The conundrum of juvenile psoriatic arthritis

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ABSTRACT

Juvenile psoriatic arthritis (JPsA) has provided paediatric rheumatologists with a controversial topic for many years. The principal area of contention centres on the discordance between its treatment as a single diagnostic category in current classification schemes and the demonstration of its heterogeneous nature. A further point of debate is the distinctiveness of JPsA as an entity. Owing to these uncertainties, the concept of JPsA has evolved over the years and there have been several changes in its definition and diagnostic criteria. Recently, strong evidence has been provided that the spectrum of JPsA include at least two distinct subgroups, one that has the same characteristics as early-onset ANA-positive JIA, and another that is part of the spectrum of spondyloarthropathies and resembles the forms of psoriatic arthritis in adults that belong to the same disease family. These findings call for a revision of the classification of childhood arthritis, that refutes the assumptions that children with JPsA constitute a single homogeneous population and that JPsA should be considered an individual disease entity.

Introduction

Juvenile psoriatic arthritis (JPsA) is probably the most discussed and controversial of the various forms of childhood arthritis (1-3). Part of the debate derives from its characterisation as a single diagnostic category in current classifications, despite numerous demonstrations of its heterogeneous nature. Another disputed issue is whether this condition exists as a distinct entity within juvenile idiopathic arthritis (JIA). These uncertainties have been reflected in the evolution of the concept of JPsA and in repeated changes in definition and diagnostic criteria. In this article, we discuss the history of the concept of JPsA, review the proposed definitions and classifications, and summarise results of the most recent studies of the disease spectrum.

Evolution of the concept of JPsA

Traditionally, JPsA has been grouped with juvenile ankylosing spondylitis, reactive arthritis, and the arthropathies of inflammatory bowel disease, an association based on the concept of the seronegative spondyloarthropathies formulated by Moll and Wright in the early 1970s (4). As a result, the category of JPsA was not incorporated in the American College of Rheumatology (ACR) classification for juvenile rheumatoid arthritis (JRA) (5), which excluded the spondyloarthropathies, but was placed within the spondyloarthropaties in the European League for Rheumatology (EULAR) classification for juvenile chronic arthritis (JCA) (6)(Table I). Although the term JIA was introduced in 1997 to replace both JRA and JCA, for sake of clarity we will use this term throughout the entire manuscript, even when earlier studies are discussed.

The attribution of JPsA to the spondyloarthropathy group was challenged by Ross Petty in a review published in 1994 (2). Based on analysis of the existing literature, he argued that grouping of JPsA with the spondyloarthropathies was untenable for several reasons: reported patients with JPsA were most frequently young girls, whereas juvenile ankylosing spondylitis (JAS) affects primarily older boys; antinuclear antibodies (ANAs) are not present in children with JAS, but were quite frequent in those with JPsA; HLA-B27 occurs in up to 90% of children with JAS and Reiter's syndrome, but in fewer than 30% of those with JPsA; axial skeleton arthritis and enthesitis are typical of JAS, but very uncommon in JPsA; uveitis is a significant complication of both JAS and JPsA, but is characteristically acute and self-limited in the former, and chronic in the latter. On the other hand, he felt that the pattern of distribution of affected joints, particularly the presence of dactylitis and of asymmetric disease in both large and small joints, set JPsA also apart from oligoarticular-onset JIA.

Table I. Comparison of classification criteria for chronic arthritis in childhood.

ACR JRA	EULAR JCA	ILAR JIA
Systemic arthritis	Systemic arthritis	Systemic arthritis
Pauciarticular arthritis	Pauciarticular arthritis	Oligoarthritis: • Persistent • Extended
Polyarticular arthritis	Polyarticular arthritis JRA (RF-positive) Spondyloarthropathies	Polyarthritis (RF-negative) Polyarthritis (RF-positive) Psoriatic arthritis Enthesitis-related arthritis Undifferentiated arthritis

Note: spondyloarthropathies include juvenile ankylosing spondylitis, juvenile psoriatic arthritis, Reiter's syndrome, and the arthropathies of inflammatory bowel disease; children with spondyloarthropathies are excluded from the ACR classification; RF positivity is not a differentiating criterion in the ACR classification although it is in the EULAR classification.
ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; ILAR: International League of Associations for Rheumatology; JCA: juvenile chronic arthritis; JIA: juvenile idiopathic arthritis; JRA: juvenile rheumatoid arthritis; RF: rheumatoid factor.

