Patients Considered as Having Undifferentiated Peripheral Inflammatory Arthritis: A Systematic Review

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ABSTRACT. ***Objective.*** To systematically review the differential diagnosis and minimal clinical investigation used prior to making a diagnosis of undifferentiated peripheral inflammatory arthritis (UPIA).

Methods. A systematic literature search was performed for articles published between January 1950 and December 2008 in Medline and Embase, and for abstracts presented at the 2007 and 2008 meetings of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR). Studies including defined cohorts of patients with UPIA were retrieved according to predefined inclusion/exclusion criteria. Selected studies were systematically reviewed and relevant data extracted. Baseline characteristics were also recorded to obtain a clinical picture of patients classified as UPIA.

Results. Seventy-four articles were included. Of those, 52 reported baseline characteristics. Tremendous variation existed among studies, reflecting the different inclusion/exclusion criteria used. Rheumatoid arthritis, spondyloarthropathies, osteoarthritis, crystal arthritis, connective tissue diseases, and infections were the most common diagnoses of exclusion for UPIA and made up the other subsets of patients in cohorts with mixed populations. The baseline investigation undertaken prior to diagnosis of UPIA was reported in 7 articles. History, physical examination, tender and swollen joint count, rheumatoid factor, HLA-B27, erythrocyte sedimentation rate, C-reactive protein, and radiographs of hands and feet were the only items mentioned in at least 50% of the reports.

Conclusion. Studies of UPIA are heterogeneous. Few studies reported on the minimal clinical investigation necessary to arrive at a diagnosis of UPIA. Differential diagnosis usually consisted of the most common rheumatologic conditions but could be vast. (J Rheumatol 2010;38 Suppl 87:3–9; doi:10.3899/jrheum.101068)

Key Indexing Terms:
UNDIFFERENTIATED ARTHRITIS DIAGNOSIS INVESTIGATION

With the importance of early treatment being recognized, rheumatologists are seeing patients earlier and a fair proportion present with undifferentiated, peripheral, inflammatory arthritis (UPIA)[1]. Prognosis will vary and management of these patients represents a new challenge for rheumatologists.

The 2008-2009 3e (evidence, expertise, exchange) Initiative in Rheumatology (an evidenced-based approach for generating recommendations) addressed the subject of how to investigate and followup UPIA. The process of the 3e Initiative and the resulting 10 recommendations have been described in detail[2]. One of the 10 selected questions addressed the phase prior to establishing an operational diagnosis of UPIA. This question was divided into 2 parts: (1) Which differential diagnoses should be considered in inflammatory arthritis? and, (2) What are the minimal clinical, laboratory, and imaging investigations necessary to confirm an undifferentiated arthritis? Our objective was to systematically review the available literature to answer the question and help rheumatologists involved in 3e arrive at a consensus recommendation.

MATERIALS AND METHODS

A systematic literature review (SLR) was carried out in several steps following the updated guidelines for Cochrane systematic reviews[3].

Rephrasing the question. When conducting a SLR, the first step is to translate the clinical question into an epidemiological question based on the PICO method (Patients, Intervention/index test, Comparison, Outcome), or, in our case, the PIO method, as there was no Comparison[4]. Thus, Patients were defined as adults; there was no Intervention for part 1 of the question (differential diagnosis); for part 2, interventions were any clinical, laboratory, or imaging investigation (minimal investigation). Finally, Outcome was UPIA. We defined UPIA as any patient with clinically apparent joint

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swelling not fulfilling diagnostic/classification criteria for any other rheumatologic disorder after initial assessment. We also retained studies in which the population was mixed [e.g., UPIA + arthralgia, UPIA + early rheumatoid arthritis (RA)], but where a subgroup of UPIA could be clearly identified.

