Psoriatic juvenile idiopathic arthritis: a tale of two subgroups

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Purpose of review

The International League of Associations for Rheumatology criteria parse out juvenile idiopathic arthritis (JIA) into seven groups, with the aim of creating homogeneous subgroups suitable for clinical and research evaluation. However, prior studies have shown that psoriatic JIA (psJIA) may be a heterogeneous entity.

Recent findings

PsJIA is composed of two subgroups, differentiated by age at onset. Older children with psJIA have features of spondyloarthritis, including relative male preponderance, increased risk of axial involvement, and enthesitis. Extrapolating from studies on adults with psoriatic arthritis, the mechanism of older-onset PsJIA appears to involve autoinflammatory dysregulation centered at the synovial-entheseal complex; there may also be a role for gut inflammation in a subset of patients. In contrast, patients with early-onset PsJIA bear similarities to early-onset oligoarticular and polyarticular JIA patients, including female preponderance, antinuclear antibody (ANA) positivity, and certain human leukocyte antigen types, suggesting a possible role for traditional autoimmune mechanisms. Both groups, however, share a high frequency of dactylitis.

Summary

This review demonstrates that PsJIA is a heterogeneous entity, with different clinical, genetic, and possibly pathophysiological features. Future studies are needed to explore the mechanisms of arthritis in both subgroups, particularly in the early-onset children.

Keywords

age of onset, juvenile idiopathic arthritis, psoriatic arthritis

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Introduction

Juvenile idiopathic arthritis (JIA) has an annual incidence of 4–8 per 100 000 children [1,2]. About 5% of JIA is composed of the psoriatic subtype (PsJIA) [3,4], for a calculated incidence of ~3 per million. Its classification has changed repeatedly over the years [5], and there has long been debate about whether the condition rightfully exists as its own entity within JIA [6–9]. Part of the confusion stems from the heterogeneous nature of PsJIA, as children with early-onset disease are clearly different from their late-onset counterparts, despite falling within the same diagnostic category [10]. In this review, we discuss the history of the diagnosis of psoriatic arthritis (PsA) in children, discuss possible mechanisms of disease, and review treatment and outcome data.

Historical background

The first description of psoriasis occurring in a child with arthritis was published in 1962 [11]. In 1976, Lambert *et al.* [12] published what was at that time the largest description of children with PsA. An important observation in this study was that in many cases, the arthritis preceded the psoriasis, often by several years. These findings were echoed by several subsequent studies [13–16]. Several decades ago, features relatively unique to children who would subsequently develop psoriasis were identified [13,14], prompting the generation of the Vancouver criteria in 1989 [17]. Subsequently, the Vancouver criteria were replaced with the International League of Associations for Rheumatology (ILAR) criteria, which sought to create mutually exclusive homogeneous subgroups of JIA [18]. The most recent iteration defines PsJIA as arthritis in the presence of psoriasis or at least two minor criteria, in the absence of specific exclusions; the minor criteria are nail pits or onycholysis, dactylitis, and a first-degree family history of psoriasis [19].

A debate ongoing throughout much of this period has been whether PsA even merits its own diagnostic entity. This question was raised in 1994 by Petty [7], who noted multiple features similar to oligoarticular JIA and distinct from the spondyloarthritides, with which PsA is classified in adults. Several subsequent articles have noted clinical differences between children with PsJIA and related subtypes of JIA [20,21,22•]. One recent study [9] failed to identify substantial clinical differences between the

two groups; however, this study was criticized on methodological grounds [6].

