Algorithm for Identification of Undifferentiated Peripheral Inflammatory Arthritis: A Multinational Collaboration Through the 3e Initiative

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ABSTRACT. ***Objective***. To develop an algorithm for identification of undifferentiated peripheral inflammatory arthritis (UPIA).

Methods. An algorithm for identification of UPIA was developed by consensus during a roundtable meeting with an expert panel. It was informed by systematic reviews of the literature used to generate 10 recommendations for the investigation and followup of UPIA through the 3e initiative. The final recommendations from the 3e UPIA Initiative were made available to the panel to guide development of the algorithm. The algorithm drew on the clinical experience of the consensus panel and evidence from the literature where available.

Results. In patients presenting with joint swelling a thorough evaluation is required prior to diagnosing UPIA. After excluding trauma, the differential diagnosis should be formulated based on history and physical examination. A minimum set of investigations is suggested for all patients, with additional ones dependent on the most probable differential diagnoses. The diagnosis of UPIA can be made if, following these evaluations, a more specific diagnosis is not reached. Once a diagnosis of UPIA is established, patients should be closely followed as they may progress to a specific diagnosis, remit, or persist as UPIA, and additional investigations may be required over time.

Conclusion. Our algorithm presents a diagnostic approach to identifying UPIA in patients presenting with joint swelling, incorporating the dynamic nature of the condition with the potential to evolve over time. (J Rheumatol 2011;38 Suppl 87:54–58; doi:10.3899/jrheum.101076)

Key Indexing Terms:
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A significant number of individuals with peripheral inflammatory arthritis do not readily fall into a specific diagnostic group. These individuals may be described as having an undifferentiated peripheral inflammatory arthritis (UPIA). Defining UPIA, however, is difficult and there is no agreed-upon classification or diagnostic criteria. It is a diagnosis of exclusion that can only be made after a thorough evaluation for other specific diagnoses. This may be challenging as the differential diagnosis is broad, and because UPIA is a dynamic condition. Over time, patients with UPIA can persist as UPIA, progress to a specific diagnosis, or enter remission[1]. Algorithms can help organize diagnostic decision-making. Unfortunately, most algorithms for the investigation of patients with inflammatory arthritis omit UPIA despite a prevalence of between 7% and 60% in cohorts of patients with early arthritis[1,2,3].

Recently, 10 recommendations for investigation and followup of UPIA were developed from a multinational collaboration and extensive literature review, through the 3e (Evidence, Expertise, Exchange) Initiative in Rheumatology[4]. These recommendations assumed a diagnosis of UPIA had already been established. The algorithm presented is designed to provide an approach to establishing a diagnosis of UPIA and is therefore the recommended step prior to implementing the 3e recommendations.

MATERIALS AND METHODS

An expert panel was assembled, comprising 19 rheumatologists and 4 rheumatology fellows from 15 countries. Panel members were participants in the 3e Initiative on the investigation and followup of patients with UPIA. Summaries of the results of the 10 systematic literature reviews (SLR) and the final recommendations from the 3e Initiative for UPIA were made available to the panel to guide development of the algorithm. The literature searches for the 10 SLR, described elsewhere in this supplement series, were broad-based searches up to February 2009 conducted in Medline, Embase, and the Cochrane Library; abstracts presented at the 2007 and 2008 meetings of the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) were also searched.

The algorithm was developed by consensus during a round table meeting. MindManager software (version 8) was used to assist with the structure of the algorithm as it was developed[5]. The algorithm drew heavily upon the clinical experience of the consensus panel, and evidence was integrated where possible. Further revisions to the algorithm were made to the draft document and these were approved by all committee members.

RESULTS

We developed an algorithm for investigation of new-onset arthritis and identification of UPIA (Figure 1). The algorithm is intended for use by rheumatologists or other clinicians with expertise in diagnosis and management of inflammatory arthritis, and not as a tool to guide treatment decisions or to help primary care practitioners decide when to refer a patient with suspected inflammatory arthritis.

Starting point: At least 1 swollen joint. The starting point for the algorithm was chosen as patients having at least one clinically swollen joint. This is in line with the recently proposed ACR/EULAR classification criteria for RA[6].

Is there a history of trauma? Prior to considering other causes of arthritis, it is important to exclude trauma as a cause of joint swelling, as urgent therapy may be required and management falls outside the scope of a rheumatology practice. The diagnosis is usually readily apparent on history. It is, however, important to consider that minor trauma may precipitate flares of other forms of arthritis, particularly crystal-related arthritis.

