Classification and categorization of psoriatic arthritis

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For over 30 years, investigators have used the simple but nonvalidated classification criteria suggested by Moll and Wright. Several authors have suggested modifications to these, but most remain invalid or require human leukocyte antigen analysis. Now, a worldwide initiative has developed new criteria which include both clinical and radiological features. These will require further study before they are fully adopted for future studies, although improved performance should result in less variation between study cohorts. The recurring question of disease heterogeneity continues to occupy researchers in this field. Despite recent pleas to abandon the original five subgroups, a case can be made for retaining at least the two subgroups of peripheral and axial disease and, possibly, splitting the peripheral disease into oligo- and polyarthritis.

Virtually all published studies of psoriatic arthritis use the criteria suggested by Moll and Wright in their classic paper published in 1973 (**Box 1**) [1]. The criteria are simple to use and specify three conditions: the presence of psoriasis, an inflammatory arthritis and a negative test for rheumatoid factor. Interestingly, people classified as having psoriatic arthritis by subsequent authors appear to differ from those included by Moll and Wright, particularly with reference to the number of involved joints – Moll and Wright found polyarthritis in 15% of cases whereas, in later series, 65% had polyarthritis [2–6]. Furthermore, later series included patients who were rheumatoid factor positive, in up to 13% in some cases [2], and this raised the specter of cases of seronegative (and in some cases seropositive) rheumatoid arthritis (RA), with coincidental psoriasis, being classified as psoriatic arthritis. Moll and Wright, in their desire to keep the criteria simple and sensitive, may have omitted the other defining features of psoriatic arthritis, such as dactylitis and enthesitis, from their stated criteria while still using these in clinical practice.

In fact, the notion that current case series of psoriatic arthritis are infiltrated by cases of RA appears unfounded. Data from the ClASsification of Psoriatic ARthritis (CASPAR) study group found that cases of polyarticular psoriatic arthritis had clinical, laboratory and radiological features that more closely resembled oligoarticular psoriatic arthritis than RA (**Figure 1**) [7] . Why, then, the paradox? This has been discussed in more detail elsewhere [8], but Moll and Wright did not give clear definitions for oligo- and polyarthritis, so the confusion may simply be due to insufficient clarity. Joint-by-joint comparison of the CASPAR cases with cases from publications of Moll and Wright (paper in preparation) should help resolve this issue.

In addition to those proposed by Moll and Wright, there have been several other criteria sets [2,9–13]. Until recently, none had been validated and none were founded on patient-derived data. All were developed to add some specificity to the criteria, usually a feature which is enhanced at the cost of reduced sensitivity. Recently, these criteria sets have been compared, firstly in a retrospective cross-sectional study in two centers and secondly in a prospective multicenter design [14,15]. The specificity of all the criteria sets was found to be high but the sensitivity varied from 0.42 to 0.98. Furthermore, not all cases could be classified because of missing data – this was particularly true in the retrospective study where data was extracted from routine clinical case notes – and for the Fournié classification which included human leukocyte antigen (HLA) status among its criteria [13]. The results of the comparison from the retrospective study are given in **Table 1**.

The CASPAR study group was established to derive new data-driven classification criteria for psoriatic arthritis. Data were collected in 32 centers worldwide by people with acknowledged expertise in this condition. On average, each center contributed 20 cases and 20 controls, the controls being cases of other inflammatory arthritis, with the additional stipulation that at least half of these should have RA. Data were collected to a standard format on consecutive clinic attendees with psoriatic arthritis (a total of 588 subjects) and the next case of inflammatory arthritis (a total of 536 subjects). Over 70% of the controls had RA and a further 13% suffered

