Editorial

Juvenile Psoriatic Arthritis: Bathwater or Baby?

Arthritis in children represents a markedly heterogeneous family of conditions. To get a handle on this complexity, pediatric rheumatologists have developed an evolving set of classification criteria. The most recent iteration of the juvenile idiopathic arthritis (JIA) nomenclature recognizes 7 subgroups defined on the basis of compelling features of the clinical phenotype, supported in some cases by laboratory tests such as rheumatoid factor or HLA-B27[1]. One of these subgroups is juvenile psoriatic arthritis (JPsA), which may be diagnosed in children with arthritis (1) in the presence of psoriasis, or (2) in the absence of psoriasis, if 2 features suggestive of a psoriatic diathesis are present, including dactylitis, nail changes, or psoriasis in a first-degree relative, all in the absence of specified exclusions.

Unfortunately, the differentiation of psoriatic from non-psoriatic arthritis in children is challenging. In about half of children with JPsA, the classic rash presents after the onset of arthritis, with a lag time that may be 10 years or more[2]. Manifestations of psoriasis in the young child are often atypical or incompletely specific, such as erythema and scale behind the ears, features taken into consideration by an earlier (Vancouver) set of JPsA criteria but excluded under the JIA nomenclature[3]. Even in cases where evidence for psoriasis is unambiguous, it remains an open question whether psoriasis is relevant to proper categorization of the child with arthritis. Is JPsA sufficiently distinct from other forms of JIA to merit its own category?

In this issue of *The Journal*, Butbul and colleagues examine this question from a practical vantage point[4]. They ask: Do patients meeting JIA criteria for JPsA exhibit a different phenotype and outcome from patients who do not? To answer this question, they identified about half the patients with JPsA followed at the Hospital for Sick Children in Toronto and paired them with non-JPsA patients matched for onset type (oligo- or polyarticular), gender, age of onset, and date of diagnosis. Using a case-control design, they examined whether differences could be identified between these groups across a set of variables such as pattern of joint involvement and clinical course. The authors found that such differences were scant, which they conclude casts doubt upon the validity of JPsA as an independent diagnostic entity.

This study represents a thought-provoking contribution to the ongoing debate about the classification of juvenile arthritis. The results highlight the challenges of attempting to draw lines between diseases in the absence of biological understanding. Yet before proceeding too far down the path of skepticism, it is worth considering whether the current study was designed optimally to discern the presence of psoriasis-associated arthritis in children. Reasons for concern arise in 3 areas: classification of study patients, assumptions of homogeneity in the groups studied, and limitations imposed by demographic matching.

Classification. The key initial step in any case-control study is to determine who is a case and who is a control. This turns out to be rather difficult in JPsA because many children develop psoriasis years after arthritis, a problem that is especially acute among younger children. Did the current study assign all patients correctly? Within the non-psoriatic group, 4 patients (7.5%) had dactylitis while an additional 7 (13%) exhibited nail pits, findings with a specificity of 95–98% for adult psoriatic arthritis (PsA) and recognized in children with arthritis and psoriasis well before the advent of current JPsA criteria[5-7]. Further, 4 patients with oligoarticular-onset non-psoriatic JIA exhibited small joint inflammation at presentation, a pattern suggestive of JPsA[8]. These cases raise the possibility that there was admixture of JPsA into the non-JPsA category. Indeed, among patients followed at Children's Hospital Boston, strict application of JIA criteria was found to scatter more than half the patients with Vancouver-defined JPsA into other JIA subgroups, despite the presence of nail pits, dactylitis, or other findings suggestive of a psoriatic diathesis[9]. While all classification debate is hampered by a lack of gold standard, these results

See, Comparison of patients with JPsA, non-JPsA, and nonpsoriatic JIA, *page 2033*

have gained support from a recent study by Flatø and colleagues[10]. As part of an inquiry into the longterm outcome of JPsA, these investigators compared patients with JIA-defined JPsA, patients fulfilling Vancouver but not JIA criteria for JPsA, and patients with undifferentiated JIA. After a median followup of 15 years, the prevalence of overt psoriasis was equivalent in both JPsA groups and much higher than in non-psoriatic JIA. To the extent that development of psoriasis is an unambiguous declaration of the psoriatic diathesis, these data support the suggestion that current JIA criteria for JPsA are drawn too narrowly.