Heterogeneity of psoriatic juvenile idiopathic arthritis

Any discussion on distinctions between PsJIA and related subtypes of JIA must take into account the heterogeneity of the former. Prior to introduction of the ILAR criteria, PsJIA was noted to represent a heterogeneous entity, with girls presenting at an earlier age compared with boys [14,17]. Using the Vancouver criteria, we showed that children with PsA demonstrated a biphasic age of onset distribution, with a peak at age 2–3 and a later peak around age 10–12 [10]. We noted substantial clinical differences between children with early-onset vs. late-onset arthritis, including increased likelihood of being female and ANA-positive among younger children, compared with increased incidence of enthesitis and axial disease among the older cohort. When the data set was reanalyzed using the more restrictive ILAR criteria, a similar age of onset distribution was observed, with similar clinical differences between early-onset and late-onset children [23].

As discussed above, children with early-onset PsJIA share substantial clinical features with their early-onset oligoarticular and polyarticular JIA counterparts. These patients share a predisposition to females, ANA-positivity, and chronic uveitis [7,8]. It has been proposed that ANA-positive arthritis should be classified as a single diagnostic entity, regardless of number of joints and presence of psoriatic features [24•]. The only difference between PsJIA and other subtypes of JIA appears to be increased small joint and wrist disease in the former, particularly among children with oligoarticular disease [20,22•]; this distinction holds true when the population is limited to those with an early age of onset. In contrast to their early-onset counterparts, children with late-onset PsJIA share substantial features with other patients with spondyloarthritis (SpA), including male predisposition, enthesitis, axial disease, and HLA-B27 positivity, albeit some of these patients are classified into enthesitis-related arthritis or undifferentiated arthritis by the ILAR criteria [23,25].

Possible mechanisms involved in psoriatic juvenile idiopathic arthritis

In light of these clinical differences, we would argue that any analysis of potential mechanisms underlying PsJIA must take age of onset into account.

Older-onset psoriatic juvenile idiopathic arthritis

As discussed above, this subgroup of PsJIA has features consistent with SpA, including relatively higher male: female ratio, HLA-B27 positivity, enthesitis, and axial disease [23]. Research by Benjamin and McGonagle [26] has posited a relationship between the synovial-entheseal complex (SEC) and SpA. The entheses are sites of repeated biomechanical stress, resulting in foci of microtrauma. These small injuries cause the release of fragments of fibronectin, hyaluron, and other molecules from damaged connective tissue, all of which may directly activate synovial macrophages via toll-like receptors and other pattern-recognition molecules. Activation of these molecules results in the up-regulation of approximately 600 stress-related genes [27,28]. Because of the anatomical connections between the enthesis and the synovium, as well as the marked vascularity of the latter, it was suggested that inflammation in the enthesis may spill over into the synovium, causing local arthritis [29].

The concept of the SEC likely accounts for a feature of psoriatic disease that is rarely encountered in other subtypes of JIA: nail involvement [30]. Studies have demonstrated an association between small joint disease and psoriatic nail changes [31•,32]. It emerges that the nail bed is linked to the distal intraphalyngeal joint (DIP) by fibers from the extensor tendon; furthermore, dermis beneath the nail bed is linked to the periosteum of the distal phalynx [33••,34]. MRI studies have shown that the inflammation encompasses the DIP, as well as the local nail structure, indicating a strong anatomical association between the nail and the joint [34].

Another characteristic feature of SpA is subclinical gut inflammation. The link between inflammatory bowel disease and SpA has been recognized for over 50 years [35], with several studies showing a high incidence of arthritis in both adult and pediatric patients with inflammatory bowel disease (IBD) as well as a striking correlation between the timing of the gut and joint flares [36–38]. Additionally, up to two-thirds of SpA patients have subclinical gut inflammation as well, often demonstrating changes similar to those observed in patients with Crohn's disease [39–42]. In the largest of such studies, 209/354 (59%) of SpA patients had subclinical gut inflammation, with 121/209 (58%) demonstrating

Key points

- Psoriatic juvenile idiopathic arthritis (PsJIA) is a heterogeneous condition.
- Late-onset PsJIA has features of spondyloarthritis.
- Early-onset PsJIA bears substantial similarities to other subtypes of ANA-positive early-onset juvenile idiopathic arthritis.
- The mechanism of late-onset PsJIA in many patients appears to involve autoinflammatory activation at the synovial-entheseal complex, whereas early-onset PsJIA may involve more traditional autoimmune processes.