Keywords: classification criteria, clinical features, diagnosis, psoriatic arthritis, spondyloarthropathy

future Medicine

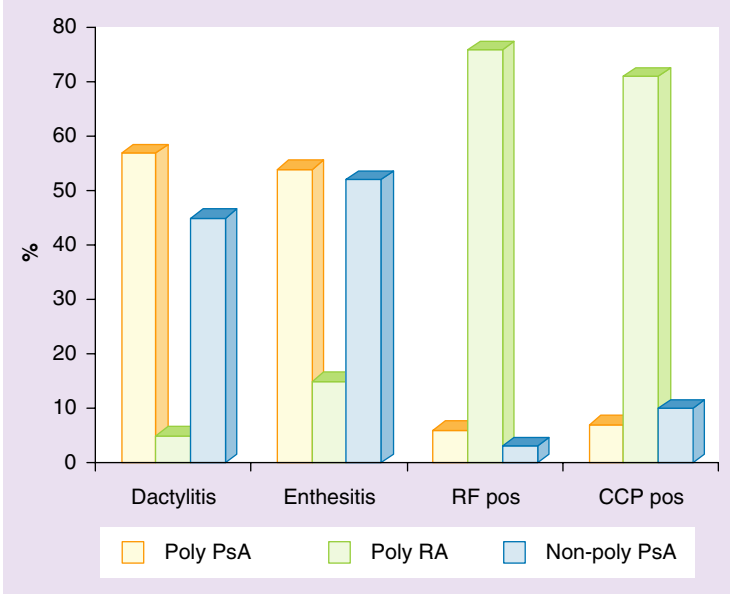
Box 1. Classification criteria of Moll and Wright [1].

- Inflammatory arthritis
- Plus the presence of psoriasis
- In the absence of a positive serological test for rheumatoid factor (in the original paper this was described as the 'usual' absence of rheumatoid factor, measured by the Rose Waaler test)

ankylosing spondylitis. Altogether over 100 clinical, radiological and laboratory variables were collected. The new criteria were derived by logistic regression and classification and regression tree (CART) analysis (as a cross check), and the performance of the new criteria compared with the other existing criteria.

The new CASPAR criteria (**Table 2**) gratifyingly have both characteristic dermatological, clinical and radiological features and have both high sensitivity and very high specificity. It is also interesting to note that, with these criteria, it is possible to be rheumatoid factor positive and still have a diagnosis of psoriatic arthritis, providing that other characteristic features are present. Also of interest is the observation that the dermatological features contribute more to the criteria than the other features – in fact the CART analysis was dominated by the skin disease: the combination of psoriasis and an inflammatory arthritis alone gave the very respectable figures of 0.96 and 0.97 for sensitivity and specificity, respectively.

Figure 1. Data from the CASPAR study.



Polyarticular psoriatic (poly PSA) arthritis has clinical and laboratory features that more closely resemble oligoarticular psoriatic arthritis (non-poly PSA) than RA (poly RA) [7].
CASPAR: CIASsification of Psoriatic ARthritis; CCP: Anti-cyclic citrullinated peptide antibodies; PSA: Psoriatic arthritis; RA: Rheumatoid arthritis; RF: Rheumatoid factor.

Perhaps the weakest aspect of the CASPAR criteria is the initial qualification criterion: inflammatory arthritis including spinal, peripheral and entheseal disease. As cases were physician diagnosed and without other stipulation in the selection process, it was impossible to be more precise with this description. In fact, the majority cases had a peripheral arthritis pattern, although 72 had a combined axial–peripheral pattern, and 21 did not have any peripheral joint involvement at all. Of these 21, two had pure axial disease, 12 enthesitis and ten inflammatory spinal pain (in combinations).

A further weakness concerns the applicability of the criteria to early disease, as the mean duration of disease of the cases was 12.5 years. Clearly, further work will have to be done in this respect, but it is tempting to suppose that other features of spondyloarthropathy, such as entheseal pain and inflammatory spinal pain, would be included in any early criteria.