The possible relationship between psoriasis and arthritis was explained by Petty in two ways: a portion of the patients diagnosed as having JPsA may have the coincidental association of two diseases, psoriasis and either JIA or JAS; another group, however, has a distinctive arthropathy which occurs predominantly in children who also have psoriasis and is characterised by asymmetric and oligoarticular disease with involvement of large and small joints, with or without dactylitis. He concluded that the latter form could represent "true" JPsA and suggested that it should be classified separately from both JIA and the spondyloarthropathies. In his opinion, a direct effect of psoriasis on arthritis could be deduced from the association of isolated dactylitis with pitting of the nail of the same finger.

In an editorial published 9 years later, one of the authors of this article, Alberto Martini (3) put forward his view that JPsA is a heterogeneous condition. He noticed that several published case series had shown a bimodal distribution of age at disease onset, with a first peak in the preschool years (mainly in girls) and a second during mid to late childhood. In addition, patients with early onset had an asymmetric oligoarthritis that could extend over time. Chronic anterior uveitis occurred with a frequency similar to that seen in early-onset oligoarticular JRA (roughly 20%) and was associated with the presence of ANAs. An increase in DRw8 was recorded on HLA typing in JPsA patients with early-onset disease. His interpretation of these findings was that that early-onset JPsA closely resembles early-onset oligoarticular JIA, the only difference being a higher reported frequency of dactylitis (which was, however, part of the diagnostic criteria) and of small joint involvement, and a more rapid spread of arthritis. Conversely, the older group of patients with JPsA had a male predominance and shared the features of spondyloarthropathies. Notably, in studies of children with psoriasis and arthritis in which patients with enthesitis were not excluded, some patients presented with arthritis and enthesitis or developed sacroiliitis during follow-up, similarly to several adult patients with psoriatic arthritis who share features with spondyloarthropathies (7).

Martini's conclusion was that JPsA is not a unique condition, but includes two distinct subsets: one is very similar to early-onset ANA-positive oligoarthritis, with the possible few aforementioned differences; the other shares the features of enthesitis-related arthritis and, therefore, appears to be part of the spectrum of spondyloarthropathies. The consideration that the former patient group has the same key clinical features (asymmetric arthritis, early onset, female predominance, frequent ANA positivity, high risk for chronic anterior uveitis, and association with HLA-DR8) that are present in other JIA categories (oligoarthritis which is persistent or extended, and RF-negative polyarthritis) and suggest a common background, led Martini to propose that these features may be more meaningful to define a homogeneous disease entity than the distribution of joint involvement or the presence of psoriasis.

In Martini's opinion therefore age at onset and ANA positivity may be more suitable criteria for disease classification than the number of joint involved or the presence of psoriasis

Definitions and classifications of JPsA

Moll and Wright defined psoriatic arthritis in adults as arthritis occurring together with psoriasis. However, this definition was judged too simplistic to capture all forms of psoriatic arthritis in the paediatric age group (2). The first definition of psoriatic arthritis in childhood was proposed in 1976 by Lambert *et al*. (8), who defined it as "arthritis beginning before the age of 16 years, associated with psoriasis either preceding the onset of arthritis or occurring within the subsequent 15 years, and usually with the absence of rheumatoid factor in the serum". This definition accounted for the possible asynchronous occurrence of the two essential components of the disorder, arthritis and psoriasis. However, its application in two subsequent studies showed that it only seldom allowed the diagnosis of JPsA early in the disease course (9, 10). These observations raised the concern that JPsA was underdiagnosed due of the frequently long interval between the onset of arthritis and the onset of a typical psoriatic rash (10). Notably, in reported series arthritis was found to precede psoriasis in a substantial proportion of patients (23–58%), often by several years (11).