In the present study[4], potential misclassification of cases and controls becomes particularly problematic because of sample size. With 31 oligoarticular-onset and 21 polyarticular-onset JPsA patients, matched 1:1 to non-psoriatic JIA controls in parallel analyses, the study had limited power to detect differences of potential importance. For example, the authors found that small joint disease was more common in oligoarticular-onset JPsA (14/31 vs 9/31 in JIA, odds ratio 2.0) but had to reject this result as non-significant. By contrast, a larger study identified oligoarthritis with small joint disease as a hallmark pattern within JPsA[8].

A second limitation intrinsic to the study design arises out of heterogeneity within disease categories. Earlier series suggested, and we have recently confirmed, that younger (< 5 yrs at onset) and older children with JPsA differ substantially in gender ratio, pattern of joint involvement, antinuclear antibody (ANA) status, and clinical course[2,11]. Age-dependent differences have also been noted within non-psoriatic oligoarthritis. By grouping younger and older patients together, the current study pools apples and oranges, obscuring true differences (and similarities) while introducing variability that constrains statistical power.

A final caveat to the current study arises out of the case-control methodology. By matching on age and gender, Butbul, *et al* gain the ability to control for these variables but lose the ability to assess the demographics of JPsA and JIA. In adults, one of the most compelling arguments that PsA is distinct from rheumatoid arthritis (RA) is a striking difference in gender ratio between these entities[5,12]. A case-control study of JPsA will necessarily be blind to such demographic clues.

These concerns notwithstanding, there is something intuitively right about the results of Butbul, *et al*. When faced with a young patient with arthritis, it matters little whether the patient also has nail pits, dactylitis, or even frank psoriasis. Clinical similarities outweigh differences, patients tend to respond to the same general range of therapies, and with conscientious therapy the outcome is usually positive. Does this mean that we should dispense with JPsA as a diagnostic category?

Here I believe the answer is no, or at least not yet. The express purpose of the JIA nomenclature was to define disease subgroups for research, not clinical decision-making[1]. As long as there is reason to suspect that the pathogenesis of JPsA differs from that of other JIA subtypes, then there are grounds for maintaining the category. Indeed, the evidence that psoriasis and arthritis are related is overwhelming. Adults with psoriasis manifest inflammatory arthritis with a frequency exceeding 20% in some studies, a dramatic increase over the general population[12]. Arthritic changes accompany a murine model of psoriasis[13]. Large adult cohorts show that PsA exhibits distinctive demographics, joint distribution, radiographic pattern, and associated extraarticular features, despite responsiveness to the same medications used in RA[5,12,14]. Psoriatic synovium differs from rheumatoid synovium in vascular pattern and cellular infiltrates[15,16]. Synovial fluid from seropositive RA shows depletion of complement, while psoriatic fluid does not[17]. Even more fundamentally, inflammation in adult PsA frequently involves, and may originate at, periarticular entheses — a mechanism that offers a potential explanation for both dactylitis and nail pits, features common in JPsA[18-20]. These studies have yet to be replicated in children, and it may of course be that children are entirely different. However, the initial presumption should be that shared phenotype reflects at least some degree of shared pathophysiology.

There will undoubtedly be something uniquely pediatric about JPsA, at least in the youngest children. The epidemiology of JPsA mirrors that of JIA as a whole, with an early-onset incidence peak (before age 5 or 6 yrs) that parallels that of non-psoriatic JIA[2]. As highlighted by Professor Alberto Martini, younger children with arthritis tend to be female, ANA positive, seronegative, and at risk for subacute anterior uveitis — features that cut across not only the psoriatic/non-psoriatic boundary but also the traditional oligoarticular/polyarticular divide[21]. Early-onset JPsA may well have more in common with early-onset JIA than with JPsA in older children. Yet uncertainty about these young patients should not translate into doubt about older children with JPsA. These patients exhibit a near 1:1 male:female ratio, tend to have oligoarticular involvement, often manifest enthesitis and occasionally sacroiliitis, and therefore bear an unmistakable resemblamce to PsA in the adult[12]. Much more work will be required before we can accurately assess the true biological subdivisions within childhood-onset arthritis, including the role of the psoriatic diathesis in modulating, or defining, the juvenile arthritic phenotype.

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