changes consistent with Crohn's disease [40]. Smaller longitudinal studies have suggested that gut inflammation at baseline may predict a chronic course of arthritis [43]. Further evidence demonstrating a causal link between IBD and SpA is suggested by surgical studies showing cure of arthritis in patients with ulcerative colitis who underwent colectomy [44]. The genetic and immunological basis of the link between IBD and SpA is suggested by their shared genetics, with polymorphisms of the genes coding for the IL23R and the tumor necrosis factor ligand superfamily, member 15 present in both subtypes of IBD as well as in ankylosing spondylitis (AS) [45•,46,47••,48]; in addition, the NOD2 polymorphism linked to Crohn's is also associated with SpA patients exhibiting intestinal inflammation [49]. As these genes play important roles in mucosal and innate immune responses, we have recently hypothesized that the gut provides a chronic autoinflammatory stimulus that is necessary but not sufficient for the propagation of the synovitis in patients with SpA [50•].

Here, however, PsA appears to depart from the remainder of the spondyloarthropathies. It has long been established that PsA in adults is a heterogeneous condition, with some patients presenting with axial disease and/or an asymmetric oligoarthritis, and others presenting with symmetrical polyarticular arthritis [51]. Consistent with this heterogeneity, patients with features of SpA, including axial involvement and oligoarticular arthritis were more likely than other patients with psoriatic disease to demonstrate subclinical gut inflammation [52]; indeed, none of the patients with polyarticular PsA demonstrated gut inflammation.

To summarize, innate immunologic mechanisms likely play a critical role in the older-onset PsJIA patients, many of whom share features of SpA [10]. These innate mechanisms manifest as either inflammation at the entheses, as inflammation in the intestinal tract, or both. As reviewed by ourselves and others, this extraarticular inflammation appears to be responsible for the synovitis of PsA and other SpA [33••,50•].

Early-onset psoriatic juvenile idiopathic arthritis

Because there is no adult counterpart to early-onset arthritis, there are minimal histologic or imaging data that could shed light on the pathophysiology of this group. Genetically, early-onset PsJIA patients may be more likely to have HLA types such as DR5 that are associated with features such as early age of onset, ANA positivity, and chronic uveitis, and less likely to express HLA-B27 [16,53–55]. As discussed above, these patients are frequently ANA positive, with similar likelihood of carrying a positive ANA compared with their early-onset JIA counterparts [10,22•]. These findings raise the possibility of a more important role for adaptive immune mechanisms compared with their older-onset counterparts.

Yet unexplained is how dactylitis fits into the picture. Although dactylitis is recognized as a SpA feature in all of the widely used adult classification systems for adult SpA [56–58], this feature was shown to be present in higher percentages of PsJIA patients with an early compared with those with an older age of onset [23]. Even prior to the introduction of the ILAR criteria, dactylitis was only infrequently observed in children with nonpsoriatic JIA but was routinely observed in children with PsJIA, often long before the onset of frank psoriasis [14,17]. Thus, case definitions aside, dactylitis has long been and continues to be a clear discriminating feature between early-onset PsJIA and early-onset nonpsoriatic JIA, and is at least as common in early-onset PsJIA as in late-onset PsJIA. This finding may be perplexing, because dactylitis appears to be an autoinflammatory phenotype, analogous to enthesitis and psoriatic nail disease [59,60], and in adults is a marker of SpA. However, these early-onset PsJIA patients with dactylitis are otherwise clinically and demographically distinct from patients with older-onset PsJIA and other patients with SpA (Table 1 and [7]).