A third concern with these criteria is located in the composition of the controls. Approximately 70% of the controls had RA, but 13% had ankylosing spondylitis and so the statistical analyses were influenced against selecting spinal features as characteristic of psoriatic arthritis. Although it has been suggested that the spondylitis of psoriatic arthritis is qualitatively and quantitatively different from that seen in classical ankylosing spondylitis, these differences did not appear as discriminating features. Of course, had the controls only consisted of RA cases, it is then possible that the spinal features would have appeared in the final criteria set.

The criteria derived, and the figures for sensitivity and specificity (and those for post-hoc calculations like the likelihood ratios) are therefore very dependent on the control population (non- or alternative disease) used to derive them. Furthermore, it may be possible to manipulate the sensitivity and specificity according to the use to which the criteria are likely to be put. If classification criteria are required to identify as many cases as possible, then a high sensitivity in a population, similar to that in which the criteria will be applied, is appropriate. If, however, cases are required for a therapeutic trial in which a treatment specific for that condition has been formulated, then it is necessary to derive criteria with a high specificity. It is therefore important to be aware that the composition of the patient

Table 1. Test performance of classification rules.

Rule	Rheumatoid arthritis	Psoriatic arthritis	Sensitivity	Specificity	Proportion unclassifiable
Gladman					
Positive	1	321	0.97	0.993	0.042
Negative	146	10			
Unclassifiable	9	12			
McGonagle					
Positive	5	341	0.994	0.965	0.026
Negative	138	2			
Unclassifiable	13	0			
Fournié					
Positive	9	304	0.993	0.882	0.234
Negative	67	2			
Unclassifiable	80	37			
ESSG					
Positive	3	189	0.563	0.979	0.034
Negative	143	147			
Unclassifiable	10	7			
Moll and Wright					
Positive	1	301	0.940	0.994	0.042
Negative	155	19			
Unclassifiable	0	20			
Bennett (5 of 8 version)					
Positive	1	224	0.693	0.994	0.040
Negative	155	99			
Unclassifiable	0	20			
Vasey and Espinoza					
Positive	1	340	0.991	0.993	0.018
Negative	146	3			
Unclassifiable	9	0			

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groups, and the analysis procedures, are important factors influencing the appropriate use of new criteria sets.

In the case of psoriatic arthritis, most clinicians would claim that they have little difficulty diagnosing this condition. Bedside diagnosis is, of course, a separate issue to classification criteria, but once classification criteria have been published, clinicians frequently misuse them for clinic or bedside diagnosis. However, from a clinical point of view, physicians not otherwise recognized for their specialization in psoriatic arthritis still have difficulty making the diagnosis [16], and there is even some doubt about the ability of 'experts' to agree on the diagnosis in 'gray' cases [17]. A typical scenario is the patient with seronegative symmetrical polyarthritis and psoriasis. The mere presence of psoriasis is usually sufficient for a diagnosis of psoriatic arthritis to be made but, inevitably, there will be cases of true RA in which coincidental psoriasis occurs. Thus, bedside diagnosis continues to provide problems ,but the new classification criteria should provide some uniformity for therapeutic trials and also a more homogenous group for laboratory studies.

Is there any purpose in wishing to distinguish psoriatic arthritis from RA or psoriatic arthritis from other spondyloarthropathies? Does it matter in terms of treatment and outcome? With regards to the first contrast, between psoriatic arthritis and RA, as they both essentially cause a deforming inflammatory arthritis, should not they be treated in the same way? Recent developments in cytokine research would support this, but, on the other hand, there is evidence supporting the concept of psoriatic arthritis as a disease distinct from RA both radiologically [12] and pathologically [18,19]. Furthermore, RA is often a systemic disease with

Table 2. The CASPAR criteria.

