Diagnostic and Prognostic Value of Synovial Biopsy in Adult Undifferentiated Peripheral Inflammatory Arthritis: A Systematic Review

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ABSTRACT. ***Objective.*** Our aim was to systematically review the literature on the diagnostic and prognostic value of synovial biopsy in undifferentiated peripheral inflammatory arthritis (UPIA) as an evidence base for generating clinical practice recommendations. The results lead to multinational recommendations in the 3e Initiative in Rheumatology.

Methods. We performed a systematic literature review according to the PICO strategy (Patients, Intervention, Comparator, and Outcome). Using a designed search strategy we ran literature searches using Medline, Embase, the Cochrane Library, and abstracts presented at the 2007 and 2008 meetings of the American College of Rheumatology and European League Against Rheumatism. Articles fulfilling predefined inclusion criteria were reviewed, and quality appraisal was performed.

Results. Six publications from a total of 3265 diagnostic and 3271 prognostic studies were included, of which 2 were review articles. Data pooling was impossible because of significant clinical and statistical heterogeneity. Three themes of outcome were identified: anti-citrullinated peptide antibody (ACPA) staining in synovium, immunohistochemistry (CD22, CD38, CD68), and vascular patterns. Prognostic and diagnostic value was poor for these themes, although diagnostic trends favoring a particular diagnosis were identified. In contrast to serological ACPA testing, ACPA staining was shown not to be specific for diagnosis of rheumatoid arthritis (RA). Synovial CD22 and CD38 positivity seem to differentiate between RA and non-RA, while synovial CD38 and CD68 positivity can differentiate among RA, spondyloarthritis (SpA), and other diagnoses. Vascular patterns in undifferentiated arthritis are insufficiently specific to differentiate between SpA and RA.

Conclusion. There is sparse evidence that synovial biopsy has diagnostic or prognostic value in patients with UPIA in clinical care. We urgently need systematic studies investigating the diagnostic and prognostic potential of synovial markers. A clear, broadly accepted, and unequivocal definition of undifferentiated arthritis is required as a starting point. (J Rheumatol 2011;38 Suppl 87:45–47; doi:10.3899/jrheum.101074)

Key Indexing Terms:
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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 follow up undifferentiated peripheral inflammatory arthritis. The process of the 3e Initiative and the resulting 10 recommendations have been described[1]. The objective of the current work was to systematically review the available literature concerning synovial biopsy in patients with undifferentiated arthritis (UA).

As stated in an earlier review, synovial biopsy is not routinely performed in daily clinical practice[2]. Most often, history-taking, physical examination, radiographic examination, and serum markers are sufficient to make a diagnosis. In rarer cases, synovial biopsy can be of interest, as there are chronic infectious diseases, some connective tissue diseases, and malignancies, etc. Although there are many studies about pathogenesis in rheumatic disease, there is sparse correlation with clinical use. Some clinicians attach value to pathologic examination of the synovium to either differentiate between rheumatoid arthritis (RA) and non-RA, or to gain insight into the pathogenesis of the underlying disease.

Our systematic literature review provides an overview of

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the available evidence on synovial biopsy in UA to address our research question: What is the contribution of synovial biopsy in undifferentiated peripheral inflammatory arthritis?

MATERIALS AND METHODS

The systematic literature review was carried out in several steps following updated guidelines for Cochrane systematic reviews[3]. First, the research question was translated into an epidemiological research question according to the PICO (Patients, Intervention, Comparator, and Outcome) method[4]. Patients were defined as adults with undifferentiated peripheral inflammatory arthritis. Intervention was defined as taking a synovial biopsy of an affected joint. Patients without joint problems (normal patients) or patients with a well defined rheumatic disease were taken as Comparator. Outcomes were two-fold: we looked at the value of biopsy both as a diagnostic marker and also as a prognostic marker, with respect to both well defined rheumatic disease [rheumatoid arthritis, systemic lupus erythematosus, spondyloarthritis, psoriatic arthritis (PsA), inflammatory arthritis, infectious arthritis, crystal arthritis, mixed connective tissue disease, and sarcoidosis] and other connective tissue disease.

Next, a systematic literature search for published articles was carried out in Medline, Embase, and the Cochrane Library, using a comprehensive search strategy (see online appendix 1, available from www.3eupia.com) in collaboration with an experienced librarian. The search was limited to English language literature without a time limit. Review articles were also retrieved for identifying additional references via hand search. The abstracts of the annual scientific meetings of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) from 2007 and 2008 were also searched for findings that had not been fully published. Initially we selected the articles based on titles and abstracts, applying the following exclusion criteria: (1) defined rheumatic disease, (2) pediatric rheumatic disease, (3) non-English language, (4) treatment, (5) non-human investigations, (6) no outcome of interest, and (7) synovial fluid analysis. The remaining articles were selected by reading the complete study. Each selected study was assessed with regard to levels of evidence according to the Oxford Centre for Evidence-based Medicine[5]. Lastly, each included study was quality-assessed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies tool)[6]. We aimed to extract all the data from the articles and to calculate sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), negative likelihood ratio (LR–), and positive likelihood ratio (LR+) where possible.

