Developing Classification Criteria for Peripheral Joint Psoriatic Arthritis. Step I. Establishing Whether the Rheumatologist's Opinion on the Diagnosis Can Be Used as the "Gold Standard"

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ABSTRACT. ***Objective.*** The study of psoriatic arthritis (PsA) is hampered by the absence of a widely accepted, validated case definition. We investigated whether the physician's opinion can be used as a gold standard when developing classification criteria for peripheral joint PsA.

Methods. UK rheumatologists who had published on PsA and attendees at 3 international meetings on PsA held in the UK were polled by questionnaire. There were 3 phases. The first questionnaire asked whether rheumatologists believed in the construct of PsA. The second survey developed a list of features thought to distinguish patients with PsA from other forms of peripheral arthritis. The final phase was development of a series of 61 "paper" patients with various combinations of the features of PsA. The paper patients were assessed by 15 rheumatologists who were asked whether, in their opinion, the patient had PsA. Latent class analysis was used to identify subgroups of patients and cross-tabulations were used to identify which clinical and laboratory features were associated with each subgroup.

Results. Rheumatologists agreed on the construct of PsA and that not all patients with psoriasis and an inflammatory polyarthritis have PsA. Latent class analysis identified 3 classes, corresponding to definite PsA; a middle group that was very likely to be given a diagnosis of PsA by some rheumatologists (high diagnosers), but unlikely to be given the diagnosis by others (low diagnosers); and a third group corresponding to "probably not PsA."

Conclusion. For the group of patients with "definite PsA" the physician's opinion can be taken as the gold standard when developing classification criteria. However, for patients in the "middle group" there will always be disagreement with the gold standard whether the standard is based on the opinion of the high diagnosers or the low diagnosers. (J Rheumatol 2006;33:552–7)

Key Indexing Terms:
CLASSIFICATION CRITERIA PSORIATIC ARTHRITIS

The study of the epidemiology, treatment, and prognosis of psoriatic arthritis (PsA) is severely hampered because there is no widely accepted, validated case definition. The absence of an accepted case definition is, in part, due to controversy about the nature and even existence of PsA. It is well established that psoriasis and inflammatory arthritis occur together more often than would be expected by chance[1]. However, obesity and osteoarthritis (OA) occur together more often than would be expected by chance, but this does not mean that "obese arthritis" is a distinct disease entity; it is just that obesity is a "visible" risk factor for OA. Similarly, psoriasis could be a visible trigger for inflammatory polyarthritis, and patients may then have the clinical features of whatever arthritis they may be predisposed to [usually rheumatoid arthritis (RA) or a spondyloarthropathy]. However, patients with psoriasis and peripheral arthritis are less often rheumatoid factor-positive than other patients with RA[2]. Various other clinical features such as nail dystrophy, dactylitis, and distal interphalangeal (DIP) joint involvement have been observed to occur more frequently in patients with inflammatory polyarthritis and psoriasis than in those without psoriasis. There is thus a general view among rheumatologists that PsA is a distinct disease entity.

It is also generally agreed that there is no single clinical, pathological, or radiological feature that is unique to PsA. The

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same is true for almost all other rheumatological conditions. The development of a case definition therefore has to be based on some other "gold standard" or conceptual construct. The development of classification criteria in rheumatology has generally taken the "physician's opinion" as the gold standard. The underlying assumption is that rheumatologists share a common view (or construct) on what constitutes the disease in question.

Previous attempts have been made to develop classification criteria for PsA (Table 1). None has found widespread acceptance, either because other rheumatologists disagreed with them or because they were presented in a format that could not easily be applied[2]. Newer data-driven methods of classification criteria development are now available and could be applied to the study of PsA[10-12]. However, we felt that it was important, as a first step, to establish whether rheumatologists do have a shared construct of what constitutes PsA. We chose to test this in rheumatologists with a special interest in PsA since they would be most likely to be involved in developing classification criteria. We also chose to look only at peripheral arthritis in PsA as the definition and construct of axial disease is probably a separate issue[13]. If experts do share a construct, and the construct can be defined, it will then be possible to establish whether patients who satisfy this construct have different demographic characteristics, different response to treatment, or different prognosis — in other words whether PsA is truly a distinct disease entity. It will also establish whether it is reasonable to use the physician's diagnosis as the starting point for the development of a more robust set of criteria.

