement were more likely to have nail pits, psoriasis, or a family history of psoriasis than those without ($p<0.05$), supporting the association of this joint pattern with the psoriatic diathesis.

Conclusion

Even taking into account age of onset and number of joints, oJIA and psJIA remain clinically distinct, though important demographic overlap remains. These findings support separate diagnostic categories but justify further investigation into the similarities as well as differences among these children.

Key words

juvenile idiopathic arthritis, psoriatic arthritis, oligo-articular arthritis

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Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous set of conditions, currently parsed out by the International League of Associations for Rheumatology (ILAR) group into seven mutually exclusive categories (1). Although the ILAR criteria capture some of the clinical diversity observed in paediatric arthritis, the current system fails to take into account heterogeneity introduced by age of onset (2). Many studies have demonstrated that juvenile-onset arthritis exhibits an age of onset distribution characterised by a peak at 2–3 years, in some cases followed by a second peak in mid- to late-adolescence (3-6). Children who develop arthritis within the first 5-6 years of life are distinct from older-onset JIA patients in a number of important respects, including uveitis risk (7), HLA associations (5), and gene expression signatures (8), even within the same JIA category.

Several groups, including ours, have demonstrated that psoriatic JIA (psJIA) displays a similar biphasic age of onset distribution (9-11). Older patients, typically adolescents at disease onset, have an even male-female ratio and exhibit axial joint involvement and enthesitis, suggesting a close relationship with the spondyloarthropathies (9). By contrast, early-onset psJIA peaks at the same time as JIA, and resembles early-onset JIA in its female predominance and tendency to manifest antinuclear antibodies (ANA) (9).

Such similarities have given rise to the suggestion that the psoriatic diathesis is of limited utility in the classification of juvenile arthritis, especially among younger children (2). More broadly, recent work that compared psoriatic- to non-psoriatic arthritis, not stratified by age of onset, found that differences between these populations were modest, again questioning whether psJIA is appropriately included within the JIA classification system (12).

Elimination of psoriatic arthritis from the JIA system would impose a sharp divide between paediatric rheumatology and its adult counterpart, where psoriatic arthritis is well established on the basis of clinical features as well as epidemiologic, serologic, histologic and immunopathologic considerations (13-15). Furthermore, earlier work comparing psoriatic and non-psoriatic JIA types as a whole, without consideration of age of onset, found subtle but clear differences in pattern of joint involvement, supporting the retention of psoriatic arthritis as a subcategory within JIA (16). Taking advantage of recent gains in the understanding of psJIA as a heterogeneous disease, we therefore wished to examine the subset of psJIA which is most plausibly controversial, early-onset children with oligoarthritis, to ask whether these patients are better understood as having typical oJIA. We hypothesized that if early-onset oligo-psJIA is identical to oJIA, then clinical, laboratory and demographic features of these children will be similar. If the two conditions represent different entities, then we should most likely be able to identify phenotypic differences between these populations.

Materials and methods

Study design

This was a retrospective study involving children with oligoarticular onset juvenile idiopathic arthritis (oJIA). We compared those with oJIA with children having psJIA.

Subjects

The study was conducted at two hospitals: Children's Hospital Boston (CHB, Boston, MA) and Texas Scottish Rite Hospital for Children (TSRHC, Dallas, TX). Children with psJIA were identified from both locations, while the oJIA cohort was derived exclusively from TSRHC. The study was limited to patients who had oligoarticular onset within the first six months, with or without an extended course; to ensure exclusion of children who might subsequently be classified with polyarticular JIA, we required at least six months of disease.

PsJIA: Children with psJIA in the Boston cohort were identified as described previously (9). Briefly, we reviewed the charts of every patient seen in the rheumatology clinic of Children's Hospital Boston between January 1997 and February 2005 with a diagnosis code of psoriasis (International Classification of Disease Codes [ICD] -9 696.1), pso-

riatic arthritis (ICD-9 696.0), or spondyloarthritis (ICD-9 756.11). Children in the Dallas cohort of patients were identified through a local database of clinical diagnoses of psoriatic arthritis made by attending physicians from January 1985 through December 2008. *Oligoarticular JIA:* We identified children through the TSRHC clinical database as above, limited to patients whose final visit was after the year 2000. Diagnoses searched included pauciarticular and oligoarticular arthritis (17).