Inflammatory articular disease (joint, spine, or entheseal), with three or more points from the following:			
1. Evidence of psoriasis (one of a, b, c)			
	(a) Current psoriasis*	(b) Personal history of psoriasis	(c) Family history of psoriasis
	Psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist	A history of psoriasis that may be obtained from patient, family doctor, dermatologist, rheumatologist or other qualified healthcare provider	A history of psoriasis in a first or second degree relative according to patient report
2. Psoriatic nail dystrophy			
	Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination		
3. A negative test for rheumatoid factor			
	By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range		
4. Dactylitis (one of a, b)			
	(a) Current	(b) History	
	Swelling of an entire digit	A history of dactylitis recorded by a rheumatologist	
5. Radiological evidence of juxta-articular new bone formation			
	Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain x-rays of hand or foot		

Specificity 0.987, sensitivity 0.914 CASPAR.
**Current psoriasis scores 2 whereas all other items score 1.*
CASPAR: Classification of psoriatic arthritis; ELISA: Enzyme-linked immunosorbent assay.
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significant extra-articular features and an adverse prognosis. Although the level of disability is similar between hospital-based cohorts of patients with these diseases, the mortality is higher in RA – the standardized mortality ratio for psoriatic arthritis at 1.62 and, for RA, 2.64 [20,21] It appears unlikely, therefore, that we are studying a condition where otherwise typical RA is modified by the presence of psoriasis and we should strive to separate these conditions in the clinic, in intervention studies and when sending specimens to the laboratory for immunopathological studies.

Categorization of psoriatic arthritis

Wright originally proposed three subgroups for psoriatic arthritis [22]. These were distal IP (DIP) joint predominant disease, severely deforming arthritis (which included patients with axial disease) and rheumatoid-like disease. Later, Moll and Wright described five subgroups, as described in **Box 2** [1]. Since 1973, minor modifications have been made to the Moll and Wright subgroups by a number of authors, including Gladman and colleagues and Torre-Alonso and colleagues [2,5]. Rather more drastic modifications have been proposed by Helliwell and colleagues and Veale and colleagues [3,23].

Gladman expanded the five subgroups to seven: distal disease (DIP only affected), oligoarthritis (<4 joints), polyarthritis, spondylitis only, distal plus spondylitis and oligoarthritis plus spondylitis, polyarthritis plus spondylitis. In this cross-sectional study, 33% of the 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 also concluded that, since DIP arthritis occurs in any other subgroup, this particular category is not valid but otherwise distinguished the other four Moll and Wright categories.

Box 2. The subgroups described by Moll and Wright in 1973 [1].

- Predominant distal interphalangeal joint disease (5%)
- Asymmetrical oligoarthritis (70%)
- Polyarthritis (15%)
- Spondylitis (5%)
- Arthritis mutilans (5%)

The frequency of each of these subgroups is given as a percentage (in brackets).

Wright was later the senior author on a paper from Leeds, UK, that suggested an alternative, simplified classification. Using scintigraphy to identify the distribution of both clinically apparent disease and subclinical disease, a three-subgroup classification was suggested: peripheral polyarthritis, spondoarthritis and synovitis/acne/pustulosis/hyperostosis/osteomyelitis (SAPHO) – because of an appreciable incidence of extra-articular disease seen on scintigraphy. However, Veale and colleagues concluded that the peripheral arthritis group was too broad, containing patients with a symmetrical polyarthritis (SP) and an asymmetrical oligoarthritis (AO), which may differ with respect to deforming arthritis and radiographic erosive disease. They also agreed with the notion that DIP involvement did not require a separate category and concluded with the following three-group classification: asymmetrical oligoarthritis, symmetrical polyarthritis and predominant spondylitis.

However, it could be argued that there is no useful purpose served by distinguishing the different patterns of peripheral joint involvement and that articular disease in psoriatic arthritis should be classified as either axial or peripheral [24]. Arguments both for and against can be adduced.

First, to be useful from a clinical and prognostic point of view, subgroup classification ought to be stable over time. Although the study by Helliwell and colleagues suggested that this was so, Jones and colleagues found frequent progression from an oligoarticular pattern at presentation to a polyarticular pattern at the final assessment [6], and this was further corroborated by Marsal and colleagues [25]. On the other hand, Kane and colleagues found polyarthritis common at presentation but not at follow up, probably as a result of treatment [26].