MATERIALS AND METHODS

This study had 3 phases.

Phase I. The aim of Phase I was to establish whether consultant rheumatologists believe that PsA is a distinct disease entity. This phase was conducted in June 1998 at a UK meeting on PsA. A questionnaire was circulated to all those present who were medically qualified. It asked 2 questions: (1) Do you believe that there is a separate disease entity of psoriatic arthritis? (2) Do you believe that all patients with psoriasis and an inflammatory arthritis have psoriatic arthritis? The questionnaire also gave a list of features (taken from existing PsA criteria sets and other published literature) and asked participants which they thought would favor a diagnosis of PsA. They were also asked to suggest other features.

Phase II. The second phase aimed to identify a core set of features of PsA that could be agreed on by rheumatologists. A questionnaire was developed with 5 parts. It asked about the definition of "psoriatic," the definition of "arthritis," features that help to distinguish PsA from RA, features that help distinguish PsA from reactive arthritis (ReA), and the radiological features of PsA. The items included under these headings were based on the responses to Phase I and a review of the literature. The questionnaire was sent by mail to the 18 consultant rheumatologists who had participated in Phase I. In addition we conducted a Medline search and identified 11 other UK consultant rheumatologists who had published on PsA in the previous 10 years. The questionnaire was also sent to them.

Phase III. The aim of Phase III was to explore whether there was consensus on the combinations of features that might lead to a diagnosis of PsA.

Variables in the Phase II questionnaires on which at least 50% of respondents agreed were considered to be potential discriminators between PsA and other forms of peripheral arthritis. A form was prepared that included these items, and it was circulated to 13 rheumatologists who had been present at the UK Psoriatic Arthritis Meeting in 2000 at which the results of Phase I and II had been presented. They were asked to complete these forms for up to 10 of their patients who might be considered to have peripheral joint PsA. They were asked to include some patients whom they considered had "definite PsA," but at least half the forms should concern patients in whom the diagnosis was debatable (for example, these might be patients who were rheumatoid factor-positive). The consultants were asked to complete a 10 cm visual analog scale (VAS) that indicated the certainty of their diagnosis of PsA: 0 cm represented complete certainty the patient did not have PsA, and 10 cm represented complete certainty the patient did have PsA.

Ten of these 13 consultants responded, submitting information on 111 patients. Some of the vignettes were very similar to one another (these were mainly the "definite PsA" cases). A maximum of 2 of any one type of case was selected, leaving a total of 61 paper patients. The paper patients were divided into 2 sets, each set representing the whole spectrum from "definite PsA" to "definitely not PsA" based on the original rheumatologist's opinion. The vignettes were anonymized and copied (minus the diagnosis and the VAS on diagnostic certainty from the original rheumatologist) and sent to 18 rheumatologists. They comprised the 10 who had submitted cases plus 8 others who had expressed an interest in participating, either following Phase II

Table 1. Main characteristics of existing classification criteria for PsA.

	Moll and Wright[2]	Bennett[3]	Vasey and Espinoza[4]	Gladman[5]	ESSG[6]	McGonagle[7]	Fournie[8]
Evidence of psoriasis	✓	✓	✓	✓	✓	✓	✓
Peripheral joint inflammatory arthritis	✓	✓	✓	✓	✓	✓	✓
DIP involvement	—	✓	✓	—	—	✓	✓
RF-negative	✓	✓	✓	—	—	✓	✓
Clinical sacroiliitis	✓	—	—	✓	✓	✓	✓
Clinical spondylitis	✓	—	✓	✓	✓	✓	✓
Dactylitis	—	✓	—	—	—	✓	✓
Radiographic features	—	✓	—	—	—	✓	✓
HLA	—	—	—	—	—	—	✓
Family history of psoriasis	—	—	—	—	—	✓	✓
Other features	—	Absence of nodules Asymmetry	—	Excluding other arthritides	Asymmetrical lower limb pattern	—	—

DIP: distal interphalangeal joint, RF: rheumatoid factor. HLA: human leukocyte antigen, RF: rheumatoid factor, ESSG: European Spondylarthropathy Study Group. Adapted from Taylor[9].

or at the UK Psoriatic Arthritis Meeting in 2000. All 18 participating consultants had a special interest in PsA.