Literature search. We performed a systematic literature search of Medline (1950 to December Week 3 2008), Embase (1980 to 2008 Week 52), and the Cochrane Library, using a search strategy for "undifferentiated peripheral inflammatory arthritis" that was developed in collaboration with an experienced librarian. No language restrictions were made a priori in case the abstract could reveal relevant information (see Appendix I, available from: www.3eupia.com). We also searched the abstracts of the annual scientific meetings of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) from 2007 and 2008. Review articles were also examined to identify additional studies by hand-searching reference lists.

Study selection. First, one reviewer (EV) screened titles and abstracts of all retrieved references, excluding articles that were clearly not pertinent to our question. To make sure we were not missing any relevant articles, other bibliographic fellows involved in 3e were asked to identify all articles retrieved within their own search that included a well defined UPIA population. Second, the full text of selected articles was reviewed applying the following criteria: ≥ 18 years of age, distinct patients with UPIA (within a mixed population or not). Articles that did not fulfill the inclusion criteria or had insufficient data for analysis were excluded.

Data extraction and quality assessment. Two reviewers (EV, BK) independently extracted data. Discrepancies were resolved through discussion. First, to provide members of the 3e Initiative a picture of what kind of patients were considered to have UPIA in the literature, we extracted baseline clinical characteristics of the patients when available. In order to discern the potential differential diagnoses of UPIA, we looked at the diagnoses listed as exclusion criteria in the studies including only UPIA patients and at diagnoses of other groups in articles where the population was mixed, but included a well defined subgroup of UPIA patients (Figure 1A). Study quality was not assessed as we were looking only at baseline data and not at the study conclusion. To identify the minimal clinical, laboratory, and imaging investigations necessary to confirm a diagnosis of UPIA, we extracted the investigations mentioned as inclusion/exclusion criteria as well as the baseline investigations done in the early arthritis cohort from which some articles originated (Figure 1B).

Data analysis. Baseline characteristics that were continuous variables were most often reported as mean ± standard deviation (SD) so we chose to extract means and not medians. To present these characteristics, we calculated the weighted mean, since the number of patients included in each study varied widely. We presented the minimum and maximum mean to reflect the wide range of values across studies. Dichotomous variables were reported as number and percentage. For diagnoses reported as exclusion criteria or other baseline subgroups as well as the minimal clinical investigation, we calculated how frequently they were reported across studies in which these items were mentioned.

RESULTS

A total of 6953 references were identified by the systematic search strategy (see Appendix II, available from: www.3eupia.com). After screening of the title and abstracts, 225 articles were retrieved for full text review, of which 74 fulfilled the inclusion criteria. No congress abstract was included. Fifty-four had a mixed population and 20 included only patients with UPIA. Of those, 52 reported baseline characteristics[5-56], 13 (65%) of the 20 studies including only UPIA reported other diagnoses as exclusion criteria[10,17,24,29,33,36,42,44,51,57,58,59,60], and all studies (100%) with a mixed population described the other subgroups[5,6,7,8,9,11,12,13,14,15,16,18,20,21,22,23,25,26,27,28,30,31,34,35,37,39,40,43,45,46,50,52,53,54,55,56,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78]. In all, 18 studies reported the type of minimal clinical investigation performed[8,23,39,47,48,49,50,51,52,53,56,60,61,65,73,74,76,77].

Baseline characteristics. Baseline characteristics were reported in 52 studies, although studies did not necessarily report the same set of characteristics[5-56]. Table 1 presents the most commonly reported items. Overall, the weighted mean (range) age was 47.0 years (22.5–55.4), 59.3% (7–87) were women, and weighted mean disease duration was 8.8 months (1.7–38.5). The mean percentage of patients who were rheumatoid factor (RF)-positive was 24.2% (0–81%), and anti-cyclic citrullinated peptide antibody (anti-CCP)-positive was 21.4% (3.8–70.6%). The mean percentage of HLA-B27-positive patients was 25.8% (9.3–39%). Weighted mean for erythrocyte sedimentation rate (ESR) was 27.6 mm/h (12–52), and for C-reactive protein (CRP), 20.2 mg/l (5–91). Overall, 13.2% (0–35%) of patients presented with erosions.