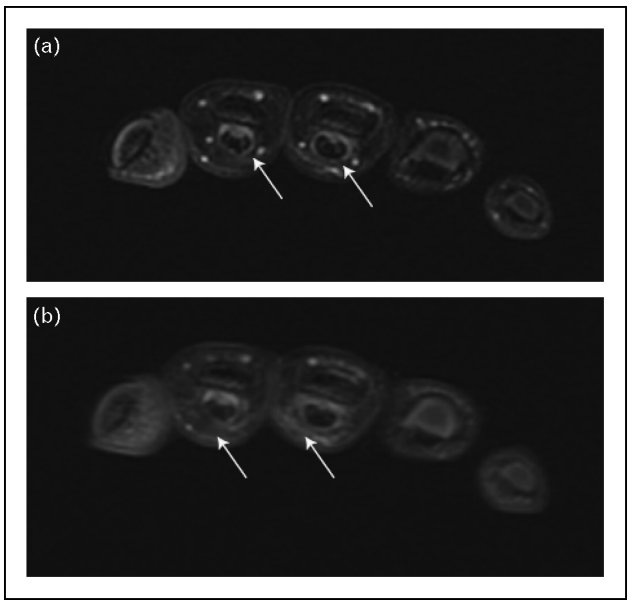
One possible explanation is that PsJIA may be a hybrid disease, characterized both by the adaptive immunologic dysregulation potentially observed in early-onset nonpsoriatic JIA but also by autoinflammatory mechanisms that appear to underlie enthesitis. Alternatively, it may be the case that the dactylitis observed in children with PsJIA, particularly those with early-onset disease, may be intrinsically different than that observed in adults with SpA, perhaps representing more of a tenosynovitis. MRI studies have demonstrated that the dactylitis in PsA includes abundant flexor tenosynovitis and localized soft tissue edema, with or without local synovitis or enthesitis ([61–63] and Fig. 1). However, finger tenosynovitis is not unique to PsA, as it is also present in rheumatoid arthritis (RA) [64,65]. There are subtle

Table 1 Comparison of early-onset and late-onset psoriatic juvenile idiopathic arthritis

Feature	Early-onset PsJIA	Late-onset PsJIA
Sacroiliitis	−	+
HLA-B27	−	+
HLA-DR5	+	−
Enthesitis	−	+
Dactylitis	+	+
Peak age	1–2 years	8–12 years
Gender balance	Female > male	Female = male
ANA	+	−
RF	−	−
Chronic uveitis	+	Unknown
Acute anterior uveitis	−	Unknown

ANA, antinuclear antibody; HLA, human leukocyte antigen; PsJIA, psoriatic juvenile idiopathic arthritis; RF, rheumatoid factor. Adapted from [10,25].

Figure 1 Dactylitis in psoriatic juvenile idiopathic arthritis



MRI of left hand in 3-year-old girl with psoriatic juvenile idiopathic arthritis, whose age of onset was at 2 years. Extensive flexor tenosynovitis of the second and third proximal phalanges in T1-post contrast images (1A, arrows), as well as soft tissue edema of the same phalanges in proton-density fat-saturated images (1B, arrows) can be appreciated. There is no evident enthesitis.

imaging differences between the tenosynovitis of RA and that of PsA, with more synovitis in the former and extra-articular inflammation in the latter [66], but these differences may not be clinically evident, particularly in small children. Thus, what we perceive as dactylitis may be different anatomically than that involving adult and even older-onset pediatric PsA. Potential supporting evidence for this hypothesis is our recent study [67•] showing that among children with enthesitis-related arthritis (ERA), multivariable analysis revealed that dactylitis appeared to have been protective against the development of sacroiliitis. In contrast, features typically associated with SpA, including hip arthritis and enthesitis, have in this and other studies been associated with an increased risk of sacroiliitis [68,69•]. Thus, the mechanisms underlying dactylitis in early childhood may be different than the mechanisms of dactylitis in late childhood and in adults. Future imaging studies should be directed toward evaluating anatomical differences between the dactylitis of early-onset and late-onset PsJIA.