Each participating consultant was sent one of the 2 sets of paper patients. These consultants were told how the paper patients had been derived and were asked to say whether or not they thought each paper patient had PsA. One clinician (SMJ) rated both sets of paper patients.

Statistical methods for Phase III. Assessing agreement. The referring consultant and the assessing consultant were each asked to state whether or not they believed that the patient had PsA. Agreement between the consultants was assessed using Cohen's kappa[14].

Predicting the diagnosis. The probability that a given patient would be classified as having PsA was assessed using logistic regression. The regression equation was:

$$\text{Logit}\,(p_{ij}) = b_i + c_j$$

where p_{ij} was the probability that the i^{th} patient was classified has having PsA by the j^{th} consultant, c_j was a term to capture differences between consultants, and b_i was a term to capture differences between patients. The b_i terms were treated as discrete random effects (latent classes), and the c_j terms as fixed effects. A likelihood ratio test was used to determine the number of b_i terms to include; more latent classes were added until adding a class no longer showed a significant improvement in the fit of the model. This means that we suppose that b_i had a limited number of values in the population (the classes), but that we are unable to measure the values directly in an individual (which makes them latent). All we can do is assign to individuals the probability that they belong to each of the classes.

The clinician who rated all 61 subjects was used as the reference for the c_j terms. A likelihood ratio test was used to determine whether including the c_j terms improved the fit of the model significantly. The model was then simplified by assigning clinicians with similar values of c_j to a single group. This new model was compared to the more complex model using a likelihood ratio test: if the reduction in the goodness of fit of the model was not statistically significant, the simpler model was preferred. These random effects logistic regression models were fitted using the generalized linear latent and mixed models (GLLAMM) module of Stata 8.0.

Patients were assigned to a given latent class if the probability of belonging to that class was 0.9 or more. The prevalence of particular symptoms and signs in each class was then calculated.

RESULTS

A total of 23 people (18 consultants and 5 trainees) responded to Phase I. All stated that they believed in the disease entity of PsA and 22 (including all 5 trainees) stated that they did not believe that all patients with psoriasis and an inflammatory arthritis have PsA. There was much less agreement about which particular features might discriminate between a diagnosis of PsA and RA or ReA in a patient with peripheral arthritis, suggesting different concepts of what constitutes PsA.

Twenty-one (72%) people responded to the questionnaire of Phase II after one reminder. Many of the respondents would accept the label "psoriatic" in the absence of clinically obvious psoriasis if the patient had a previous diagnosis of psoriasis from a dermatologist (90%) or general practitioner (57%), had a history of psoriasis in a first-degree relative (52%), or had nail dystrophy (76%). No particular combination of these features was accepted by more than 5 (24%) respondents. With regard to the definition of "arthritis," respondents felt that the affected joints should be either swollen (67%) or tender and swollen (100%).

In the presence of psoriasis and peripheral arthritis the following features were felt to favor a diagnosis of PsA over RA or ReA by more than 50% of respondents: DIP joint involvement, family history of PsA, nail dystrophy, and dactylitis. The respondents were much more uncertain about the features that would distinguish PsA from ReA than those that would distinguish PsA from RA (Table 2). The following radiological features were felt to be characteristic of PsA by more than 50% of respondents: entheseal spurs/erosion, DIP disease, and "pencil in cup" deformity (Table 3).

Fifteen of the 18 rheumatologists returned the completed questionnaires on the paper patients in Phase III. In total there were 487 responses on the 61 paper patients.

Agreement between clinicians. Agreement was universal that 34 of the 61 paper patients had PsA and that 2 did not. For the remaining 25 subjects, the proportion of clinicians who believed that they had PsA is shown in Table 4. The overall kappa statistic was 0.45 (95% CI 0.40, 0.50), which represents moderate agreement.