Differential diagnoses. Thirteen (65%) of the 20 studies including UPIA reported other diagnoses only as exclusion criteria[10,17,24,29,33,36,42,44,51,57,58,59,60]. All 54 articles with a mixed population described their other subgroup, but 8 were from a cohort already described so they were excluded from this analysis[5,6,7,8,11,12,14,15,16,18,21,22,23,25,26,27,28,30,31,34,35,37,39,43,45,54,55,56,61,62,63,64,65,66,67,68,71,72,77,78]. Diagnoses that were mentioned as exclusion criteria in articles with a mixed population were also extracted. RA was the most frequently mentioned diagnosis in 77.6% of the studies (Table 2). The following are other differential diagnoses in order of frequency: reactive arthritis (ReA; 50%), osteoarthritis (OA; 44.8%), psoriatic arthritis (PsA; 41.4%), crystal arthritis (39.7%), spondyloarthropathies (SpA) as a group (37.9%), connective tissue diseases (CTD; 31%), septic arthritis (25.9%), and ankylosing spondylitis (AS; 25.9%). Less frequently mentioned diagnoses included sarcoidosis, trauma, polymyalgia rheumatica, Lyme disease, soft-tissue disorders, and malignancy, to name a few.

Minimal investigation. Of the 18 articles reporting on baseline investigation, 11 were duplicates of an already described cohort. This left 7 articles that reported on the minimal, baseline clinical investigation undertaken prior to inclusion as UPIA in their study/cohort[8,23,39,47,48,49,50,51,52,53,56,60,61,65,73,74,76,77]. History (including family history), disease duration, physical examination, tender and swollen joint count (TJC, SJC), rheumatoid factor, HLA-B27, ESR, CRP, and radiographs of hands and feet were the only items mentioned at least 50% of the time. Less commonly requested investigations included complete blood count, biochemistry, thyroid function test, glucose, liver function test, serum urate, C3, C4, immunoglobulin, anti-

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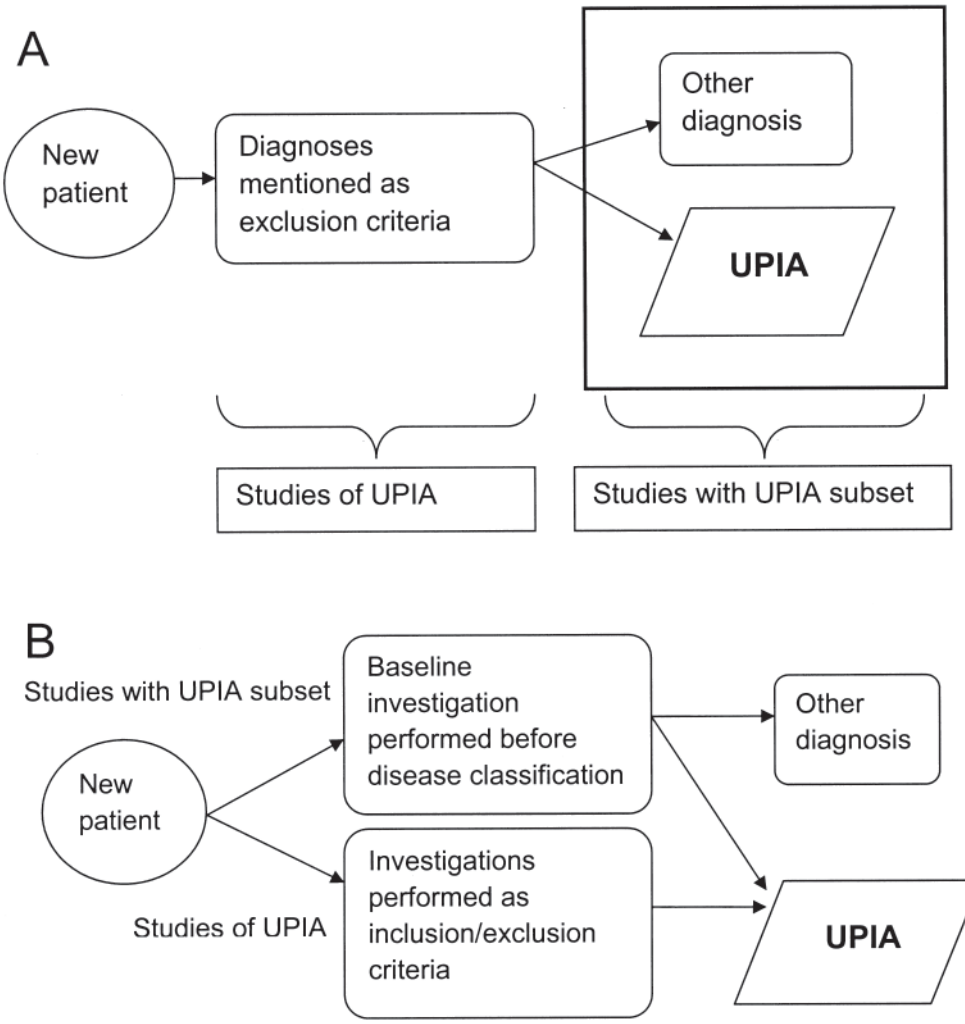