Is there a possibility of infection or crystals? Before considering other specific diagnoses or UPIA, it is important to perform a diagnostic arthrocentesis if there is any suspicion of crystal-related arthritis or joint infection. Joint infection refers to direct microbial invasion of the joint and not other infection-related arthritides, such as Lyme disease, parvovirus-associated arthritis, or infectious triggers of reactive arthritis. These are considered separately, as the pathogenesis differs and arthrocentesis with routine studies is not diagnostic.

Infection and crystal-related arthritis were considered together, as they both warrant arthrocentesis and synovial fluid analysis and because their clinical features often overlap. Diagnostic clues may include rapid onset and severe joint pain, with striking signs of inflammation. Crystal-related arthritis, however, may also present as a chronic polyarticular form, and infectious arthritis may be relatively indolent, particularly in elderly or immunocompromised patients. Suspicion of these disorders, therefore, requires assimilation of the available historical features, including risk factors and findings on clinical examination as well as any available investigations. In general, there should be a low threshold for arthrocentesis.

Finally, arthrocentesis is not 100% sensitive, so a nega-

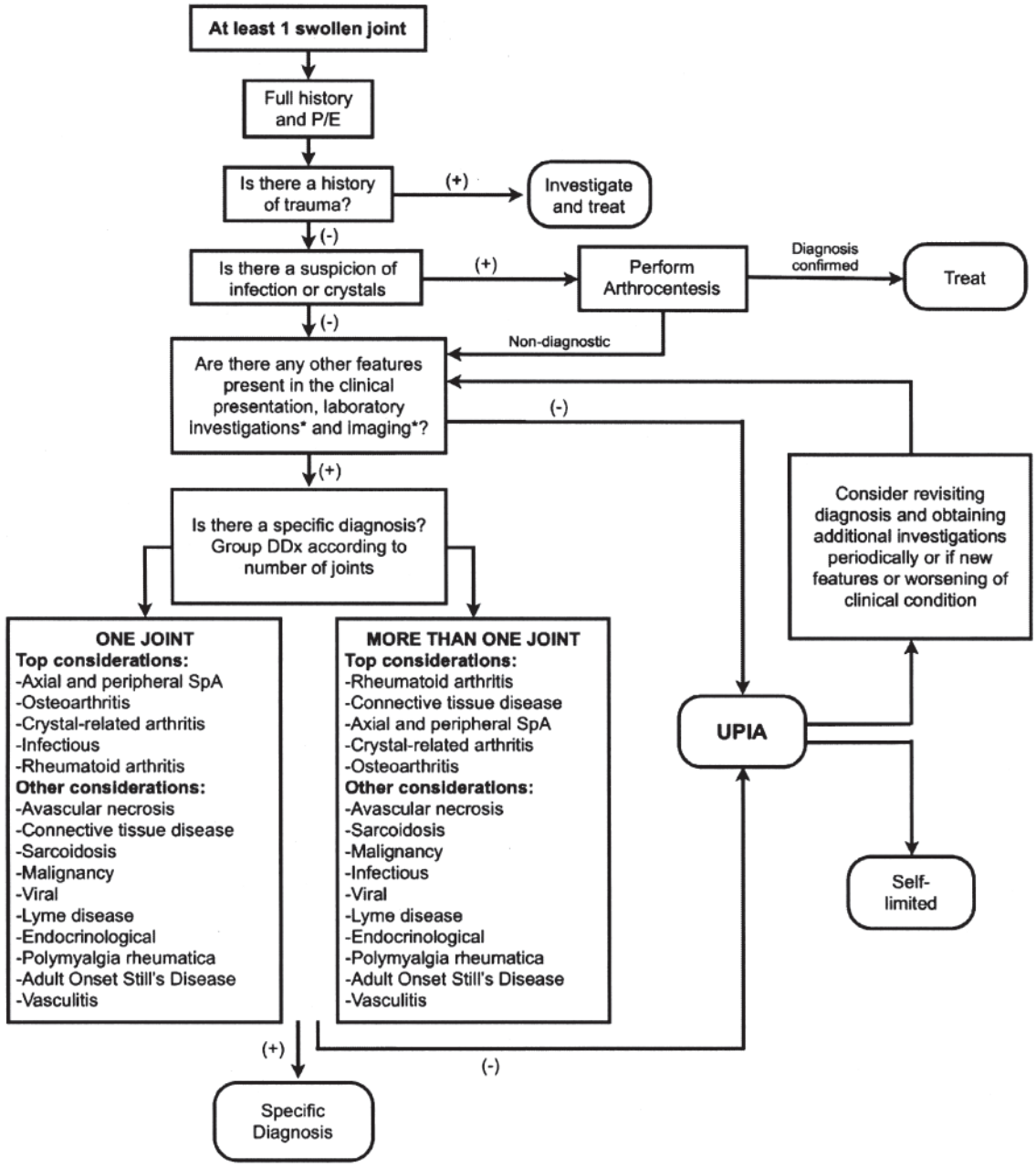

Figure 1. Algorithm for identification of undifferentiated peripheral inflammatory arthritis. *Recommended minimum investigations in all patients: rheumatoid factor and/or anticitrullinated peptide antibodies, erythrocyte sedimentation rate and/or C-reactive protein, complete blood count, and radiographs of affected joints. Radiographs of hands, wrists, and feet should be considered, particularly if rheumatoid arthritis is a diagnostic consideration. P/E: physical examination; DDx: differential diagnosis, SpA: spondyloarthritis; UPIA: undifferentiated peripheral inflammatory arthritis.

tive aspiration does not necessarily rule out crystal-related arthritis or infection. If clinical suspicion remains, these diagnoses should still be considered prior to a diagnosis of UPIA, and repeat arthrocentesis may be necessary. This is particularly important prior to starting immunosuppressive therapy if suspicion of infection remains.

Are there any other features present in the clinical presentation, investigations, or imaging? UPIA is a diagnosis of exclusion, and a search for a specific diagnosis is the next step in the algorithm. A thorough history and physical examination is a necessity in every patient and will help establish a differential diagnosis. An exhaustive list of investigations is not necessary prior to making a diagnosis of UPIA; investigations should be directed towards the differential diagnosis. As a minimum, however, it was considered that certain investigations are warranted in every patient presenting for