Treatment of psoriatic arthritis

There are scant prospective pediatric data on treatment of PsA, with one open-label study [70••] showing effectiveness of tumor necrosis factor inhibitors (TNFi). In adults, methotrexate appears to be the most commonly used agent [71]. Unfortunately, it is also one of the least studied. One recent randomized trial [72] demonstrated improved swollen and tender joint counts in individuals treated with methotrexate compared with patients receiving nonsteroidal anti-inflammatory drugs for three months, whereas a more recent trial [73•] demonstrated symptomatic relief but no improvement in the PsA Response Criteria (PsARC), American College of Rheumatology (ACR) 20, or DAS28. Other conventional disease-modifying antirheumatic drugs (DMARDs) such as sulfasalazine, leflunomide, and cyslosporine have demonstrated modest benefits [74,75].

There have been multiple randomized trials evaluating the effectiveness of biologic therapy in treatment of adults with PsA, with most of the data evaluating TNFi. All four TNFi studied have demonstrated effectiveness in the treatment of the articular and cutaneous manifestations of PsA, with long-term follow-up studies demonstrating sustained benefits [76–79]. A meta-analysis [80] reported similar ACR-50 responses among the active-drug groups in the etanercept, infliximab, and adalimumab trials. More recently, a prospective study [81•] comparing the same three therapies demonstrated improved cutaneous responses in patients treated with infliximab and adalimumab as compared with etanercept, whereas the latter resulted in better improvement in Health Assessment Questionnaire scores and tender joint counts; the method of allocation was not explained, however.

There are fewer data on biologic therapy outside of the TNFi family. A recent study [82••] demonstrated that T-cell costimulation blockade with abatacept at the dose approved for RA also benefitted cutaneous and articular manifestations of PsA. However, T-cell blockade with alefacept and efalizumab has shown minimal benefit in the articular manifestations of PsA [83,84]. Similarly, ustekinumab had a statistically significant but modest effect in the articular outcomes of PsA [85]. Finally, there are no randomized trials involving anakinra; an open-label study [86•] of 20 adults with PsA showed that only six continuously met the primary outcome of a PsARC throughout the 24-week study period.

In our experience, traditional DMARDs have generally been effective in children with PsJIA, although 15–20% are treated with biologics [10]. In light of the limitations of traditional DMARDs in the axial manifestations of AS [87], we recommend using TNFi in children with axial SpA. There are no data as to whether children with early-onset PsJIA respond differently to traditional DMARDs or biologics as compared with older-onset children.

Outcome

Several of the older series of children with PsJIA reported a difficult course in a subset of patients, manifested as growth abnormalities, functional limitations, joint

replacement surgery, radiographic changes, and even amyloidosis [12,14,88]. More recent studies, including our own, have shown more encouraging responses, with 56% of patients developing inactive arthritis after median follow-up of 22 months ([10] and unpublished data). This apparent improvement from the initial series undoubtedly reflects more aggressive use of immunosuppressive therapy, as 74% of patients were treated with at least one conventional DMARD or biologic [10]. Although long-term follow-up studies of patients treated in the biologics era have yet to be published, these short-term studies at least offer encouragement.

Conclusion

PsJIA is a heterogeneous disease, providing a window into both SpA and early-onset ANA-positive JIA. These two disparate subgroups of PsJIA share a high incidence of dactylitis, long recognized as a distinguishing feature from other subtypes of JIA. There are very few imaging data on PsJIA, and thus it is unclear whether dactylitis in this population represents a synovial-based tenosynovitis common to RA patients [64,65] as compared with an inflammatory process based in extra-articular tissues characteristic of SpA [59,66]. Imaging and serologic studies could help clarify the respective places of early-onset and late-onset PsJIA on the autoimmune/autoinflammatory spectrum of diseases [89].

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 498).

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