Figure 1. A. Strategy to answer the question about differential diagnosis. B. Strategy to answer the question about minimal clinical investigation.

nuclear antigen (ANA), anti-citrullinated peptide antibody (ACPA) or anti-CCP, HLA typing, extractable nuclear antigens (ENA), double-stranded DNA (dsDNA), and microbiologic assessment. Obtaining radiographs of the chest and/or other affected joints was also mentioned in some articles.

DISCUSSION

The term undifferentiated arthritis was first introduced to describe arthritis that could not be classified as RA or another definite inflammatory arthritis. It may represent the early phase of a specific disease, a condition that will remit spontaneously, or an entity by itself that will remain undifferentiated. As rheumatologists are seeing patients earlier, more and more patients are given the diagnosis of undifferentiated arthritis. Our systematic review evaluated the available evidence to help answer the question of what differential diagnoses should be excluded and what minimal investigations should be performed prior to diagnosing a patient with UPIA.

Our results reflect the tremendous clinical heterogeneity among patients with UPIA included in these studies. The baseline clinical characteristics varied widely. This is in part because many of the studies were actually trying to get patients with a specific disease at an early stage and hence had inclusion criteria that were created for that purpose. For example some studies were excluding patients who were RF-positive, while in others a positive RF was an essential inclusion criterion. It also reveals that the concept of undifferentiated arthritis can vary widely from one rheumatologist to another, making it very difficult to draw recommendations on the management of this evolving entity. Fortunately, over recent months, the ACR and EULAR have combined efforts to develop classification criteria for major inflammatory arthritis such as RA and axial and peripheral SpA that can be applied in early disease[79,80,81]. This will help standardize disease definitions and enable studies to assess treatment strategies in this group of patients in a more uniform manner.

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Table 1. Baseline clinical characteristics of patients with undifferentiated peripheral inflammatory arthritis.

Characteristic	No. of Studies	Total	Weighted Mean	Minimum	Maximum
Female, %	47	4028	59.3	7	87
Mean age, yrs	40	3443	47.0	22.5	55.4
Disease duration, mo	19	830	8.8	1.7	38.5
Swollen joint count	9	786	2.6	1	4.2
RF+, %	32	2948	24.2	0	81
Anti-CCP+, %	13	2277	21.4	3.8	70.6
HLA-B27+, %	14	689	25.8	9.3	39
ESR, mean	14	774	27.6	12	52
CRP, mean, mg/l	15	730	20.2	5	91
Patients with erosions, %	13	2039	13.2	0	35

RF: rheumatoid factor; CCP: anti-cyclic citrullinated peptide antibody; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 2. Frequency of the diagnoses mentioned as exclusion criteria in studies including undifferentiated peripheral inflammatory arthritis, or as other subgroups in studies with a mixed population.