RESULTS

Using Medline and Embase we found 3271 articles for prognostic studies and 3265 articles for diagnostic studies. Based on title and abstract, and the predefined inclusion and exclusion criteria, we excluded 3242 and 3241 articles for prognostic and diagnostic studies, respectively. The remaining articles were reviewed by reading the complete study. Five diagnostic and 5 prognostic articles could be included for detailed review. Four articles (2 of them review articles[2,11]) were duplicates (see online appendixes 2 and 3, available online from www.3eupia.com).

After in-depth review, 3 themes were distinguished: vascular morphology, synovial anti-citrullinated peptide antibody (ACPA) staining, and synovial immunohistochemical analysis.

Vascular morphology. Two studies dealt with vascular morphology in synovial biopsy specimens. Correlations between diagnosis and any pattern of vascular morphology were weak. RA tended to have a straight vascular pattern while spondyloarthritis (SpA) and PsA had a tortuous vascular pattern.

In one study there were 17 patients defined as having UA at the start. Six patients were definitely diagnosed during 2 years' followup. Four patients had a tortuous vascular pattern, of which 2 had RA and 2 had PsA and SpA. Two other patients had a straight vascular pattern and were diagnosed as having RA. In patients with a definite diagnosis at start of study, sensitivity and specificity varied among different diseases. A straight pattern had a sensitivity and specificity for RA of 77% and 70% (LR+ 2.57, LR– 0.33), respectively. A tortuous pattern had a sensitivity and specificity for PsA and SpA of 61% and 95% (LR+ 12.2, LR– 0.41), respectively[7].

Varying results were seen in a second article investigating vascular morphology. At the start of study, 87 patients were defined as having UA, since they did not meet any existing classification of a known established diagnosis. On reevaluation after a period of 6 months, 53 patients met an established diagnosis. Of those, 19 patients had RA. Presence of a straight vascular pattern had a sensitivity of 47% and a specificity of 77% (LR+ 2.04, LR– 0.69). In total, 21 patients had SpA, in which presence of a tortuous vascular pattern had a sensitivity of 57% and a specificity of 66% (LR+ 1.68, LR– 0.65)[8].

Synovial ACPA staining and synovial histopathology. Synovial histopathology was investigated in 3 studies. There were different markers of interest: ACPA staining, monoclonal antibody against epitope 12A (mAb 12A) and mAb against B cells, plasma cells, macrophages, and fibroblast-like synoviocytes. Of 87 patients with UA at the start of study, 53 patients fulfilled an established diagnosis after 6 months' followup. Of those, 19 patients had RA. Anticitrulline staining and mAb 12A reached a sensitivity of 53% with a specificity of 97% (LR+ 17.7, LR– 0.48). Patients who remained undifferentiated after 6 months were not analyzed[8].

In a later study other authors investigated local production of ACPA by comparing the concentration of the antibodies in paired samples of serum and synovial fluid. They found that anti-cyclic citrullinated peptide antibodies are present in higher concentration in synovial fluid from RA patients compared to control patients, but the presence of ACPA in synovial tissue was not specific for RA[9].

Immunohistological analysis of synovial tissue. Analysis of the expression of different markers may be used to differentiate between RA and non-RA according to a study including 95 patients. All patients had an unclassified active arthritis at the time of presentation, with at least one affected knee and a disease duration of less than one year. After 2 years' followup, patients either fulfilled criteria for an established rheumatic disease or remained undifferentiated. Markers were semiquantitatively scored by 2 independent observers.

Logistic regression analysis showed that RA and non-RA could be classified correctly in 85% and 96% of the patients, based on CD38 and CD68 markers[10].

DISCUSSION

Our systematic review gives an overview of the available literature on the diagnostic and prognostic value of synovial biopsy in patients with UA. This overview served to guide the process of creating recommendations on use of synovial biopsy in making a diagnosis in patients with inflammatory arthritis.

To select studies and compare results of different studies it is necessary to have a clear diagnosis of UA. However, UA is very difficult to define: specific criteria for UA are lacking, which jeopardizes scientific research and data analysis in these patients. Most studies try to differentiate between RA and non-RA or have UA defined as early RA. Although we selected all articles that included patients with UA and early RA, results remain very sparse when focused on the diagnostic and prognostic value of synovial biopsy. When synovial biopsy has been performed, it is unclear which further analysis is best.

Our systematic review showed that immunohistochemical analysis and evaluation of the vascular pattern may be useful in evaluating patients presenting with UA. But the number of studies is very limited and there is considerable heterogeneity in terms of the definition of UA. Therefore, to date we do not recommend synovial biopsy in routine clinical practice.

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