In an attempt to resolve this problem, Southwood *et al*. (10) devised the so-called "Vancouver criteria" (Table II), which were aimed to allow a diagnosis of JPsA in the absence of psoriasis. Recognising that the psoriatic diathesis may be suggested by features beyond the classic eruption, including dactylitis, nail pits, and a family history of psoriasis, these authors extended the diagnosis of JPsA to patients with such features even in the absence of the typical rash. Both the study of Southwood *et al*. (10) and a subsequent validation analysis (12) revealed that including children with more subtle psoriatic manifesta-

tions allows for the identification of a population of patients of a younger age at onset than those reported in earlier series and with clinical characteristics that differ both from the spondyloarthropaties and from classic JIA, as outlined in the aforementioned review of Petty.

The new classification of childhood arthritis was promulgated in 1994 (13), and revised in 1997 (14) and again in 2001 (15), by the Pediatric Task force of the International League of Associations for Rheumatology (ILAR) (Table I). The ILAR criteria provided new categories for various forms of JIA, including JPsA (Table III). This condition was defined as the association of arthritis and psoriasis or, if psoriasis is absent, with two of the following: dactylitis, nail pitting or onycholisis, or psoriatic arthritis in a first-degree relative. This definition is similar to that of the Vancouver criteria. However, under ILAR criteria, the diagnosis of JPsA cannot be made if the patient has a first-degree family history of an HLA-B27-associated disease or if the arthritis began in a boy over the age of 6 years who is HLA-B27 positive. In addition, the simultaneous presence of JPsA and ERA leads the patient to fall into the "undifferentiated arthritis" category. Thus, the ILAR scheme excludes *de facto* children with spondyloarthropatic features from the JPsA group. This limitation appears undesirable as it precludes identification of those patients who have a form of psoriatic arthritis similar to that seen in adults (16).

Table II. Vancouver criteria for diagnosis of juvenile psoriatic arthritis (JPsA) (adapted from ref. 10).

Definite JPsA
Arthritis with typical psoriasis
or
Arthritis with at least 3 of the following minor criteria:
- Dactylitis
- Nail pitting or onycholisis
- Psoriasis-like rah
- Family history of psoriasis

Probable JPsA
Arthritis with 2 of the minor criteria listed above

Definitions
Arthritis: joint swelling or at least 2 of the following: limited range of motion of the joint, pain on movement, or tenderness, persisting for at least 6 weeks.
Typical psoriasis: unmistakable psoriatic rash observed by the physician or diagnosed as such by a dermatologist;rash not necessarily coincident with arthritis.
Dactylitis: Diffuse digit swelling, extending beyond the margin of the joint capsule.
Pitting: 2 or more pits on the fingernails at any examination.
Psoriatic-like rash: historical or examination features of a psoriatic rash, but evidence not conclusive.
Family history of psoriasis: diagnosis of psoriasis in first or second-degree relatives.

Table III. ILAR criteria for psoriatic arthritis (adapted from ref. 15).

Arthritis and psoriasis
or
Arthritis and at least 2 of the following:
- Dactylitis
- Nail pitting or onycholysis
- Psoriasis in a first degree relative

Exclusion criteria
a. Arthritis in an HLA-B27-positive male with arthritis onset after 6 years of age.
b. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative.
c. Presence of IgM rheumatoid factor on at least two occasions more than 3 months apart.
d. Presence of systemic arthritis.

Definitions
Arthritis: swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness, which persists for at least 6 weeks, is observed by a physician, and is not due to primarily mechanical disorders or to other identifiable causes.
Dactylitis: swelling of one or more digits, usually in an asymmetric distribution, which extends beyond the joint margin.
Nail pitting: a minimum of 2 pits on one or more nails at any time.