evaluation of joint swelling, after exclusion of trauma and infection/crystal arthritis. Laboratory investigations recommended for all patients are: rheumatoid factor (RF) and/or anticitrullinated peptide antibodies (ACPA), erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), and complete blood count (CBC). Additional autoantibody testing is suggested if a connective tissue disease/systemic inflammatory disorder is suspected, and HLA-B27 may be helpful when spondyloarthritis is suspected[4]. Radiographs of the affected joints should be performed in all patients, and radiographs of the hands, wrists, and feet should be considered, particularly if rheumatoid arthritis (RA) is a diagnostic consideration[4].

These recommendations are in agreement with 3e recommendations for when a diagnosis of UPIA has been established[4]. CBC was added as an obvious test prior to establishing a diagnosis, as it may be helpful in the setting of inflammation or infection and may identify cytopenias, which are part of the classification criteria for systemic lupus erythematosus[7].

If none of the above investigations are revealing and the clinical presentation does not indicate a specific diagnosis or does not warrant additional investigations, then a diagnosis of UPIA can be made. It is recognized that other investigations will commonly be performed, including liver function tests, kidney function tests, and serum uric acid level. The appropriateness of these investigations, however, was felt to be dependent on features present in the clinical presentation.

Is a specific diagnosis present? Using available clinical information from the history, physical examination, and preceding investigations, a specific diagnosis should now be sought. The approach to establishing a specific diagnosis was divided into patients presenting with one swollen joint and those presenting with more than one. For each group, a list of possible diagnoses can be ordered according to diagnostic probability. In Figure 1, the top diagnostic considerations and other considerations are listed. They are listed in no particular order, as the ordering of relative probabilities of the differential diagnosis will depend on the assimilation of findings of a thorough evaluation, including patient demographics and geographic location.

Some rheumatologic diagnoses have established diagnostic or classification criteria. These are periodically revised, so it is important to use the most updated version. Other diagnoses have no specific criteria, but have findings on history, physical examination, and investigations that can confirm diagnosis with reasonable certainty. The process of arriving at a specific diagnosis is complex and was felt to be best left to the expertise of the clinician. If a specific diagnosis cannot be established, then a diagnosis of UPIA can be made.

Revisiting the diagnosis. The diagnosis of UPIA should be reexamined over time. Specific time intervals for review were not provided due to a lack of available evidence. In addition, new clinical features or functional deterioration should also prompt reevaluation of the diagnostic strategy. With each round of reevaluation, more specific and advanced investigations and imaging may be required. Magnetic resonance imaging (MRI) and ultrasonography (US) have shown promise in predicting outcomes in patients with UPIA, but there is insufficient evidence to recommend their routine use[4].

