Editorial

Problems with the Definition of Axial and Peripheral Disease Patterns in Psoriatic Arthritis

For the last 30 years research in psoriatic arthritis (PsA) has acknowledged the contribution of Moll and Wright in 2 ways. First, the suggested diagnostic criteria — an inflammatory arthritis associated with psoriasis in the absence of rheumatoid factor — have been widely adopted. Second, their subgroup classification, the signs and symptoms of which are useful for describing the varied manifestations of the disease, has mandated other authors to describe their disease population in these terms. However, an obsession with subgroups has distracted authors from the important question of diagnostic disease classification.

To date there is only one validated system, developed by Fournie and colleagues[1], for case definition based on patient data. Their definition includes clinical and radiological features and HLA status as criteria and consequently is of limited use clinically.

Among the several proposed definitions of distinct subsets of PsA the simplest approach is to form 2 classes: axial (with or without peripheral features) and peripheral alone. We review the different approaches taken since Moll and Wright's original formulation in 1973 and suggest research designs that might help to resolve the issue.

In 1959, Wright originally proposed 3 subgroups[2]. These were "distal interphalangeal (DIP) predominant disease," "severely deforming arthritis" (which included patients with axial disease), and "rheumatoid-like disease." Later, Moll and Wright described 5 subgroups of PsA (relative proportions in parentheses): predominant DIP joint disease (5%), asymmetrical oligoarthritis (70%), polyarthritis (15%), spondylitis (5%), and arthritis mutilans (5%)[3]. This classification was supported by cluster analysis of a large number of cases of PsA across several centers[4]. Minor modifications have been made to the Moll and Wright subgroups by authors including Gladman, *et al*[5], Torre-Alonso, *et al*[6], Helliwell, *et al*[7], and Veale, *et al*[8].

Before discussing modifications to the criteria, it is interesting to note marked differences between original Moll and Wright series and subsequent reports with respect to relative proportions of asymmetrical oligoarthritis and symmetrical polyarthritis subgroups: indeed, in most series proportions are the reverse. Assuming that there have been no fundamental changes to the disease in the last 40 years, and acknowledging that established cases were included in all series, it must be concluded that subsequent authors have interpreted the diagnostic criteria and/or the subgroup criteria of Moll and Wright in different ways.

Moll and Wright described 5 subgroups. Gladman, *et al* expanded this (7 groups) to distinguish between pure axial disease or axial disease with and without peripheral features[5]: distal disease (DIP affected only), oligoarthritis (< 4 joints), polyarthritis, spondylitis only, distal plus spondylitis, oligoarthritis plus spondylitis, and polyarthritis plus spondylitis. In their cross-sectional study, 33% of patients had axial disease with or without peripheral features. Arthritis mutilans was not seen sufficiently frequently to require its own subgroup and was believed to be an indicator of severity, rather than a distinct group. Torre-Alonso, *et al* also concluded that since DIP arthritis occurs in any other subgroup, this particular category is not valid but otherwise distinguished the other 4 Moll and Wright categories. They explicitly included patients with peripheral manifestations in combination with axial manifestations in the spondylitis subgroup, but did not report whether spinal radiographic changes and/or axial symptoms were required for the axial appellation. Helliwell, *et al*[7] took an empiric approach to classification using scintigraphy to identify the distribution of both clinically apparent disease and subclinical disease. This led to only 3 subgroups: peripheral polyarthritis; spondarthritis; and synovitis/acne/pustulosis/hyperostosis/osteomyelitis (SAPHO) — because of an appreciable incidence of extraarticular disease seen on scintigraphy. Veale, *et al*[8] applied the Moll and Wright and Helliwell formulations to their cohort and concluded that the peripheral arthritis group of Helliwell was too broad, containing patients with symmetrical polyarthritis (SP) and asymmetrical oligoarthritis (AO). Since it was possible to show that there were significant differences in clinically deforming arthritis and radiographic erosive disease between these 2 groups (SP and AO), the distinction appeared valid. They also agreed that DIP

involvement did not require a separate category and proposed the following 3-group classification: asymmetric oligoarthritis, symmetric polyarthritis, and predominant spondylitis. It is not clear from their article how the diagnosis of spondylitis was operationalized. The low numbers of diagnosed spondylitis (4%) and the absence of cervical or lumbar spinal radiographs suggest that a definition requiring radiographic sacroiliitis was required, although this is not clear.

