Peripheral Spondyloarthritis and Psoriatic Arthritis; Overlaps and Distinctions: A Report from the GRAPPA 2012 Annual Meeting

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ABSTRACT. For over 40 years the concept of psoriatic arthritis (PsA) has slowly evolved as new knowledge has emerged. This has been facilitated by the development of new criteria for classification, improvement on existing criteria by the use of updated methodologies, and new information about the disease. At the same time, there has been discussion about categorization within the generic term spondyloarthritis. At the 2012 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), some of this history was reviewed, along with the current thinking about the taxonomy of PsA within spondyloarthritis. (J Rheumatol 2013;40:1446–9; doi:10.3899/jrheum.130460)

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The term "spondarthritis" was introduced by Moll and Wright in their 1976 book *Seronegative Polyarthritis*[1], and would have been introduced 2 years earlier if the editor of *Medicine* had agreed to this title rather than the protracted version published[2]. The insertion of "ylo," making "spondyloarthritis" (SpA), came later. Moll and Wright identified inflammation of the sacroiliac joint as the unifying clinical feature of SpA, which also shared other clinical features: iritis; peripheral seronegative anodular large joint arthropathy, often asymmetrical; psoriasis or psoriaform skin lesions (as in keratoderma blenorrhagica); ulceration of mucus membranes; erythema nodosum, thrombophlebitis; and a strong tendency to familial aggregation. Coincidentally, this concept was supported by the association of the HLA-B27 gene with ankylosing spondylitis; subsequently, other diseases were included in this group[3].

The relative prevalence of these diseases observed in rheumatology practice in the USA is shown in the following data from the SPondyloarthritis: Assessment of CuRrent Epidemiology, Management, and Knowledge (SPARK) survey[4]: rheumatoid arthritis (RA) 59%; and SpA 41% — of which ankylosing spondylitis (AS) 29%, psoriatic arthritis (PsA) 37%, arthritis of inflammatory bowel disease (IBD) 11%, reactive arthritis (ReA) 9%, and undifferentiated arthritis 14%.

With the advent of new information on pathophysiology[5] and new classification criteria not only for SpA as a whole[6] but also peripheral SpA and PsA in particular[7,8], there is a need to review the data behind the new criteria and to suggest ways of pursuing this matter with future research efforts.

Phenotypic variation and genetic correlation

The SpA concept has been supported by the association with HLA-B27. However, this association varies considerably with the SpA subtype, being strongest in those with predominant axial involvement and weakest in those with predominant peripheral manifestations. In relation to those with peripheral disease — is there evidence available that there are significant clinical differences between the disease subtypes or that these clinical phenotypic differences might be further determined by genotype?

A few studies have compared and contrasted clinical features including outcomes in distinct cohorts of SpA with predominantly peripheral manifestations. In one study, a cohort of 157 patients had SpA pattern of peripheral arthritis: 82 with psoriatic spondyloarthritis (PsS), 59 with undifferentiated SpA (uSpA), and 16 with ReA. Symptom duration at presentation was progressively shorter, and the

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erythrocyte sedimentation rate/C-reactive protein (ESR/CRP) incrementally higher in the ReA, uSpA, and PsS cohorts, respectively[9]. A higher swollen joint count (SJC) was observed in PsS compared with uSpA. In PsS, strong positive correlations were observed between ESR/CRP and articular indices. Initially, functional impairment was greater in ReA compared with uSpA and PsS but resolved completely in ReA. Clinical remission rates at 2 years were ReA 61% and uSpA 63%, compared with PsS 14%. Remission at 2 years could be predicted in SpA by disease category and SJC at presentation. Baseline erosions in PsS (28%) and uSpA (5%) increased to 45% and 25%, respectively, at 2 years. These results suggest that there are significant clinical variations within SpA subgroups with predominantly peripheral manifestations. At presentation, the acute-phase markers in ReA and uSpA reflect a systemic process, whereas in PsS they reflect articular manifestations. Although the clinical presentations are indistinguishable, PsS has a more aggressive clinical course with a poorer functional and radiologic outcome.

A more recent study has focused on patients with PsA (n = 361) compared to those with psoriasis only, where arthritis was carefully excluded (n = 214). Detailed clinical assessments and sequence-based HLA-typing were compared[10]. In PsA, the frequency of C*06:02 was lower than that in patients with psoriasis (28.7% vs 57.5%; $p = 9.9 \times 10^{-12}$). Three haplotypes containing B*27:05 or B*39:01 were significantly increased in frequency in patients with PsA, but not in those with psoriasis. Initial correlations with clinical features showed that B*27 was associated with an interval of 0.98 years between skin and musculoskeletal disease ($p = 2.05 \times 10^{-6}$), compared with an interval of 10.14 years for C*06. In further analysis as yet unpublished, both sacroiliitis and peripheral joint erosive disease could also be determined by certain HLA alleles and most strikingly particular haplotypes. These results strongly suggest that phenotypic disease expression in PsA may be genetically determined. These observations have been confirmed in a subsequent article[11].

Additional understanding of the diverse clinical spectrum in SpA will only come with studies where clinical features are carefully quantified and documented. It does not serve the study of SpA simply to lump peripheral SpA into one disease category. It might indeed be extremely useful for GRAPPA and the Assessment of SpondyloArthritis international Society (ASAS) to consider conducting a detailed clinical and radiographic study of SpA cohorts with predominant peripheral disease where patient phenotype is carefully compared with genotype.

The CASPAR criteria

PsA is an heterogeneous disease presenting with several different phenotypic subtypes[12]. Although there are hints that disease expression is governed by genetic factors (e.g., the presence of HLA-B27 in the axial subgroup), much remains to be learned about what governs the clinical manifestations. Until we have that knowledge, it seems premature to split the group into further subdivisions or to subsume this disease under a yet broader taxonomy.