In general, we limited the patient population to children who met the ILAR criteria for oJIA or psJIA (1). The only exception to this was children with both dactylitis and nail pits but lacking a personal or family history of psoriasis, who were included as having psJIA, even though technically they would be classified as undifferentiated due to meeting criteria for both psJIA and oJIA. This modification of the ILAR criteria was justified by our previous study of the JIA classification criteria for psoriatic arthritis (18) and affected a total of 10 of 390 (2.6%) patients.

Definitions

The following definitions were used in this chart review. Oligoarticular onset was defined as involvement of less than 5 joints, cumulatively, within the first 6 months of symptoms. A patient was considered to have psoriasis if that diagnosis was made conclusively by a physician, including the attending rheumatologist. First-degree relatives were considered to have psoriasis only if there was a history of a definitive diagnosis. The diagnosis of arthritis required either the finding of a swollen joint without any other cause, or the combination of restricted range of motion accompanied by pain or tenderness; these symptoms had to be present for at least six weeks (1, 19). Small peripheral joints included the MCPs, PIPs, and DIPs of the hands, as well as the corresponding joints of the feet; PIP and DIP involvement of the toes was considered together as toe arthritis. Large peripheral joints included the hips, shoulders, elbows, wrists, knees, and ankles. Dactylitis was defined as digital swelling extending beyond the margin of the joints; because dactylitis can reflect tenosynovitis in the absence of synovitis, the latter was not assumed to be present, unless specifically documented (20). Enthesitis was defined as tenderness or swelling at the location of a tendinous insertion into bone; in practice, entheseal sites were limited to the plantar fascia, Achilles tendon, and tibial tuberosity. ANA values were considered positive if above the upper limits of normal for the laboratory in which the test was performed (generally ≥1:40).

Data analysis

We compared categorical data and proportions using the chi-square test or Fisher's exact test as indicated. Means were compared with the Student t-test and medians with the Mann-Whitney U-Test. Odds ratios and 95% confidence intervals were calculated with the Cochran-Mantel-Haenszel test. We set α equal to 0.05. All of the analyses were performed using SPSS Version 16 (Chicago, IL.)

Approval

Institutional Review Board approval for the chart review was obtained at both centres.

Results

Patient population

390 children were included in this study: 303 (78%) had oJIA and 87 (22%) had psJIA. As discussed above, all of the children with oJIA were derived from the Dallas cohort, as were 35/87 (40%) of the children with psJIA. Among the 253 children with early-onset arthritis (age of onset <5), 215 (85%) had oJIA and 38 (15%) had psJIA. Of those 38, 22 (58%) came from the Dallas cohort. There were no patients present in both the Dallas and the Boston cohorts.

Age of onset distribution of oJIA and psJIA

The age of onset of children with oligoarticular psoriatic and non-psoriatic JIA is shown in Figure 1. The overall appearances of both curves showed a peak age of onset around 2–3 years. The primary difference between the curves is that onset of oligoarticular psJIA continued into adolescence, such that the median age of these patients was substantially higher (6.1 *vs*. 3.0 years, $p<0.001$).

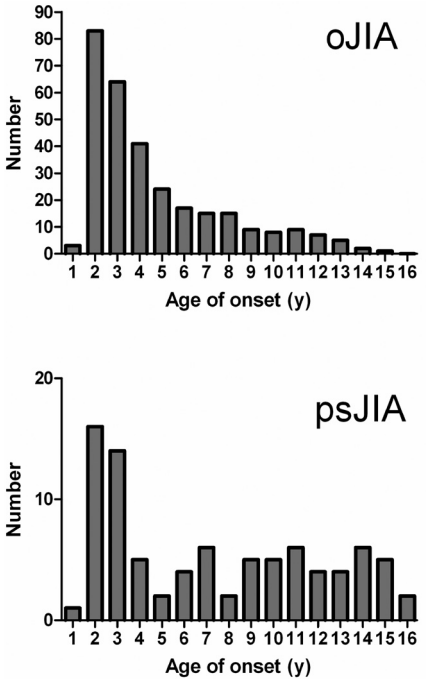

Fig. 1. Age of onset of oligoarticular JIA (n=303) and oligoarticular-onset psoriatic JIA (n=87). Note similar peak age of onset in early childhood, but higher proportionate frequency of psJIA in later childhood.

Comparison of children with oJIA vs. psJIA

Demographic and clinical features of children with oligoarticular psoriatic and non-psoriatic JIA are shown in Table I. Aside from median age of onset, no demographic differences were observed. Children with psJIA were more likely to have small joint and wrist disease, but less likely to have involvement of the knees or of large joints. They were also more likely to extend to a poly-articular course (29.9 *vs*. 7.6%, $p<0.001$). Other differences emerged as a direct consequence of the classification criteria, including the absence of psoriasis in the oJIA group and a higher prevalence of dactylitis and nail pits in the psJIA group. Measurement of HLA-B27 in our populations was performed with insufficient frequency to analyse.