Predicting diagnosis. The log-likelihoods for the discrete latent variable models with 2, 3, or 4 latent classes are given in Table 5. There is a clear improvement in the fit of the model when increasing from 2 to 3 latent classes, but not when increasing from 3 to 4 latent classes. Therefore, subsequent models all had 3 latent classes. It was possible to assign 51 patients to one of these latent classes. There were substantial differences between clinicians in the probability of giving a diagnosis of PsA: the fit of the model improved significantly when including the term for consultants. However, it appeared that the consultants fell into 2 groups: one group with similar probabilities of diagnosing PsA to the reference consultant, and one group who were considerably less likely to do so. Combining the consultants into 2 groups (9 high diagnosers and 6 low diagnosers) did not reduce the fit of the model significantly. The predicted and observed proportions of positive diagnoses in each of the 3 latent classes are given in Table 6. For patients in Group 1, both groups of consultants were likely to give a diagnosis of PsA, while for subjects in Group 3, both groups of consultants were unlikely to diagnose PsA. The patients in Group 2 were commonly believed to have PsA by the "high diagnosing" group of consultants, but not by the "low diagnosing" group. The median diagnostic certainty of the rheumatologists who had originally supplied the details of the paper patients was: Group 1, 9.5 [interquartile range (IQR) 8, 10]; Group 2, 5.5 (IQR 2, 7.5); and Group 3, 5 (IQR 2, 6).

Prevalence of clinical features in the latent classes. Table 7 shows the prevalence of those clinical features that differed significantly between the 3 groups, and some that had marked differences but were not statistically significant because the prevalence of the feature was low. Because of the very strong correlations between some of the features, it was not sensible to produce multivariate models to predict class membership from the features. However, there were 5 clinical features that predicted the latent classes — presence of psoriasis, number

Table 2. Clinical and laboratory features that may distinguish psoriatic from other forms of peripheral arthritis. Results from Phase II.

	Distinguishing PsA from RA A patient with psoriasis presents with a peripheral arthritis. The differential diagnosis lies between PsA and RA. Given the following additional factors, which diagnosis would you favor:			Distiguishing PsA from Reactive Arthritis (ReA) A patient with psoriasis presents with a peripheral arthritis. The differential diagnosis lies between PsA and ReA. Given the following additional factors, which diagnosis would you favor:		
	RA (%)	PsA (%)	Don't Know (%)	ReA (%)	PsA (%)	Don't Know (%)
RF-positive: titer 1/40	7 (33.3)	6 (28.6)	8 (38.1)	2 (9.5)	1 (4.8)	18 (85.7)
RF-positive: titer 1/80	19 (90.1)	0	2 (9.5)	1 (4.8)	1 (4.8)	19 (90.1)
Symmetry (≥ 50% of the involved joints are involved symmetrically)	14 (66.7)	2 (9.5)	5 (23.8)	0	9 (42.9)	12 (57.1)
DIP joint involvement	0	20 (95.2)	1 (4.8)	0	18 (85.7)	3 (14.3)
Family history of RA	12 (57.1)	1 (4.8)	8 (38.1)	0	2 (9.5)	19 (90.1)
Family history of psoriasis	0	18 (85.7)	3 (14.3)	0	15 (71.4)	6 (28.6)
Inflammatory low back pain	0	20 (95.2)	1 (4.8)	2 (9.5)	5 (23.8)	14 (66.7)
Oligoarthritis (≤ 4 joints)	4 (19.1)	10 (47.6)	7 (33.3)	0	5 (23.8)	16 (76.2)
Asymmetrical	0	20 (95.2)	1 (4.8)	1 (4.8)	4 (19.1)	16 (76.2)
Polyarthritis (> 4 joints)						
Symmetrical	15 (71.4)	3 (14.3)	3 (14.3)	0	11 (52.4)	10 (47.6)
Asymmetrical	0	19 (90.1)	2 (9.5)	6 (28.6)	1 (4.8)	9 (42.9)
Nail dystrophy						
Fingernails	0	21 (100)	0	0	18 (85.7)	3 (14.3)
Toenails	0	14 (66.7)	7 (33.3)	0	13 (61.9)	8 (38.1)
Dactylitis	0	21 (100)	0	1 (4.8)	12 (57.1)	8 (38.1)
HLA-B27-positive	0	19 (90.1)	2 (9.5)	8 (38.1)	1 (4.8)	12 (57.1)
Uveitis	0	20 (95.2)	1 (4.8)	8 (38.1)	1 (4.8)	12 (57.1)
Arthritis mutilans	0	16 (76.2)	5 (23.8)	0	19 (90.1)	2 (9.5)