For many years PsA was classified according to the original definition of Moll and Wright: arthritis and psoriasis with the (usual) absence of rheumatoid factor[12]. That these criteria needed revising was evident from their rather broad definition and lack of specificity (characteristic features of PsA, such as axial manifestations, dactylitis, and enthesitis, were not included). Thus, wide variation was seen in measures of prevalence and incidence and in the composition of the subgroups included in case series, which tended to become more polyarticular as time progressed[13,14]. The ClASsification criteria for Psoriatic ARthritis (CASPAR) collected data from 32 centers around the world to characterize 588 patients with PsA and compare them to 580 controls, 70% of whom had RA[7]. Crucially, about 15% of the controls had AS or another form of SpA. The CASPAR criteria were the first validated criteria for PsA derived from patient data contributed by a global group of acknowledged experts in this field. They have been widely adopted by the international rheumatology community since their publication in 2006 (560 citations in the peer-reviewed literature to date). An analysis in 2007 found the CASPAR criteria to fulfill all but 2 of the proposed quality criteria (external validation, testing by other groups), most likely because the relatively recent publication of the CASPAR criteria precluded the fulfillment of these items[15]. Since that time, further publications completed this evaluation gap, with evidence for validity in other cohorts of patients[16], early arthritis[17,18,19], and family medicine clinics[20]. Further, the CASPAR criteria have been widely adopted for use in clinical trials and epidemiological studies[21,22,23,24].

It is often asked why the CASPAR criteria did not include such clinical features as axial disease and enthesitis, and such characteristic radiological features as pencil-in-cup appearance. The answer lies in the methodology used. No preconceptions about the content of the criteria were made prior to the study and the analysis was therefore entirely data-driven. At least 3 approaches to analyzing the data were applied (logistic regression, classification and regression tree analysis, and latent class analysis), and results were largely in agreement. Further, clinicians were asked to include patients who in their opinion had PsA; therefore, physician judgment was the gold standard. That these physicians included patients with predominantly axial disease and predominant enthesitis, in addition to peripheral arthritis, meant that the "stem" of CASPAR included these patients under the description "inflammatory musculoskeletal disease." Features of axial disease did not appear in the CASPAR criteria because both cases and controls may have

had axial disease, and thus were not discriminatory. Similarly, clinical enthesitis (and entheseal new bone formation)[25] and pencil-in-cup appearance on plain radiographs did not appear because they were not sufficiently discriminatory or sufficiently frequent in the PsA group, given the composition of the control group used in the CASPAR study. Such a broad inclusion definition ensured that the criteria captured all the ways in which PsA may manifest in the judgment of clinical experts worldwide. These criteria have enabled collection of cases (for epidemiology or clinical trials) using agreed, accepted, and identifiable criteria; that they may include several subtypes of disease is important. Further phenotyping will be the subject of future research efforts.

The ASAS peripheral SpA criteria

ASAS has published classification criteria for peripheral spondyloarthritis (pSpA)[8]. The primary entry criterion is current arthritis, enthesitis, or dactylitis at clinical examination without current back pain. In addition, at least one of the following SpA features must be present: psoriasis, IBD, uveitis, previous infection, HLA-B27, sacroiliitis on imaging; or at least 2 of the following SpA features: (current or history of) arthritis, enthesitis, or dactylitis, ever inflammatory back pain, or positive family history of SpA. Thus, patients with pSpA can have had back pain in the past, but in patients with current back pain, the ASAS axial SpA (axSpA) criteria should be applied[26]. Combining axSpA and pSpA criteria represents the entire group of SpA patients[8]. The ASAS criteria for pSpA aim to encompass the broad concept of patients with SpA whose symptoms are predominantly peripheral. There is an overlap with patients with PsA according to the CASPAR criteria. However, the pSpA criteria also include many patients not fulfilling the CASPAR criteria; conversely, CASPAR criteria include patients that do not fulfill the pSpA criteria. In a comparison of the various criteria sets at the Leiden early arthritis clinic (EAC) in patients with arthritis symptoms < 2 years, with the rheumatologist's diagnosis as the external standard, a partial overlap of the criteria was demonstrated[26].

In patients diagnosed with PsA by the rheumatologist, the positive likelihood ratio (LR+) of the pSpA criteria was 5.1 (sensitivity 52.0%, specificity 89.8%), and it was clearly higher for the CASPAR criteria: LR+ 20.0 (sensitivity 88.7%, specificity 95.6%). However, in patients diagnosed with SpA by the rheumatologist, the pSpA criteria perform better: LR+ 4.8 (sensitivity 48.7%, specificity 89.8%) versus the CASPAR criteria: LR+ 1.2 (sensitivity 5.3%, specificity 95.6%). These data provide information only on patients presenting with arthritis and not patients with enthesitis or dactylitis only. However, they do show that there is a partial overlap: the CASPAR criteria are more comprehensive in diagnosing all patients with PsA, and the pSpA criteria better diagnose patients with peripheral SpA, confirming the way the criteria have been developed. Moreover, patients with psoriasis with axial involvement but without peripheral involvement are not captured by the pSpA criteria, but might be captured by the axial SpA criteria, which also can be combined in the ASAS criteria for general SpA[26,27]. The Leiden EAC comparison was performed in patients with short symptom duration; a comparison in patients with established disease might yield different results. The choice for either the pSpA or CASPAR criteria depends entirely on the study question.

Conclusions

Concepts and taxonomies evolve in the light of new knowledge and understanding. PsA is a heterogeneous disease, which is likely to be a mix of distinct entities. Careful phenotyping is the key to unraveling this mixture, as laboratory-based studies, biomarkers, and genetics are used to discern the differences underlying the clinical heterogeneity.

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