Comparison of psoriatic and non-psoriatic children with early-onset oligoarticular JIA

We compared the demographic and

Table I. Comparison of patients with oJIA with those with oligoarticular psJIA.

Characteristic	oJIA*	psJIA*	*p*-value
n.	303	87	n/a
Duration of follow-up (yrs: median, IQR*)	3.8, 1.7–6.9	3.4, 1.3–5.6	0.147
Females (%)	80.9	69.0	0.018
Age of onset (yrs: median, IQR)	3.0, 1.8–5.7	6.1, 2.2–10.8	<0.001
Age under five (%)	71.0	43.7	<0.001
Extended course (%)	7.6	29.9	<0.001
Affected joints (%)			
Any large joint	97.0	81.6	<0.001
Shoulder	0	0	N/A
Elbow	8.9	13.8	0.181
Wrist	12.5	27.6	0.001
Hip	1.3	3.4	0.188
Knee	83.8	60.9	<0.001
Ankle / subtalar	38.3	49.4	0.062
Any small joint	19.1	52.9	<0.001
MCP*	6.6	17.2	0.002
Hand PIP*	14.9	42.5	<0.001
Hand DIP*	0.7	10.3	<0.001
MTP*	2.0	14.9	<0.001
Foot IP*	2.3	10.3	0.003
Extra-articular features (%)			
Psoriasis	0	60.9	<0.001
Nail pits	3.6	48.3	<0.001
Dactylitis	16.8	50.6	<0.001
Enthesitis	0	27.6	<0.001
Uveitis	29/298, 9.7%	6/57, 10.5%	0.854
Laboratory values			
Baseline WBC / µl: mean, SD	8.9, 2.6	8.6, 3.1	0.392
Baseline ESR, mm/hr: mean, SD	26.3, 20.4	21.1, 14.6	0.013
Baseline platelets x 10^3 / µl: mean, SD	375, 110	350, 84	0.069
ANA	215/299, 71.9%	36/73, 49.3%	<0.001
RF	8/269, 3.0%	0/41	0.603
HLA-B27	17/178, 9.6%	3/25, 12.0%	0.719
Treatments (%)			
IAC*	43.2	21.8	<0.001
Any traditional DMARD*	35.6	74.7	<0.001
Any TNF* inhibitor	7.6	18.4	0.003

*oJIA: oligoarticular juvenile idiopathic arthritis; psJIA: psoriatic juvenile idiopathic arthritis; IQR: inter-quartile range; MCP: metacarpal phalyngeal joint; PIP: proximal intraphalyngeal joint; DIP: distal intraphalyngeal joint; MTP: metatarsal phalyngeal joint; IP: intraphalyngeal joints; IAC: intra-articular corticosteroids; DMARD: disease-modifying anti-rheumatic drug; TNF: tumour necrosis factor.

clinical features of children with early-onset oligoarticular psJIA with those with early-onset oJIA (Table II); we used age 5 years as the cut-off based on our previous findings (9). With the exception of laboratory values, most differences between the two groups from the all-ages comparison held when the comparisons were limited to the early-onset children. Specifically, children with early-onset psJIA were less likely to have arthritis affecting the knee (68% *vs*. 85%, p=0.012) or any large joint (89.5% *vs*. 98%, p=0.02), but were more likely to have involvement of the small joints (58% *vs*. 22%, p<0.001) or wrists (34% *vs*. 13.5%, p=0.002). Similar differences were observed when we compared the late-onset oJIA and psJIA patients (data not shown).

Analysis of a composite criterion for psoriatic JIA

Huemer *et al*. (2002) showed that a composite criterion defined by the presence of one or more of wrist arthritis, small joint involvement, or dactylitis was predictive of psJIA among children with oligoarticular-onset arthritis (16). Reversing our earlier analysis, we pooled our cases to determine whether patients meeting this criterion were more likely to have features of the psoriatic diathesis (Table III). For the diagnosis of psJIA, the composite criterion yielded a statistically significant OR of 5.6 among the entire group and 9.96 among the early-onset cohort. In part this is definitional, as dactylitis is part of the classification criteria for psJIA. However, as further evidence that the composite criterion meaningfully identifies the psoriatic diathesis, children meeting it were also more likely to have psoriasis (OR for the entire cohort and for the early-onset patients of 3.19 and 3.23 respectively), a first-degree family history of psoriasis (OR for the entire cohort and for the early-onset patients of 5.20 and 23.6 respectively), and nail pits on examination (OR 2.91 and 4.96 for the entire cohort and early-onset group respectively). In contrast, we found no significant differences in the frequencies of features common to early-onset arthritis children (uveitis, ANA positivity, and female gender). Because the composite criterion is not neutral with respect to the case definitions, in that dactylitis is part of the classification criteria for psoriatic JIA, we modified the composite criteria to limit it to small joint or wrist involvement and repeated the above analyses. The results were largely unaffected (data not shown).