Table 3. Radiological features that may distinguish psoriatic from rheumatoid arthritis. Results from Phase II.

In your opinion, what are the characteristic radiological features of psoriatic arthritis? (i.e., that do not occur in RA)*	N (%)
Enthesitis	1 (4.8)
Sacroilliitis	11 (52.4)
DIP disease	12 (57.1)
Pencil in cup	12 (57.1)
Entheseal spurs/erosion	18 (85.7)
Spinal fusion	3 (14.3)
Asymmetry	1 (4.8)
Erosions in toe IP joints	1 (4.8)
Periosteal thickening	5 (23.8)
New bone formation	5 (23.8)
Whittling	3 (14.3)
Bony ankylosis	3 (14.3)
Syndesmophytes	3 (14.3)
In your opinion, what characteristic radiological features of RA do not occur in PsA?**	
Atlantoaxial subluxation	3 (14.3)
Juxtaarticular osteoporosis	8 (38.1)
Periarticular erosions	2 (9.5)

* No responders considered juxtaarticular erosions to be a characteristic radiological feature of PsA. ** No responders considered erosions, crico-arytenoid involvement, protrusio, avascular necrosis, geodes, or radial styloid erosions to be characteristic radiological features of PsA. DIP: distal interphalangeal joints.

of affected joints, dactylitis, and rheumatoid factor and antinuclear antibody status (Table 8).

DISCUSSION

It is important to note that this study did not include patients with psoriasis and spondylitis alone. Rheumatologists agree that peripheral joint PsA is a separate disease entity and that not all subjects with psoriasis and peripheral joint inflammatory arthritis have PsA. There is general agreement on what might be termed "definite peripheral joint psoriatic arthritis"

Table 4. Percentage of consultants who thought that each of the 61 paper patients had a diagnosis of PsA. Results from phase III.

Does the patient have psoriatic arthritis? % Yes	No. of Cases
0	2
11	1
22	2
29	1
33	1
43	1
56	3
57	1
67	1
71	5
78	2
83	1
86	3
89	3
100	34
Total	61

Table 5. Log-likelihoods for logistic regression models with different numbers of latent classes and different handling of between-consultant differences. Results from Phase III.

No. of Latent Classes	No Consultant Terms	Term for Each Consultant	Two Groups of Consultants
2	–180.9	–162.9	–166.2
3	–173.4	–154.4	–157.6
4	–173.4	–154.1	–157.4

Table 6. Frequency of diagnosis of PsA in each latent class (%).

	Latent Class		
Consultant Group	1, n = 34	2, n = 12	3, n = 5
High Diagnosers			
Predicted	0.99	0.85	0.25
Observed	1.00	0.85	0.14
Low Diagnosers			
Predicted	0.96	0.46	0.05
Observed	1.00	0.36	0.06

(latent class 1); 34 of the 61 paper patients fell into this group. We deliberately biased the composition of the Phase III sets of patients toward those in whom there was diagnostic uncertainty. It is likely that, in an average rheumatology clinic, a much greater proportion of patients would have "definite disease."

A substantial subgroup of the remaining patients were considered to have PsA by one group of physicians, but not by a second group. These are the patients that will create problems in using a physician's opinion as the gold standard: "low diagnosers" would disagree with the gold standard if it was based on a "high diagnoser" and vice versa.