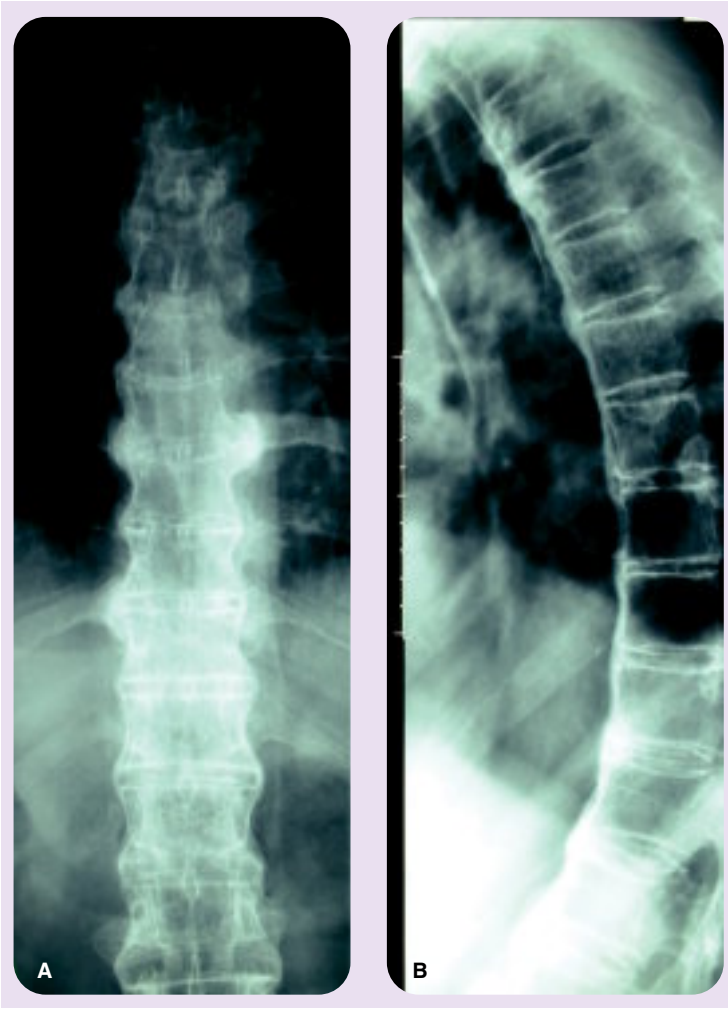
Peripheral disease pattern may change with treatment, but subgroup definition may also be a function of the way joint involvement is assessed. Clinical examination is a relatively insensitive way of identifying articular involvement – the use of other modalities, such as X-rays, bone scintigraphy, color Doppler ultrasound and magnetic resonance imaging (MRI), suggest that patterns of articular involvement are quantitative rather than qualitative [27]. In this way, different methods of evaluation will produce different patterns of joint and entheseal involvement with the trend in favor of accumulating involvement: what appears oligoarticular by one method may be polyarticular by another.

There is also evidence of instability in the axial subgroup. First, the longer the duration of disease the more likely axial involvement will be. Second, axial involvement may be apparent on, for example, MRI when clinically absent [28]. Third, the definitions previously used for ankylosing spondylitis – such as the modified New York criteria – may not be applicable to psoriatic arthritis as spinal changes may develop in the absence of sacroiliac disease (**Figure 2**) [14,29].