Discussion

In this study, we compared the clinical features of children with oJIA with the features of children with oligoarticular psJIA. Not unexpectedly, both groups demonstrated a peak age of onset at age 2–3 years. We confirmed the findings of Huemer *et al*. (16), who demonstrated that children with oligoarticular psoriatic arthritis were more likely than their oJIA counterparts to have involvement of the small joints and wrist, as well as dactylitis. Correspondingly, we found that children with oligoarticular psJIA were less likely to have knee and large joint involvement. Additionally, we found that these differences extended even to the most demographically similar clinical subgroup, children with early-onset oligoarticular arthritis.

In adults, the most persuasive evidence that psoriasic arthritis exists as an independent entity is epidemiological: psoriatic patients develop arthritis much more often than the general population and with a gender ratio more balanced

than typical for rheumatoid arthritis (RA) (13, 14). Furthermore, adult PsA can have distinctive clinical features, including dactylitis, nail pits, and a joint distribution atypical for RA (21).

A comparison of psJIA with other types of JIA yields analogous contrasts in many respects, though not all. The frequency of psoriatic arthritis among patients with JIA (approximately 7% in most series, with a range extending to 20%) greatly exceeds that of psoriasis in the general paediatric population (0.5-1%), suggesting more than a chance association (10, 22, 23). The gender ratio of psJIA beginning in late childhood is balanced, though early-onset psJIA exhibits a female predominance similar to early-onset JIA (9). Finally, dactylitis and nail pits are hallmarks of psJIA, even (or especially (9)) among the youngest patients, and we confirm here the findings of Huemer *et al*. that patients with psJIA exhibit a distinctive pattern of joint involvement even in the subgroup that is demographically most similar to non-psoriatic JIA (16).

The biological basis for clinical differences between psJIA and oJIA remains unknown. However, similarities with adult disease – in particular nail pits and dactylitis – could be informative. Careful imaging studies in adults have implicated enthesitis in the pathogenesis of each of these clinical features, and in adult psoriatic arthritis generally (20, 24). While such studies have yet to be performed in children, it is plausible to suggest that enthesitis may be a hallmark feature of psoriatic arthritis across the age spectrum.

In this context it is remarkable that we observed either dactylitis or nail pits in a number of patients classified as non-psoriatic oligoarthritis (Table I). This result could represent either the lack of specificity of these findings in children or the difficulty of identifying psoriatic arthritis in this population, where the classic rash may lag for 10 years or more, potentially further obscured by anti-psoriatic DMARDs such as methotrexate or TNF inhibitors (25). In adults, where psoriasis generally precedes psoriatic arthritis, the specificity of dactylitis and nail pits for psoriatic arthritis is in the range of 95-98% (21).

Table II. Comparison of patients with early-onset oJIA with those with early-onset oligoarticular-psJIA.

Characteristics	oJIA	psJIA	*p*-value
n.	215	38	n/a
Duration of follow-up (yrs: median, IQR)	4.0, 1.7–7.3	5.4, 2.5–7.9	0.276
Females (%)	80.9	84.2	0.632
Age of onset (yrs: median, IQR)	2.2, 1.7–3.2	2.1, 1.4–2.5	0.094
Extended course	9.8	34.2	<0.001
Affected joints (%)			
Any large joint	98.1	89.5	0.020
Shoulder	0	0	n/a
Elbow	9.8	18.4	0.155
Wrist	13.5	34.2	0.002
Hip	0.5	0	1.000
Knee	85.1	68.4	0.012
Ankle/ subtalar	43.7	60.5	0.055
Any small joint	22.3	57.9	<0.001
MCP	7.0	15.8	0.102
Hand PIP	17.7	50	<0.001
Hand DIP	0.5	10.5	0.002
MTP	2.3	13.2	0.008
Foot IP	3.3	10.5	0.065
Extra-articular features			
Psoriasis	0	50.0	<0.001
Nail pits	2.8	39.5	<0.001
Dactylitis	20.5	76.3	<0.001
Enthesitis	0	7.9	0.003
Uveitis	23/212, 10.8%	6/34,17.6%	0.256
Laboratory values			
Baseline WBC / µl: mean, SD	9.3, 2.7	9.5, 3.1	0.748
Baseline ESR, mm/hr: mean, SD	28.0, 21.0	24.2, 15.9	0.307
Baseline platelets x 10^3 / µl: mean, SD	387, 109	396, 83	0.669
ANA	164/212, 77.4%	23/33, 69.7%	0.335
RF	2/188, 1.1%	0/21	1.000
HLA-B27	13/113, 11.5%	1/14, 7.1%	1.000
Treatment (%)			
IA steroids	39.5	26.3	0.121
Any traditional DMARD	40.5	73.7	<0.001
Any TNF inhibitor	6.0	21.1	0.006