Subgroup classification ought to be stable over time, otherwise the validity of the different distinctions becomes questionable. Jones, *et al* studied 100 patients and found frequent progression from an oligoarticular pattern at onset to a polyarticular pattern at final assessment[9]. Marsal, *et al* studied 73 patients over a median followup of 8 years using a standard clinical protocol[10]. They also showed that oligoarthritis was common at presentation (52% with fewer than 4 affected joints), but not at followup (6.8%). Using radiographic sacroiliitis (1966 New York criteria) to define axial disease (with or without peripheral arthritis), 29% had axial disease. The authors felt that a 2-group classification system was likely to be most robust: axial or peripheral. It was noted, however, that radiographic sacroiliitis can develop over time. In a further longitudinal study of patients with early arthritis[11], there was significant progression over time from polyarticular to oligoarticular that was attributed to disease treatment effects.

In any study of patterns of joint involvement it must be recognized that clinical examination is a relatively insensitive way of identifying articular involvement; the use of other modalities to identify involvement, such as radiographs, bone scintigraphy, color Doppler ultrasound, and magnetic resonance imaging (MRI), suggests that differential articular involvement is a quantitative rather than a qualitative distinction[12]. In this way different methods of evaluation produce different patterns of joint and entheseal involvement: what appears oligoarticular by one method may be polyarticular by another.

Based on data reported at this point, the following conclusions about disease patterns can be drawn:

1. DIP predominant and arthritis mutilans are probably not distinct subgroups, but may occur as a general manifestation of PsA or as a representation of severity of disease.
2. The distinction between oligoarticular and polyarticular disease is not useful since one form evolves into another (and in both directions), and subclinical disease may be present to confound these groupings.
3. SAPHO may be a separate subgroup, but its clinical rarity makes this hard to study among cohorts of patients with PsA. Further work is needed on this group of patients in order to complete the taxonomy.
4. The definition of axial disease remains problematic.

Turning to this last issue, it is apparent from the preceding discussion that there are a number of ways to define axial disease: alone or in combination with peripheral manifestations; and based on inflammatory spinal symptoms, radiographic sacroiliitis, other radiographic signs of spondylitis, or on combinations of features such as the European Spondylarthropathy Study Group criteria for spondyloarthritis[13].

Is there a way of empirically determining the best way of defining axial disease? The similarities between axial PsA and ankylosing spondylitis suggest that similar definitions of disease can be employed. However, although the New York criteria for diagnosing (and classifying) people with ankylosing spondylitis are widely used, these criteria still require validation. The New York criteria for ankylosing spondylitis require a symptom (back pain), a clinical sign (restriction of back or chest expansion), and a radiological feature (sacroiliitis)[14]. The restriction of back or chest expansion and the radiological feature are based on earlier approaches where diagnosis was made relatively late, usually after several years of symptoms[15]. As a further complication, some cases of established ankylosing spondylitis and axial PsA are clearly asymptomatic for many years, the diagnosis only being made by chance[16].

On the other hand, the dissimilarities between axial PsA and ankylosing spondylitis suggest that these features could be employed to distinguish between true axial PsA and psoriasis with coincidental ankylosing spondylitis. These differences were originally described by McEwen and colleagues[17] and, in part, later confirmed by Helliwell, *et al*[18]. The features more often seen in association with psoriasis (and reactive arthritis) can be summarized as follows:

- Asymmetrical sacroiliitis
- Non-marginal syndesmophytes
- Asymmetrical syndesmophytes
- Paravertebral ossification
- More frequent involvement of cervical spine

In fact, the later study by Helliwell, *et al* found paravertebral ossification to be so rare as to be of little value in discrimination, and predominance of cervical spine involvement was a result of a relative sparing of the lumbar spine in psoriatic spondylitis. Further work by de Vlam, *et al* has suggested a possible mechanism for the non-marginal "bulky" syndesmophytes, which are seen more frequently in association with psoriasis. de Vlam and colleagues argue that syndesmophyte morphology is simply a function of the amount of mobility in the adjacent facet joints, and that the relative sparing of the zygapophyseal joints in PsA preserves mobility, resulting in more prolific new bone anteriorly between the vertebral bodies[19].

Can the differences between psoriatic and classical ankylosing spondylitis be, as in the case of peripheral arthritis, ascribed to quantitative rather than qualitative differences? There would certainly be some support for this, particularly if the difference in syndesmophyte morphology can be explained by the coexisting involvement of the zygapophyseal joints.