A limitation of our study is the small number of paper patients. The aim of this exercise, however, was to establish whether or not there is agreement among consultant rheumatologists on what constitutes PsA. It was not our aim to develop or evaluate a set of classification criteria for PsA. We felt it was important to know, before anyone else attempts the tricky task of developing such classification criteria, whether it is reasonable to use the physician's diagnosis as the gold standard (as was done in the development of the American College of Rheumatology criteria for RA and systemic lupus erythematosus, for example).

So what is the way forward? If future researchers wish to develop classification criteria for PsA using the physician's diagnosis as the gold standard then there are 2 possible approaches. One (which might be appropriate for inclusion criteria for clinical trials) is to focus only on the patients in whom there is diagnostic certainty and to develop criteria in these. This will not, for example, comprise all patients with psoriasis plus inflammatory arthritis. The alternative approach is to acknowledge the agreed diagnostic uncertainty and to allow at least 2 categories in the criteria (say, definite and possible). However, the second latent class did not comprise subjects about whom the physicians were less certain of their diagnosis. They were subjects over whom physicians disagreed more about the diagnosis, so one individual's assessment of "definite" versus "possible" may not correspond to another's. It is important to note that consultants in this study fell into 2 distinct groups — one with a consistently high probability of diagnosing PsA and one with a consistently low probability of diagnosing PsA. It will be important to take this into account in any study using the physician's diagnosis as the gold standard.

Just because consultants agree does not mean they are right! We did, in any case, select consultants who were most likely to agree since they had either attended national meetings on PsA or published reports on the disease. Rheumatologists whose main interest is, for example, RA might have very different views. We focused on rheumatologists with a special interest in PsA because they would be most likely to be involved in developing classification criteria for PsA in the future. A more independent way forward would be to collect data prospectively on a very large group of patients with inflammatory polyarthritis of all etiologies and see whether some or all of those with a history of psoriasis have a different prognosis or response to treatment.

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Table 7. Prevalence of clinical features in the patients included in each latent class (%). Results from Phase III.

Clinical Feature	Latent Class 1, n = 17	Latent Class 2, n = 34	Latent Class 3, n = 5	p for Differences
Psoriasis				
Any	100	83	20	< 0.001
Diagnosed by general practitioner	71	67	0	0.009
Diagnosed by rheumatologist	79	75	0	0.001
Fingernail involvement				
Any	68	17	20	0.003
Diagnosed by rheumatologist	56	17	0	0.009
Diagnosed by dermatologist	42	0	20	0.02
Dactylitis	44	0	0	0.005
RF > 1:40	0	0	40	< 0.001
RF > 1:80	3	8	40	0.02
Antinuclear antibody > 1:100	3	25	0	0.04
No. of joints ever affected				
1	0	8	0	
2–4	15	50	0	
5 or more	85	42	100	0.02
No. of joints affected at one time				
1	0	17	0	
2–4	36	42	0	
5 or more	64	42	100	0.05
Family history of RA	9	33	0	0.07
Uveitis/iritis	21	0	0	0.13
Sacroiliitis/spondylitis	44	17	0	0.06
HLA-B27	31	0	0	0.22
Periostitis	29	0	0	0.05
"Pencil in cup" deformity	9	0	0	0.5

RF: rheumatoid factor.

Table 8. Number of patients with each combination of clinical features in each latent class. Resutls from Phase III.

Psoriasis	2-4 Joints Ever Affected	5+ Joints Ever Affected	ANA > 1:100	Dactylitis	RF > 1:40	Latent Class 1	Latent Class 2	Latent Class 3
Yes	No	No	No	No	No	1	1	1
No	Yes	No	No	No	No	0	1	0
Yes	Yes	No	No	No	No	3	5	0
No	No	Yes	No	No	No	0	1	2
Yes	No	Yes	No	No	No	15	1	0
Yes	No	Yes	Yes	No	No	0	3	0
Yes	Yes	No	No	Yes	No	2	0	0
Yes	No	Yes	No	Yes	No	12	0	0
Yes	No	Yes	Yes	Yes	No	1	0	0
No	No	Yes	No	No	Yes	0	0	2

ANA: antinuclear antibody, RF: rheumatoid factor.

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