Recent analyses of the clinical spectrum of JPsA

In a study of 139 children meeting the Vancouver criteria, Stoll and co-workers (17) found an age at onset distribution similar to that of previous reports, with one peak in early childhood and the other near adolescence. Substantial clinical differences were noted between children with early-onset *versus* late-onset disease, young children were more likely to be female, to have dactylitis and polyarticular onset, and to be ANA positive, but less likely to have frank psoriasis, enthesitis, or axial disease. The existence of two distinct subgroups was confirmed by cluster analysis, although age at onset appeared to be a less reliable predictor of clinical phenotype than dactylitis, which was present in 100% of the younger cluster *versus* 1.3% of the older cluster. Similar findings in terms of age at onset distribution and clinical differences between early-onset and late-onset children were observed when the data were reanalysed using the more strict ILAR criteria (16).

The authors favoured the hypothesis that there are 2 distinct subsets of JPsA in children, differentiated by the age of onset and other clinical features, particularly the presence of dactylitis (11, 18), in their interpretation of the results. In a comment concerning the first article, Martini argued that the study findings are in keeping with his view that current diagnostic criteria for JPsA pull together two diverse disease entities, one that is very similar to early-onset ANA-positive oligoarthritis, the other that belongs to the spectrum of spondyloarthropaties (see above) (19).

In a large JIA cohort, we found that ANA-positive patients classified by the ILAR criteria into different categories, including JPsA, shared similar characteristics (*e.g.* strong predominance of females, early onset of disease, asymmetric arthritis, and high risk of chronic iridocyclitis) (20). This observation confirmed and expanded our previous findings (21) and substantiated Martini's original hypothesis that ANA-positive patients with JIA constitute a homogeneous subgroup, irrespective of the

course of joint disease and the presence of psoriatic features (3). That ANA-positive patients with JPsA were similar to their counterpart in other categories and much different from the ANA-negative patients in the same category adds to evidence of the heterogeneity of JPsA.

Owing to the concern that patients with a positive family history of psoriasis could "contaminate" the oligoarthritis category of JIA, thus compromising the search for homogeneity within groups, the ILAR Committee decided to include the history of psoriasis in a first-degree relative among the exclusions for various categories of JIA (22, 23). However, this exclusion, which leads to placement of a patient in the undifferentiated arthritis category, has been a matter of controversy (23, 24). In our series, as many as 82% of patients were classified as "undifferentiated arthritis" due to the presence of a family history of psoriasis in a first-degree relative (20). We found that a positive family history of psoriasis does not affect the clinical picture and course in JIA patients with oligoarthritis, which contradicts the use of such a history as an exclusion criterion (25).

Butbul Aviel (26) and colleagues reviewed the charts of 122 patients who met the Vancouver criteria (definite or probable) or ILAR criteria for JPsA. Their findings suggested that JPsA may comprise 4 distinct groups (oligoarthritis persistent or extended, RF-negative polyarthritis, RF-positive polyarthritis, and ERA) that are similar to non-JPsA JIA regarding presentation, disease course, uveitis associations, response to treatment, and outcome. They concluded that the presence of psoriasis may have little clinical relevance in the outcome or response to therapy of children with JIA and that, therefore, psoriasis may be considered as an extra-articular manifestation seen in JIA, similar to uveitis, rather as a feature requiring a distinct classification grouping.

Conclusion

There is compelling evidence that substantial clinical heterogeneity exists within the group of children with JPsA. It appears that the association of psoriasis with arthritis leads to the identification of at least two different groups of patients, one that has the same characteristics as early-onset ANA-positive JIA, and another that is part of the spectrum of spondyloarthropathies and bears a resemblance to the forms of psoriatic arthritis in adults that belong to the same disease family. There is, thus, a strong rationale to avoid the assumptions that children with JPsA constitute a single homogeneous population and that JPsA should be treated as a single disease entity, as done in current classification schemes (27). It remains unclear whether it is worth maintaining a category of JPsA in future classifications of childhood arthritis or whether the presence of psoriasis or psoriatic features should be placed only among the descriptors of the extra-articular phenotype. The need for a revision of JIA classification and nomenclature has been recently suggested (27). All related issues will be addressed at the consensus conference entitled "Evidence-based revision of the International League Against Rheumatism (ILAR) classification criteria for juvenile idiopathic arthritis", which will be held in Genoa, Italy on 3–6 December, 2015.

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