One of the main reasons to form subgroups is that they might behave differently over time, either in terms of natural history or response to treatment. With respect to the first of these points, data from the Toronto group originally found that the number of inflamed joints at presentation was an important predictor variable for long-term damage [30]. In a later extension of this study, the significant variables in the final model included the number of actively inflamed joints (odds ratio: 1.04), functional class (1.50), damage index (2.23), high number of disease-modifying antirheumatic drugs (DMARDs) use (1.83) and use of steroids (1.89) [31]. These studies are reassuring. In the clinic, it is appropriate to treat the patients with the most severe disease most aggressively. Therefore, those with polyarticular disease who are not functioning well will be targeted for early and intensive therapy, but further work is required to test the efficacy of this practice, given that the polyarticular subgroup incorporates a wide range of severity. Since those patients destined to develop arthritis mutilans will almost certainly be in this group, it will be of interest to see if an aggressive treatment strategy will eliminate this devastating condition.

In this respect, therefore, it is important to distinguish between oligo- and polyarthritis at presentation, even though patients change subgroup with time and treatment. With respect to treatment, it may be possible to select subgroups by their response to different drugs. It is clear that sulphasalazine and methotrexate work differently for peripheral manifestations compared with axial manifestations in spondyloarthropathies [32], so it is reasonable to at least examine this possibility by separately analyzing people with axial disease and peripheral disease. However, the recently introduced antitumor necrosis factor (TNF) drugs appear to be beneficial for all aspects of the disease, including SAPHO, suggesting that, at this level, there is no worth in distinguishing between subgroups [33,34].

Figure 2. Changes typically seen in the spine in psoriatic arthritis.



Examples of marginal, nonmarginal syndesmophytes are seen, together with paravertebral ossification. Spondylitis may occur in the absence of sacroiliitis in psoriatic arthritis.
Reproduced with permission from [39].

Are any other data of any help in this regard? Although psoriatic arthritis is classified as one of the spondyloarthropathies, the frequency of human leukocyte antigens (HLA) varies within the different subgroups (Table 3). A consistent association between HLA-B27 and spinal involvement has been demonstrated, especially with pure axial disease [35,36]. Other associations are weaker, although there has been a recent interest in class II HLA associations and the more severe forms of polyarthritis. Gladman originally demonstrated an association between DR4 and symmetrical polyarthritis resembling RA, and more recently the Bath group have shown that this is probably a severity marker associated with the shared epitope of DRB1, as in RA [37]. Interestingly, the presence of anticyclic citrullinated peptide (CCP) antibodies in psoriatic arthritis is associated with the presence of the shared epitope and disease severity and activity scores [38]. The HLA data therefore support the concept of peripheral and axial subgroups with the shared epitope acting as a marker for severe disease.

If the concept of subgroups is abandoned, as suggested by Taylor and colleagues, classification criteria become simplified but therapeutic trials remain problematic because of the possibility of differential treatment response between, for example, axial and peripheral groups. Furthermore, the current development of treatment guidelines and the adoption of validated, composite disease activity and outcome measures will face complicated algorithms to incorporate all the necessary aspects of the disease: it will be a challenge to synthesize these without considering, at least, two subgroups. On the other hand, cases of psoriatic arthritis often have combined axial and peripheral disease so that the idea of composite measures becomes feasible. This will be the challenge for the next few years.

Conclusions

Moll and Wright's 1973 criteria, although not validated, have been used for over 30 years in clinical trials and observational studies of psoriatic arthritis. The criteria, although simple to use, lack specificity. None of the other proposed classification criteria, except Fournié, have been validated. The new CASPAR criteria are derived from patient

Table 3. HLA associations and subgroups of psoriatic arthritis.

	Spondylitis	Symmetrical polyarthritis resembling RA	Distal interphalangeal predominant disease	Oligoarthritis
B27	62	15	41	9
B38	0	12	0	5
CW6	50	15	18	23
DR4	25 - 40	61	53	18

HLA: Human leukocyte antigen, RA: Rheumatoid arthritis.
Figures are percentages derived from [35,36].

data and are robust, with high sensitivity and specificity, but further validation is required. Nevertheless, the CASPAR criteria are now ready to use in clinical trials and epidemiological studies.