Could the diagnosis of axial involvement be based solely on axial symptoms and signs? Low back pain is ubiquitous and symptoms and signs do not correlate well with radiological evidence of sacroiliitis or spondylitis, frequently occurring in their absence. Certainly, sacroiliitis can occur in the absence of spinal symptoms in PsA[20], and clinical evaluation of sacroiliitis is especially inaccurate. In a recent series from Oxford, UK, clinical features of sacroiliitis were present in 14/42 (33%) with normal MRI scans and 10/26 (38%) with abnormal scans[21]. It has also been suggested that radiographic spondylitis can occur without sacroiliitis in PsA (in contrast to ankylosing spondylitis, where, by definition, this cannot occur). The extent of this non-overlap determines how important it is to evaluate spinal radiographs in addition to sacroiliac (SI) joint radiographs and clinical symptoms and signs. In a study of 343 patients with PsA carried out in Bradford, UK, and Milan, Italy, 94 patients had both spinal and SI radiographs[22]. Seven of 22 with radiographic spondylitis (32%) did not have radiographic sacroiliitis, and 15 of 30 (50%) with radiographic sacroiliitis did not have radiographic spondylitis. There was also poor concordance between clinical inflammatory spinal symptoms and radiographic axial disease: 16 of 43 (37%) with inflammatory axial symptoms did not have radiographic spondylitis or sacroiliitis, and 31 of 67 (46%) of those without inflammatory axial symptoms did have radiographic spondylitis or sacroiliitis. Therefore, in order to capture the totality of the axial manifestations in PsA, it is necessary to include radiographic changes (both spinal and at SI joints) and symptoms.

The next question concerns early disease. The plain radiographic changes indicated above clearly take time to develop, and represent a late stage of the pathophysiology occurring at the entheses and in the interspinous ligaments. We do know that the spinal radiographic changes progress with time in ankylosing spondylitis and we must suppose that the same is true for PsA[23]. However, abnormalities can be seen on MRI prior to plain radiographic abnormalities in ankylosing spondylitis; these changes are seen at the entheses and in the underlying bone and presumably represent the early phases of the disease process[24]. Although it has been hypothesized that disease taxonomy can be predicted early on the basis of MRI appearances of peripheral joints, this hypothesis remains unproven[25]. At this time we may have to accept that much of what is seen as very early inflammatory arthritis remains unclassifiable and possibly undifferentiated[26]. All existing criteria sets in rheumatology are fallible in this way, and it seems futile to try and encompass this problem before resolving the question of classifying established disease.

Probably the only reason that one would want to subgroup patients in the first place is that these groups might behave differently over time, either in terms of natural history or in response to treatment. It is clear that sulfasalazine works differently for peripheral manifestations compared to axial manifestations in spondyloarthropathies[27], so it is reasonable to at least examine this possibility by separately analyzing people with axial disease and peripheral disease. However, although the manifestations of PsA are heterogeneous, the same could be said for rheumatoid arthritis; yet a single set of criteria are used for this condition. There is a strong argument, therefore, for abandoning the concept of subgroups altogether. Classification sets for PsA might then include the various manifestations of the disorder within this rubric, allowing case identification on the basis of combinations of these features. In many ways the ESSG criteria for spondyloarthropathy are crafted in this way, but show poor sensitivity and specificity when applied to a case series of PsA and rheumatoid arthritis[22].

There are 2 possible ways of resolving difficulties with the meaning of axial disease in PsA: to collect data from a large number of centers on people with axial and peripheral PsA using the treating physician's opinion regarding presence of axial and peripheral disease and to have a contrasting group of patients with ankylosing spondylitis and rheumatoid arthritis. This would enable examination of the relative sensitivity and specificity of the different definitions of axial involvement, from symptoms only to combined clinical radiographic evaluation. It may also be possible to develop a method to determine the distinction between classical ankylosing spondylitis and axial PsA using a scoring system based on the observed differences between these forms of spinal involvement (including syndesmophyte morphology, symmetry of sacroiliitis, symmetry of spinal disease, and possibly paravertebral ossification). Such data have already been collected for the CASPAR classification project[28] and would require little further input before such an analysis could be performed.

The second method would be to conduct a consensus exercise among experts in PsA to determine which definition of axial disease is most acceptable. However, there is circularity with this approach, although it may offer a starting point for further studies. We would contend that a starting point has already been reached based on the studies quoted above. We are now in a position to take this matter forward using existing data. The collective interest of GRAPPA (Group for the Research and Assessment of Psoriasis and PsA) to establish a worldwide registry of cases of PsA collected prospectively will provide an ideal testing ground for any newly developed criteria[29].

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