Diagnosis	%
Rheumatoid arthritis	77.6
Reactive arthritis	50.0
Osteoarthritis	44.8
Psoriatic arthritis	41.4
Crystal arthritis	39.7
Spondyloarthropathies (SpA)	37.9
Connective tissue disease	31.0
Systemic lupus erythematosus	27.6
Septic arthritis	25.9
Ankylosing spondylitis	25.9
Sarcoidosis	15.9
Trauma	13.8
Polymyalgia rheumatica	13.8
Lyme disease	10.3
Soft-tissue disorder	6.9
Undifferentiated SpA	5.2
Malignancy-related	5.2
Hepatitis	3.4
Fibromyalgia	1.7
Endocrinologic origin	1.7
Systemic autoimmune diseases	1.7
Palindromic rheumatism	1.7

As expected, the list of potential differential diagnoses to exclude before confirming UPIA is long. In our review, the most commonly excluded diagnoses were RA, SpA, OA, crystal arthritis, CTD, and infection. Although these common conditions should be considered when seeing a patient with new-onset inflammatory arthritis, this list is far from exhaustive and their exclusion cannot definitively assure a correct diagnosis of UPIA. Rather, judgment should be guided by the patient's history, physical examination, and comorbidities, and aided by the results of baseline investigations. Further, the list of differential diagnoses will vary between patients due to geographic differences in the prevalence of diseases.

Clinical investigation was mentioned in only 7 articles. The most common reported investigations were history, physical examination, joint count, RF, ESR, CRP, and radiography of the hands and feet. Our findings compare with EULAR recommendations for management of early arthritis: "Exclusion of other diseases than RA requires careful history taking and clinical examination, and ought to include at least the following laboratory tests: complete blood cell count, urinary analysis, transaminases, and antinuclear antibodies[82]." However, UPIA remains a diagnosis of exclusion, and no test can rule it out, not RF or anti-CCP; in fact, apart from history and clinical examination, no other form of investigation is mandatory. The pretest probability is the most important factor in determining the utility of a test, and this will vary according to the phenotype of the patient and the context (prevalence of diseases in his area).

In our systematic review, we aimed to synthesize the differential diagnoses that should be considered, and summarize which minimal clinical investigations should be performed before a patient can be diagnosed with UPIA. Our results highlight the significant clinical heterogeneity of patients considered as having UPIA. We also found that the list of possible differential diagnoses can be extensive, but the most common were RA, SpA, OA, crystal arthritis, CTD, and infection. The minimal clinical investigation was infrequently reported and varied widely across studies.

In conclusion, UPIA should be regarded as a diagnosis of exclusion. The differential diagnoses are extensive and cannot be limited to a defined list and will vary according to patient history and physical examination. However, keeping in mind the major classes of disease (idiopathic, autoimmune, degenerative, infectious, malignancy, trauma, metabolic) can help ensure that no important diagnosis is omitted. No clinical investigation will ever exclude a diagnosis of UPIA. Hence, apart from history and clinical examination, no investigation can be deemed essential and should be based on the differential diagnosis of the individual patient. This conclusion has been incorporated as one of the recommendations of the 3e Initiative for investigation and

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followup of UPIA. Our review also highlights that articles on UPIA often include patients with other early, well defined rheumatic diseases or patients without presence of synovitis. This may have different implications for prognosis, and future studies should consider distinguishing between those patients. Moreover, it would be important to clearly define which diagnoses have been excluded and which investigations conducted, as these aspects were poorly reported.

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