The baseline investigations listed above — RF/ACPA, ESR/CRP, CBC, and radiographs — may be repeated periodically. Evidence to support repeat RF and ACPA over time, however, is limited. Patients with a longer duration of symptoms are more likely to be RF-positive or ACPA-positive, but in cohorts of patients with early inflammatory arthritis/UPIA, the number of seronegative patients who convert in the first 2 to 5 years is low[8,9,10]. Evidence for repeating ESR and CRP is also limited in UPIA, but are appropriate to follow over time, based on clinical experience. In keeping with 3e Initiative recommendations, radiographs of affected joints including hands, wrists, and feet should be repeated over time, at least within one year[4]. The frequency of repeating these investigations should occur in the context of the patient's overall clinical picture, including severity, persistence or progression of disease, and functional status.

The probability of UPIA progressing to certain diagnoses decreases over time. For example, the chance of discovering a malignancy-related arthritis or infection is unlikely if a patient has remained undifferentiated for a period of time. The pool of patients with UPIA will also shrink as new classification criteria are developed, allowing earlier diagnosis of specific diseases. Finally, a delay in progression of UPIA to RA may also occur with treatment[11,12].

DISCUSSION

Our algorithm outlines an approach to investigation of a patient with at least 1 swollen joint, and is, to our knowledge, the first diagnostic algorithm to incorporate UPIA. A key concept featured in the algorithm is that UPIA is an inherently unstable condition with a potential to progress over time[2]. This is reflected in the feedback loop of the algorithm, which emphasizes the need for ongoing reevaluation, while allowing progression to a specific diagnosis, spontaneous remission, or persistence as UPIA.

It is also important to recognize that individuals with UPIA are a heterogeneous population. While classified under the same umbrella of UPIA, patients within this group have differential probabilities for progression to a specific disease. Historical features, physical examination, and investigations can all be of value in determining the prognosis of an individual patient with UPIA[1]. As RA is the most common specific diagnosis at followup, most evidence available for prognosis focuses on RA as an outcome. There is limited evidence for predictors of progression to other diagnoses in cohorts of UPIA[4].

Separating the differential diagnosis into one versus more than one joint implies that clinicians are able to accurately determine how many joints are involved. This has been called into question with the use of advanced imaging techniques (MRI and ultrasound), which have shown that clinical examination is insensitive for detection of subclinical synovitis[13]. Currently, however, the role of advanced imaging in the evaluation of patients with UPIA is unclear[4].

Considering arthrocentesis early in the diagnostic algorithm for both monoarthritis and oligo/polyarthritis differs from other published algorithms[2,3]. This was done deliberately to highlight the need for arthrocentesis in any patient in whom there is suspicion of infection. The need for arthrocentesis will, however, clearly vary according to the number of joints involved. Arthrocentesis should be considered in most cases of monoarthritis, although there may be exceptions. For example, a single swollen distal interphalangeal joint in a patient with a history of psoriasis, and no other suggestion of infection or crystal-related arthritis, may not require an arthrocentesis. Similarly, many patients with polyarticular joint swelling may not require arthrocentesis. By asking if there is a possibility of infection or crystals in every patient, the diagnoses will not be overlooked.

Our algorithm includes both inflammatory and noninflammatory conditions in the differential diagnoses listed, as patients with noninflammatory arthropathies can also present with joint swelling. However, UPIA by definition is an inflammatory arthritis. The majority of cases of noninflammatory joint swelling will be osteoarthritis, for which it should be possible to make a definitive diagnosis. In situations where this is not possible, inflammatory arthritis should be established through history, physical examination, and investigations (including synovial fluid analysis if necessary) prior to diagnosing UPIA.

Classification criteria are commonly used for diagnosis but have been criticized for their inability to reflect clinical practice. They do, however, provide standardized criteria for identifying patients for clinical trials, and in turn, when identifying appropriate patients to apply the results of clinical trials. We therefore have suggested that classification criteria be used when possible. Recognizing that many diagnoses do not have established classification criteria, we have simply asked if a specific diagnosis is present. This requires the experience of a rheumatologist or experienced care provider in rheumatology. It follows, therefore, that a diagnosis of UPIA should not be made until after rheumatological consultation. A diagnosis of UPIA should also not preclude appropriate treatment, for which rheumatology consultation is also necessary.

UPIA remains an area of intense investigation. It is a dynamic, heterogeneous condition that leads to challenges when trying to establish specific diagnostic criteria. We feel an algorithmic approach may be more successful at representing the concept of UPIA. Our hope is that the algorithm will provide a conceptual framework for identifying patients with UPIA and will assist clinicians in this diagnostic evaluation.

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