If we have indeed misclassified these patients, we expect such misclassification to introduce a conservative bias and therefore not threaten the validity of our findings. By contrast, if these patients are removed from the analysis due to the ambiguity of their classification, then the link between involvement of wrist or small joint and psJIA almost doubles from OR 4.72 (2.85–7.81) to OR 8.26 (4.77–14.3), increasing slightly further to 8.30 (5.16–13.3)

Table III. Odds ratios for features of early-onset juvenile arthritis, according to presence *vs*. absence of the composite criterion.

Outcome	Entire group		Age of onset under 5	
	OR, 95% CI	*p*-value	OR, 95% CI	*p*-value
psJIA	5.60, 3.31–9.46	<0.001	9.96, 3.98–24.9	<0.001
1° FH psoriasis*	5.20, 2.27–11.9	<0.001	23.6, 3.07–182	<0.001
Nail pits	2.91, 1.60–5.29	<0.001	4.96, 1.76–14.0	0.001
Psoriasis	3.19, 1.75–5.84	<0.001	3.23, 1.18–8.79	0.017
Positive ANA	0.82, 0.53–1.28	0.384	0.84, 0.46–1.53	0.572
Uveitis	0.61, 0.28–1.31	0.200	0.61, 0.27–1.40	0.243
Female gender	1.19, 0.73–1.96	0.486	1.72, 0.88–3.37	0.110

*FH: family history; 1° FH: parents and siblings.

if patients with dactylitis or nail pits are coded as having psJIA.

We were struck by the relatively low percentage of children with oJIA who extended to a persistent course (7.6%). Previous studies have placed the risk of extension at 40–50% (26-28). This in unlikely to reflect duration of follow-up, as the median duration of follow-up of the oJIA population was 3.8 years, the period of greatest risk of extension (28). It is possible that the lower risk in our study reflects bias, as children with extended oJIA may have been coded as polyarticular JIA and therefore not captured in this study. It is also possible, however, that more aggressive use of methotrexate and TNF inhibitors prevented extension in children who were at risk. Our overall findings were not altered when we limited the analysis to patients with persistent oligoarticular disease (data not shown).

This study was limited by its retrospective nature. It took place at two hospitals, with possibilities for local differences in case ascertainment, classification and treatment. In addition, differences between the two cities (Boston and Dallas) preclude meaningful demographic comparisons between the respective patient population, since oJIA patients were all collected at one centre (TSRHC), while children at psJIA were collected from both centres. At TSRHC, we have, since the year 2000, prospectively collected the core data set on all of our JIA patients, but this was not the case at CHB. Furthermore some of the patients at TSRHC were initially evaluated before the year 2000; thus, much of the information about joint involvement in this study was ascertained directly through a review of the medical record rather than through the flow sheets. However, rheumatologists at both centres documented similarly detailed descriptions of joint involvement and extra-articular features, rendering major systematic bias in patient characterisation and classification unlikely. In addition, to ensure consistency in interpretation of findings reported in the medical records, the same investigator (MLS) was responsible for review of the medical records of both the Boston and the Dallas cohorts.

In summary, we compared a cohort of children with oJIA with a cohort of children with oligoarticular psJIA, demonstrating clinical differences that held true even when the comparison were limited to the most demographically homogeneous subset, children with early-onset arthritis. Although the observed similarities between the groups do support the hypothesis that there are important etiologic commonalities among children with early-onset arthritis, we submit that clinical differences justify the preservation of psJIA as a distinct diagnostic entity until the biological subdivisions among patients with juvenile arthritis are better understood.

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