Moll and Wright originally described five subgroups of psoriatic arthritis, but the relative frequency and utility of these is disputed. The commonest modification has been to divide the disease into axial and peripheral manifestations. Splitting the peripheral arthritis into oligo- (less than five joints) and polyarthritis remains contentious, as the pattern of peripheral arthritis may change with time and treatment. However, there is useful prognostic information to be gleaned from the peripheral pattern at presentation and, until further data become available, at least two subgroups should continue to be used. It is also important to continue to collect all other relevant data, including clinical features such as distal interphalangeal joint involvement, enthesitis and dactylitis as future developments in taxonomy may encompass these features.

Executive summary

Classification – Moll & Wright

- Moll and Wright's 1973 criteria, although not validated, continue to be used in clinical trials and observational studies of psoriatic arthritis. The criteria are simple to use and specify three conditions: the presence of psoriasis, an inflammatory arthritis and a (usually) negative test for rheumatoid factor.

Other criteria

- Numerous other classification criteria have been proposed. All but one are not based on actual patient data; the one that is based on patient data (Fournié) includes human leukocyte antigen (HLA) status as an item. These other classification criteria are, generally speaking, more specific than those of Moll and Wright. This is accomplished by the inclusion of clinical and radiological features thought to be characteristic of psoriatic arthritis, such as dactylitis, enthesitis and spondylitis.

CASPAR criteria

- The ClASsification of Psoriatic ARthritis (CASPAR) study group consisted of 32 rheumatology centers worldwide. Data were collected to a standard format on consecutive clinic attendees with psoriatic arthritis (total included: 588) and the next case of inflammatory arthritis (total: 536). Over 70% of the controls had rheumatoid arthritis, and a further 13% ankylosing spondylitis. The composition of cases and controls, with cases identified by rheumatologists acknowledged to be leaders in the field, enabled appropriate statistics to produce robust criteria with high sensitivity and specificity.
- The CASPAR criteria still need further validation work. They are not suitable for early disease and some modification will be required for this purpose. The definition of arthritis, spondylitis and enthesitis in the controls will need some clarification. Furthermore, the CASPAR criteria do not include a spinal feature, and this may prove problematic, although inflammatory spinal disease is one of the prerequisite clinical features (Box 2).

Categorization – Moll & Wright subgroups

- Moll and Wright described five subgroups (frequencies in brackets): asymmetrical oligoarthritis (70%), symmetrical polyarthritis (15%), spondylitis (5%), distal interphalangeal predominant (5%) and arthritis mutilans (5%).

Other subgroup classifications

- A number of other authors have suggested modifications to this schema. The commonest modification has been to divide the disease into axial and peripheral manifestations. Distal interphalangeal disease is rarely seen alone and can occur in any of the other types and arthritis mutilans is a severity marker rather than a distinct subgroup.
- Splitting the peripheral arthritis into oligo- (less than five joints) and polyarthritis remains contentious. The pattern of peripheral arthritis may change, with time and with treatment, and more sensitive imaging modalities suggest that the distinction is probably fallacious.
- On the other hand, there is useful prognostic information to be gleaned from the peripheral pattern at presentation, and human leukocyte antigen data may justify maintaining a subgroup classification that has at least three categories: axial, oligoarthritis and polyarthritis.
- Future challenges include developing disease outcome and activity measures which take into account all the relevant aspects of this heterogenous disease.

Future perspective

The CASPAR criteria now require further development, particularly with respect to early disease and to the definition of what clinical features constitute inflammatory musculoskeletal disease in this context. Both these aspects are currently under study in several centers. The development of biomarkers for psoriatic arthritis will also help in the process of classification and separation from the two main confounders: RA and ankylosing spondylitis. More longitudinal data are required on the utility of subgroup classification. Further imaging studies may provide useful information on subclinical peripheral and axial disease and may emphasize that the current subgroup classification is purely quantitative rather than qualitative. We are also likely to see a good deal of effort in developing composite disease outcome and activity measures which take into account all the relevant aspects of this heterogenous disease.

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